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Original Article

SCREENING OF *RICINUS COMMUNIS* LINN. LEAVES FOR ANTICONVULSANT AND ANALGESIC ACTIVITY

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ABSTRACT

Objectives: Maximal electroshock seizures (MES) in albino rats and pentylenetetrazole (PTZ) induced seizures in albino mice were used to study anticonvulsant activity of *Ricinus communis* Linn. leaves extract belonging to family Euphorbiaceae. Different extracts of *Ricinus communis* Linn. were also screened for analgesic activity by Eddy's hot plate method.

Methods: The ethanolic leaves extract of *Ricinus communis* Linn. was administered orally as (250 mg/kg) in both the experimental models and the effects were compared with phenytoin in MES method and diazepam in PTZ induced seizures method as standard control respectively. The latency of seizures and % of mortality were observed.

Results: The ethanolic leaves extract suppressed duration of tonic convulsions and showed recovery in maximal electroshock induced seizures. It also decreased number, duration of convulsions, delayed time of onset of clonic convulsions and showed mortality protection significantly in pentylenetetrazole induced seizures. The ethanolic extract delayed the occurrence of MES and PTZ convulsions, exerts their anticonvulsant effect.

Conclusion: This study confirmed the oral analgesic and anticonvulsant properties of mature fresh leaves of *Ricinus communis* Linn. claimed in the Ayurveda medicine and do have pain suppressing activities possibly mediated via PG synthesis inhibition, membrane stabilizing. The extract could have exhibited the activity by interfering with GABA, glutamate mechanisms. Phytochemical investigation reveals the presence of flavonoids, fatty acids attributed to their anti-convulsant action. Future study should focus on isolation of these components for the observed analgesic, anticonvulsant action and identification of its mechanism of action.

Keywords: *Ricinus communis* Linn., anti-convulsant, analgesic, MES, Pentylenetetrazole,

INTRODUCTION

The word 'epilepsy' is derived from the ancient Greek word *Epilepsía* means "to seize". It is a neurological disorder characterized by recurrent unprovoked seizure. This is generally due to excessive neuronal discharge in the brain. Epilepsy is a common chronic neurological disorder, characterized by recurrent unprovoked seizures [1]. However it is common to have a seizure and not have epilepsy. The rate of recurrence of a first unprovoked seizure within 5 years ranges between 23% and 80% [2]. Globally, there are nearly 50 million people suffering from epilepsy, 80% of which are in the developing countries and 90% of these do not receive appropriate treatment. India alone has approximately 8-10 million epileptics. Epilepsy affects not only the individual, but also has consequences for the family and the rest of society [3].

In developed countries epilepsy responds to treatment in upto 70% of patients. In developing countries 75% of the patients do not receive the treatment because of unavailability of the drugs and there is a high rate of mortality [4]. In recent years, the medicinal properties of plants have been investigated in the light of scientific developments throughout the world, due to their potent pharmacological activities, low toxicity and economic viability [5]. A lot of newer research strategies aim at the development of a new generation of phytopharmaceuticals which can be used alone or in combination with synthetic drugs or antibiotics [6]. Pain has been defined by International Association for the Study of Pain (IASP) as an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Most of the analgesic drugs carry potential toxic effects. Risk of gastrointestinal bleeding was significantly associated with acute use of non-steroidal anti-inflammatory drugs (NSAIDs) like regular-dose aspirin, diclofenac, ketorolac, naproxen. Piroxicam increased the risk of bleeding in both acute and chronic therapy. Opioids are the commonly used drugs for the management of acute postoperative pain [7].

Ricinus communis Linn. is a tall glabrous and glaucous annual found throughout India, commonly called as Castor, is a perennial evergreen shrub. The Sanskrit name *erandah* describes the property of the drug to dispel diseases. It is considered as a reputed remedy for all kinds of rheumatic affections. They are useful in gastropathy such as gulma, constipation, inflammations, fever, ascitis, bronchitis, cough, leprosy, skin diseases, It used in treatment of rheumatic arthritis, paralysis; epilepsy; distention of the uterus. Used in non-lowering of the fetus (during delivery): poultice Yungchuan Pt (K-1 pt) with pounded fresh leaves. Leaves applied to head to relieve headache and as a poultice for boils [8,9]. It is reported that *Ricinus communis* Seeds ethanolic extract and Isolated phytoconstituent ricinine showed anticonvulsant activity in MES induced convulsions in mice [10]. But leaves of plant were not reported anticonvulsant activity. It also reported pharmacological activities like antidiabetic, [11] anti-inflammatory, [12] anticancer, [13] anti-tubercular activity [14].

The conventional antiepileptic agents like phenytoin, carbamazepine and sodium valproate carry with them several serious side effects notably neurotoxicity. As majority of antiepileptic drugs are consumed life long, concomitant administration of other drugs predisposes to the risk of drug interaction [15].

However, newer anti-epileptics like gabapentin, vigabatrin, lamotrigine, etc. are used supplemental to the conventional agents. Thus, it is necessary to investigate for an antiepileptic agent that is highly efficacious as well as safe in items of drug related toxicity. The aim of treating an epileptic patient is not only to abolish the occurrence of seizures but also to lead a self sustained life [16]. Traditional systems of medicine are popular in developing countries

and up to 80% of the population relies on traditional medicines or folk remedies for their primary health care needs [17].

Literature survey reveals that there are no scientific reports regarding the anticonvulsant and analgesic action of ethanolic extract of *Ricinus communis* Linn. Hence present study was undertaken to evaluate the analgesic activity of different solvent extracts and anticonvulsant activity of ethanol extract *Ricinus communis* Linn. The ethanolic extract was used in this investigation because ethanol being nonpolar, the major active chemical constituents of *Ricinus communis* Linn. including fatty acids, would be expected to be more soluble in ethanol fraction of the extract.

MATERIALS AND METHODS

Drugs

Pentylenetetrazole *(*PTZ), diazepam and pentazocine were purchased from (Sigma Chemical Co. Hyderabad, India). Different concentrations of the drugs were prepared freshly by suspending in gum acacia (Hi-media, Mumbai, India) in water. The solvents used were of analytical grade ethanol, acetone (E-Merck, Mumbai) and Gum acacia in water were used as solvent and vehicle respectively.

Drug solution: The ethanolic extract and diazepam (standard) was suspended in 1% acacia solution and a stock 20 mg/ml and 0.4 mg/ml was prepared respectively. Pentylenetetrazole was dissolved in distilled water and stock solution 8 mg/ml was prepared. Phenytoin sodium (standard) 5 mg/ml was prepared in 1% acacia solution.

Collection and preparation of extracts

Fresh leaves of *Ricinus communis* Linn. were collected in the month of August 2012 from Sangli, and Miraj areas and authenticated by Smt. U. S. Shinde, Botanist from Botany department of Willingdon College, Sangli. The leaves were washed and were shade dried to obtain coarse powder. This powder was subjected to different extraction procedures.

The aqueous extract was prepared by maceration method. The air dried powdered plant material was extracted in Soxhlet apparatus with ethanol. Coarse powder was extracted successively with acetone and alcohol in a Soxhlet apparatus, finally with chloroform water by maceration. Both the extracts were distilled, dried and used for this study [18,19].

Phytochemical investigation

All the extracts were subjected to preliminary phytochemical investigation for the presence of carbohydrates, fats, oils, alkaloids, steroids, tannins, glycosides and flavonoids [20].

Acute oral toxicity study

The acute toxicity test of the extracts was determined according to the Organization for Economic Co-operation and Development (OECD) guideline number 423 [21]. No death was observed till the end of the study. The aqueous, ethanol acetone, successive ethanol extracts of *Ricinus communis* Linn were found to be safe up to the dose of 2000 mg/kg and from the results, 200 mg/kg and 400 mg/kg dose were selected for further experimentation.

Healthy male albino rats (Wistar strain) and Swiss albino mice of body weight (150–200 g) and (25–30 g) respectively were used to study the effect of test drug on MES and PTZ induced seizures respectively. Female animals were excluded because of the fact that estrus cycle influences the seizure threshold. Swiss albino mice were used for analgesic activity. The animal study was performed in the Appasaheb Birnale College of Pharmacy, Sangli with due permission from the Institutional Animal Ethics Committee (registration number 843/po/ac/04/CPCSEA.). All the experimental procedures and protocols used in this study were reviewed by the Institutional Animal Ethics Committee (IAEC) and were in accordance with the guidelines of the IAEC. Animals were housed in polypropylene cages with dust free rice husk as a bedding material under laboratory condition with controlled environment of temperature 25° ± 2°, humidity (60% ± 10%) and 12 h light/dark cycle as per CPCSEA guidelines. They were provided with conventional rodent laboratory diet and water *ad libitum* the animals were acclimatized with laboratory conditions before experiment.

Pentylenetetrazole (PTZ) induced seizures in mice

For anticonvulsant activity 24 Swiss albino mice of either sex were divided into groups of six animals (n=6) each. The animals were fasted overnight before the experimentation. Animals in Group I served as control were treated with vehicle (1 % Acacia solution) orally. Group II served as standard received diazepam (4 mg/kg i.p.). Group III and Group IV received ethanolic extract of plant at the dose levels of 200 mg/kg and 400 mg/kg orally respectively. Pentylenetetrazole (80 mg/kg i.p.) was administered 60 min. after oral and 30 min. after intraperitoneal administration of vehicle, diazepam. Each animal was placed in to individual polypropylene cage and were observed initially for 60 min and later up to 24 h. During test, the onset time and duration of myoclonic jerks and tonic-clonic convulsions were recorded. The number of animals survived within the period of observation (60 min. after PTZ administration) was expressed as % protection [22, 23, 24].

Maximal electroshock induced seizures (MES) in rats

Same experimental design was used as like PTZ induced convulsion method here phenytoin 25 mg/kg was used as standard instead of diazepam. MES seizures were induced by Electroconvulsiometer (Ambala, India). In preliminary study, the current at which rats showed extension of hind limb was recorded as the seizure threshold and were included in the study. An electroshock of the intensity 120 mA for 0.2 s was delivered through ear clip electrodes 60 min for MES seizures after oral administration of ethanolic extract and 30 min after i.p. administration of vehicle, phenytoin sodium. This current intensity elicited complete tonic extension of the hind limbs in control rats. 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 the pilot study of various phases of convulsions, like tonic flexion, extension, stupor and mortality due to convulsions were observed. The number of animals survived within the period of observation (30 min after electroshock delivery) was expressed as % protection. The abolition of extensor (tonic phase) in drug treated group was taken as criteria for anticonvulsant activity [22,23,24].

Analgesic activity by Eddy's hot plate method

The analgesic activity of the extract was measured by hot-plate method. For analgesic activity thirty albino mice were divided into six groups.

1. First group: is served as control
2. Second group: as positive control
3. Third group: received aqueous extract of *Ricinus communis* Linn.
4. Fourth group: received successive ethanolic extract
5. Fifth group: received ethanolic extract
6. Sixth group: received acetone extract

All extracts of *Ricinus communis* Linn. were given to the mice orally as a suspension in gum acacia to the respective group according to their body weight respectively. The mice were placed on a hot plate maintained at 55 ± 0.5^{o}. The reaction time was taken as the interval from the instant animal reached the hot plate until the moment animal licked its feet or jumped out. A cut off time of +30 s was followed to avoid any thermal injury to the paws. The reaction time was recorded before and after +30, +60, +90 and +120 minutes following administration of test or standard drug. The mean reaction time for each treated group was determined and compared with that obtained for each group before treatment. Increase in reaction time was noted at +30, +60, +120 and +180 min after the administration of test/standard drug [25, 26].

STATISTICAL ANALYSIS

Values were expressed as mean ± SEM from 6 animals. Statistical differences in mean were calculated using one way ANOVA followed by Dunnett's test. $p< 0.0001$, $p< 0.001$, $p< 0.01$ and $p< 0.05$ were considered.

RESULTS AND DISCUSSION

Table 1: It shows Phytochemical investigated and percent yield of various extracts of *Ricinus communis* Linn. leaves

S. No.	Name of extracts	% yield of extracts in (grams)	Phytochemical investigated
1	Aqueous	15.50	Sterol, carbohydrates, fats, oils, alkaloids, tannins and flavonoids.
2	Ethanol	12.9 2	Glycosides, carbohydrates, fats, oils, alkaloids, steroids, tannins and flavonoids.
3	Acetone	2.70	Carbohydrates, fats, oils, alkaloids and flavonoids
4	Successive ethanol	1.67	Carbohydrates, fats, oils, alkaloids, flavonoids and tannins.

Anti-convulsant activity

The most popular and widely used animal seizure models are the traditional maximum electroshock-induced seizure and pentylenetetrazole tests. Prevention of seizures induced by pentylenetetrazole in laboratory animals is the most commonly used preliminary screening test for characterizing potential anticonvulsant drugs. The maximum electroshock-induced seizure test is considered to be a predictor of likely therapeutic efficacy against generalized tonic-clonic seizures. By contrast, the pentylenetetrazole test represents a valid model for human generalized myoclonic and also absence seizures [13]. The anticonvulsant activity of *Ricinus communis* at various dose levels viz, 200 and 400mg/kg orally was studied by Pentylenetetrazole and Maximal electroshock induced seizure models.

Table 2: It shows Effect of ethanolic extract of *Ricinus communis* Linn. on PTZ induced convulsions in mice.

S. No.	Drug treatment	Onset of convulsions in (sec) (Mean ± SEM)	Duration of convulsions in (sec) (Mean ± SEM)	No. of deaths	Protection %
1	Vehicle 1% Acacia solution (0.1ml/10gm)	64.36 ± 1.892	18.89 ±1.198	6	0.00
2	Diazepam(4mg /kg)	0.00 ± 0.00#	0.00 ± 0.00#	0	100
3	Ethanolic extract (200mg/kg)	135.36 ± 2.438**	6.46± 0.757**	1	83
4	Ethanolic extract (400mg/kg)	180.17 ± 2.162**	1.457± 0.481**	0	100

Values are given as mean ± SEM for six rats in each group. # Complete protection, statistical analysis of the data was carried out by one-way ANOVA followed by Dunnet's test, **P<0.01 as compared to vehicle control.

The onset of convulsions was delayed by 110% and 180% (P<0.01) whereas the duration of convulsions was reduced by 66% and 92% (P<0.01) in animals treated with ethanolic extract of *Ricinus communis* Linn. at a dose of 200 and 400 mg/kg respectively as compared to vehicle treated i.e. control animals. It also decreased number of clonic convulsions. However, the standard drug Diazepam (4 mg/kg/i.p) and ethanolic extract 400 mg/kg provided 100% complete protection and 83% protection at 200 mg/kg. All shows statistically significant (P<0.01) protection against 24 h mortality as well as decreased number and duration of convulsions in comparison to control.

It is well documented that pentylenetetrazole induced convulsions are produced due to diminution of brain GABA (Gamma Aminobutyric Acid) level. Since the extracts delayed the occurrence of pentelenetetrazole-induced convulsion, it is probable that it may be interfering with GABA aminergic mechanisms to exert its anticonvulsant effect. However, several mechanisms are involved in anticonvulsant activity; it is very premature at this stage of the study to say that anticonvulsant action appears to be due to increased level of GABA. Thus this aspect/hypothesis requires further investigation in future.

Maximal electroshock induced seizures (MES) in rats

Table 3 It shows Effect of ethanolic extract of *Ricinus communis* Linn. on MES induced convulsions in rats

S. No.	Drug treatment	Dose	Tonic hindlimb Onset (sec) (Mean ± SEM)sec. Onset in s	extension Duration (sec) (Mean ± SEM).	% inhibition of convulsions
1	1% Acacia solution	0.1ml /10g	2.5783± 0.2423	17.9216 ± 0.7321	--
2	Phenytoin	25 mg/kg	0.00 ± 0.00#	0.00 ± 0.00#	100
3	Ethanol extract	200 mg/kg	4.79 ± 0.1235*	8.43 ± 0.4367*	83.28
4	Ethanol extract	400 mg/kg	7.46± 0.5821**	3.28 ± 0. 1652**	100

Values are given as mean ± SEM for six rats in each group. #Complete protection, statistical analysis of the data was carried out by one-way ANOVA followed by Dunnet's test. Results are statistically significant at *P<0.01 and **P<0.001 as compared to vehicle control.

Ricinus communis Linn. ethanolic extract 200 and 400 mg/kg showed significant reduction in duration of convulsion in a dose dependent manner. The onset of tonic hind-limb extension [HLE] was delayed by 86% and 189% whereas the duration of tonic hind-limb extension [HLE] was reduced by 53% and 82% (P<0.01) in animals treated with ethanolic extract of *Ricinus communis* Linn. at a dose of 200 and 400mg/kg respectively as compared to vehicle treated i.e. control animals. The standard drug phenytoin and 400mg/kg ethanolic extract showed 100% protection in animals against MES. It abolished the extensor phase completely (P<0.001),

In MES induced seizure test, shown anticonvulsant effect by increasing the onset of clonic convulsion time and by decreasing the time of extensor of test groups reduced to significant level as compared to control group (p<0.001 and p<0.01). These results indicate the strong protective effect of 200 and 400 mg/kg of *Ricinus communis* Linn. ethanolic extract against known epileptic agents in a dose dependant manner.

Protection against HLE in the MES predicts anticonvulsant activity of anti-epileptic drugs that prevent the spread of the epileptic seizure from an epileptic focus during seizure activity. Protection against HLE also indicates the ability of the testing material to inhibit or prevent seizure discharge within the brain stem substrate. The effect of most of anti-epileptic agents is to enhance the response to GABA (gamma amino butyric acid), by facilitating the opening of GABA-activated chloride channels. $GABA_A$ receptors have been formed to be involved in epilepsy and their direct activation would have an anti-epileptic effect [24]. Phenytoin sodium exerts antiepileptic effect by stabilization of neuronal membrane and thus prolongation of recovery of inactivated sodium channels. In high doses, Phenytoin can also block the calcium influx during depolarization [27].

Moreover, MES-induced tonic extension can be prevented either by

drugs that inhibit voltage-dependent Na+ channels, such as phenytoin, valproate, felbamate and lamotrigine or by drugs that block glutamatergic excitation mediated by the N-methyl-Daspartate (NMDA) receptor, such as felbamate. Thus the anticonvulsant activity exhibited by the ethanolic extract shows that it could have blocked the seizure spread by inhibiting Na+ channels and glutamatergic excitation through NMDA receptor. Since the ethanol extract showed anti-epileptic activity in the MES, it may act through any of the above-mentioned mechanisms.

The extract suppressed hind limb tonic extensions (HLTE) induced by MES and also exhibited protector effect in PTZ-induced seizures. MES and PTZ may be exerting their convulsant effects by inhibiting the activity of gamma amino butyric acid (GABA) at GABA-A receptors [28]. GABA is the major inhibitory neurotransmitter which is implicated in epilepsy. Drugs protecting against tonic-clonic seizures induced by PTZ are considered useful in controlling myoclonic and absence seizures in humans [29].

The study also suggests that the extract would be effective against generalized tonic-clonic and partial seizures. Thus, the ethanolic extract of *Ricinus communis* Linn leaves possesses anticonvulsant property against MES and PTZ induced seizures which could be by interfering with GABA, glutaminergic mechanism and Na+, Ca2+ channels. There are some evidences about anticonvulsant effect of the fatty acids [30,31] which are major phytoconstituents of *Ricinus communis* Linn.

Analgesic activity by using Eddy's hot plate method

It was first proposed by Woolfe and MacDonald, although the version most often used today is as modified by Eddy and Leimbach in 1953 [32]. Ethanolic extract had significant ($p< 0.001$) analgesic activity at 1/2 h. Aqueous extract showed significant ($p< 0.001$) activity at 1/2 and 1 h while acetone extract showed most significant ($p< 0.001$) activity at 2 h. Successive ethanolic extract of a *Ricinus communis* showed a significant increase ($P<0.001$) in reaction time at all time interval, comparable to the reference drug pentazocine, suggesting its central analgesic activity. In the hot plate method, plant extract increased the stress tolerance capacity of the animals and hence indicate the possible involvement of a higher centre.[26] On the basis of these results, it observed that all extracts of plant has analgesic activity.

Table 4: Effect of different extracts of *Ricinus communis* Linn. on latency to hot plate test:

Sr. no.	Treatment	Dose (mg/kg)	Reaction ½ hours	Time (Mean± SEM 1 hours	± SEM and P value) 2 hours
1	Control (Distilled Water)	200	9.666 ± 0.3333.	9. 688 ± 0.3393.	9.566 ± 0.08333
2	Aqueous extract	200	18.00 ±.2582***	16.00 ± 0.3651***.	10.83 ± 0.4773*
3	Successive ethanol extract	200	18.50 ± 0.5672***	17.166 ± 0.4014***	14.660 ± 0.2108***
4	Ethanol extract	200	21.00 ± 0.3651***	8.666 ± 0.333*	11.00 ±0.2582*
5	Acetone extract	200	20.833 ± 0.4041***	24.033 ± 0.4944***	30.660 ± 0.333***
6	Pentazocine	5	15.800 ± 0.3403***	20.000 ± 0.32***	17.24 ± 0.51***

Values are expressed as mean ± SEM. Statistical analysis was performed using Dunnet's test. *p< 0.05, **p<0.01 and ***p<0.001, were taken as the criterion of significance when compared to control.

CONCLUSIONS

From results, it may be conclude that ethanolic extract of *Ricinus communis* Linn. has anti-convulsant activities against seizures induced by MES and PTZ in a dose dependent manner. All extracts of plant showed analgesic activity these activities were related to the dose and these results corroborate the potential traditional use of the plant in folk medicine. At present, there are no reports on investigation to identify the active components present in ethanolic extract of *Ricinus communis* Linn. Further investigations are anticipated to identify the active components and lead to their further clinical use.

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