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EVALUATION OF ANTI-CONVULSANT ACTIVITY OF ETHANOLIC EXTRACT OF ZIZYPHUS OENOPLIA ROOTS IN EXPERIMENTAL ANIMALS

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ABSTRACT:

Objective: To evaluate the antiepileptic potential of ethanolic extract of Zizyphus oenoplia root (ZOEE) in experimental animal models.

Methods: The Antiepileptic activity of ethanolic extract of Zizyphus oenoplia root (ZOEE) was analyzed using Maximal electroshock and Pentylenetetrazole induced convulsion models in Swiss albino mice. The mice were divided into 4 groups and each group consisting of 6 animals. Group I were treated with vehicle (p.o) as control, Group II were receiving standard drugs Phenytoin (25mg/kg, i.p.) for Maximal electro-shock model and Diazepam (4mg/kg, i.p.) for Pentylenetetrazole-induced model and the Group III and IV were treated with 150mg/kg (p.o) and 300mg/kg (p.o) of Zizyphus oenoplia root extract for 14 days respectively. On the 14th day the convulsions were induced in all the study groups.

Results: The ethanolic extract of Zizyphus oenoplia root (ZOEE) in the doses (150mg/kg and 300mg/kg) shows significant, dose-dependent activity in PTZ induced convulsion model by delaying the onset, reduction in the duration of convulsion and increase in survival of animals. In the MES induced model, the extract shows antiepileptic activity by significantly reducing the Hind Limb Tonic Extension (HLTE) phase.

Conclusion: The present study concluded that ethanolic extract of Zizyphus oenoplia root possess significant antiepileptic activity by effectively inhibiting the seizures in both MES and PTZ induced convulsion model.

Keywords: Antiepileptic, Ethanolic, Maximal electroshock, Pentylenetetrazole, Zizyphus oenoplia.

Introduction:

Epilepsy is a chronic disorder of the brain that affects people worldwide. As per WHO, epilepsy is characterized by recurrent seizures, which are brief episodes of involuntary movement that may involve a part of the body (partial) or the entire body (generalized), and are sometimes accompanied by loss of consciousness and control of bowel or bladder function.[1] Epilepsy and seizures have been described and recorded throughout the entire medical history. Babylonian texts from about 1000 before Christ (BC) already mention seizure like states in humans (WHO, 2005). In earliest times, seizures were thought to be of divine or demonic origin and were treated religiously or spiritually. It was Hippocrates who was the first to state: "The brain is the seat of this disease, as it is of other very violent diseases".[2]

It is estimated that about 1% of the population suffers from epilepsy, and about one third of patients have refractory epilepsy. Seizures are divided into three categories: generalized, focal (formerly called partial), and epileptic spasms. Focal seizures originate in neuronal networks limited to part of one cerebral hemisphere. Generalized seizures begin in bilateral distributed neuronal networks. A seizure can begin focally and later generalize. Seizures can originate in the cortex or in subcortical structures. Using a detailed history, EEG findings, and ancillary information, a physician can often categorize the seizure/epilepsy type, after which an appropriate diagnostic evaluation and treatment plan is formulated. The main subtypes of generalized seizures are absence, generalized tonic–clonic (GTC), myoclonic, and atonic. Absence seizures (formerly called petit mal) involve staring with unresponsiveness to external verbal stimuli, sometimes with eye blinking or head nodding. These brief involuntary muscle contractions may affect one or several muscles; therefore, myoclonic seizures can be generalized or focal. Atonic seizures involve the loss of body tone, often resulting in a head drop or fall.[3]

While all people with epilepsy experience seizures, not all individuals with seizures have epilepsy. Epileptic seizures may also occur after an acute central nervous system (CNS) insult that can be structural, systemic, toxic, or metabolic. These acute symptomatic or provoked seizures are intended as acute manifestation of the insult.[4]

The cause of epilepsy is completely unknown. The word epilepsy does not indicate anything about the cause or severity of seizures in person some cases of epilepsy are induced by genetic factors, but can also result in brain injuries caused by blows to the head, strokes, infections, high fever or tumours. It

has been noted that heredity (genetics) plays an important role in many causes of epilepsy in very young children, but they can be a factor for people of any age. In cases, not all people who have severe head trauma (a clear cause of epileptic seizures) will develop epilepsy. Some epileptic syndromes referred to as epileptic reflex precipitating specific needs or triggers seizures such as reading, intermittent and precipitating lights such as emotional stress, sleep thermal stress deprivation, alcohol and febrile illness are examples of precipitating factors cited by patients with epilepsy. In particular, the influence of various provoking factors varies with epilepsy syndrome.[5] The menstrual cycle in women with epilepsy can affect the patterns of relapse seizure, catamenial seizure epilepsy related to the menstrual cycle.[6]

An accurate clinical diagnosis of epilepsy is essential for correct management and is usually based on a precise description of seizure events and other factors such as age of seizure onset, neurological findings, and family history, inter ictal EEG, neuroimaging evaluation and a 12-lead electrocardiogram (ECG) to exclude cardiac abnormalities. Some syndromes are easily identified, as in the case of self-limited childhood epilepsy with Centro temporal spikes, childhood or juvenile absence epilepsy and juvenile myoclonic epilepsy. When a specific structural cause is suspected, magnetic resonance imaging (MRI) can be helpful. Today, advanced imaging technologies can identify tiny epileptogenic lesions. Likewise, advances in genetics allow identification of epilepsy gene mutations which are pathogenic for many syndromes, particularly epileptic encephalopathy. [7,8]

The treatment of epilepsy is by therapeutic agents such as phenytoin, sodium valproate, carbamazepine, which control the excess abnormal electrical activity of brain neurons. These agents act by blocking sodium/calcium channels and balancing the inhibitory and excitatory neurotransmitter system in central nervous system. Studies are on-going for identification of new targets and new molecules. The draw-back of the available drugs are its adverse effects which can compromise with the quality of life. General side-effects of antiepileptics are dizziness, drowsiness, fatigue, nausea, tremor, rashes, and weight gain.[9] Bromide was the first known AED discovered in 1856, followed by phenobarbital in 1912 and phenytoin discovered in 1938.[10]

Adverse effects can develop acutely or many years after starting treatment and can affect any organ or structure. In past two decades, many efforts have been made to reduce the burden of antiepileptic drug toxicity. All these advances have expanded the opportunities to tailor treatment with antiepileptic drugs, to enhance effectiveness and minimize the risk of toxic effects.[11] Classical and new antiepileptic drugs differ in their profile of side effects. All are equally effective but some of the new AEDs result in weight loss, pain control or decreased anxiety, which may be welcome properties. Newly developed drugs are generally more expensive than established drugs, and this is also true for AEDs.[12] Most Antiepileptic drugs (AEDs) do not prevent or reverse the pathological process that underlies epilepsy, hence continuing the search for new therapies with fewer side effects and better efficacy. Moreover, 30–40% of patients typically develop pharmacoresistant or intractable epilepsy. In most cases, traditional healers are often the first line of contact in the search of therapy because of its link to supernatural powers, unavailability and high cost of conventional AEDs in developing countries.[13] Hence demand for herbal drugs is ever increasing. Herbal drugs are considered to be natural, safe, and have fewer side effects than prescription drugs. Plants may serve as the alternative sources for the development of new antiepileptic agents due to their biological activities.[14]

Therapeutic use of herbal medicine for epilepsy is centuries-old medical practice in several diverse culture. plants may serve as the alternative sources for the development of new antiepileptic agents due to their profound biological activities. Several plants used for the treatment of epilepsy in different systems of traditional medicine have shown antiepileptic activity when tested on animal models and many such plants remain to be scientifically investigated.[15]

The root of Zizyphus oenoplia was used as anthelmintic and it was used in hyperacidity and the root part is used for the treatment of epilepsy by traditional users.10 The literature review revealed the presence of anti-epileptic activity in the roots of Zizyphus oenoplia. However, there is no availability of scientific evidence to prove the effectiveness of the root of Zizyphus oenoplia for anti-anticonvulsant action. Hence, the present study has been designed to investigate the anti-anticonvulsant effect of ethanolic extract of the root of Zizyphus oenoplia on experimental animal models.[16]

Methodology:

Drugs and Chemicals

Test drug (Ethanolic extract of *Zizyphus oenoplia* root, used at doses of 150 and 300 mg/kg) [10]. Diazepam at 4 mg/kg dose was obtained from Sun Pharma Laboratories Ltd., Mumbai. Pentylenetetrazole (PTZ) at 80 mg/kg dose was obtained from HiMedia Laboratory, Mumbai. Normal saline used as control and as a vehicle. Drugs and vehicles were administered by intraperitoneal (IP) route. All the chemicals used during the study were of analytical grade.

Animals

Swiss albino mice of either sex weighing between 25-30g were used for the study. They were maintained under standard conditions (temperature 22±2°C, relative humidity 60±5% and 12 h light/dark cycle) and being given free access to standard pellet diet and water ad libitum. The animals were housed in sanitized polypropylene cages containing sterile paddy husk as bedding. All the procedures were performed in accordance with Institutional Animal ethics committee constituted as per the direction of the Committee for Control and Supervision of Experiments on Animals (CCSEA).

METHODS

Maximal electroshock seizure (MES) model

Experimental design for MES induced convulsions

The Swiss albino mice (25-30g) of either sex were divided into 4 groups, having 6 animals each.

Group I: Normal control (vehicle p.o.) + electrical stimulus (30mA; 50Hz; 0.2 sec duration).

Group II: Phenytoin (25 mg/kg i.p.) + electrical stimulus (30mA; 50Hz; 0.2 sec duration).

Group III: Ethanolic extract of Zizyphus oenoplia roots (150mg/kg p.o.) + electrical stimulus (30mA; 50Hz; 0.2 sec duration).

Group IV: Ethanolic extract of Zizyphus oenoplia roots (300mg/kg p.o.) + electrical stimulus (30mA; 50Hz; 0.2 sec duration).

PROCEDURE:

From day 1-14 the test groups (Group III and IV) were treated with respective doses of ethanolic extract of *Zizyphus oenoplia* roots via oral route. On the 14th day, mice in different groups received 150, 300 mg/kg doses of extract and vehicle through the oral route and standard drug phenytoin intraperitoneally. 30 mins after treatment with respective drugs, all the groups were induced with the electrical stimulus (30mA; 50HZ; 0.2 sec duration) through ear clip electrodes which induced the generalized tonic-clonic seizure/grand mal epilepsy. Following MES (Maximal Electroshock) convulsions, animals were observed for key seizure phases: flexion, extension, clonus and stupor. Reduction in the duration and intensity of these phases indicated anticonvulsant activity. [17,18]

Pentylenetetrazole (PTZ) induced convulsions in mice:

Experimental design for PTZ induced convulsions
The Swiss albino mice (25-30g) of either sex were divided into 4 groups, having 6 animals each.
Group I: Normal control (vehicle p.o.) + PTZ (80mg/kg i.p.)
Group II: Diazepam (4 mg/kg i.p.) + PTZ (80mg/kg i.p.)
Group III: Ethanolic extract of *Zizyphus oenoplia* roots (150mg/kg p.o.) + PTZ (80mg/kg i.p.)
Group IV: Ethanolic extract of *Zizyphus oenoplia* roots (300mg/kg p.o.) + PTZ (80mg/kg i.p.)

From day 1-14 the test groups (Group III and IV) were treated with respective doses of ethanolic extract of *Zizyphus oenoplia* roots via oral route. On the 14th day, mice in different groups received 150, 300 mg/kg doses of extract and vehicle through the oral route and standard drug Diazepam intraperitoneally. 30min after drug administration and 45min after treatment with the extracts all the groups were induced with clonic-type convulsion by intraperitoneal administration of PTZ (80mg/kg),[19]
The time interval between PTZ injection and occurrence of seizures is measured i.e., on set time of the convulsions and duration of convulsions was measured. The delay of onset was calculated in comparison with the control group.[20]

Results :

MES Model

The ethanolic extract of *Zizyphus oenoplia* roots of 150mg/kg and 300mg/kg (p.o) doses and vehicle were given for 14 days respectively and standard drug (phenytoin 25mg/kg i.p) were administered on the 14th day 30min prior to electrical stimulus. The effect of different doses of ZOEE and standard phenytoin in MES induced seizure in animals are shown in the Table No. 1
Duration of HLTE phase of convulsion induced by MES in standard group Phenytoin (25mg/kg) and ZOEE groups (150mg/kg and 300mg/kg) is compared with control group. ZOEE (150mg/kg) showed moderately significant ($P<0.05$) whereas ZOEE (300mg/kg) dose showed significant ($P<0.01$) reduction in time spent in HLTE phase of convulsion when compared to control group. Whereas Standard group administered with Phenytoin (25mg/kg) resulted in complete disappearance of Hind Limb Tonic Extension (HLTE). Percentage inhibition of HLTE phase was observed to be (0%) in control group. Standard group administered with phenytoin resulted in complete inhibition of HLTE phase (100%). Whereas administration of ZOEE (150mg/kg) resulted in 28.41 % and ZOEE (300mg/kg) resulted in 43.22 % inhibition of HLTE phase respectively.

Table No. 1: Effect of ethanolic extract of *Zizyphus oenoplia* roots in MES induced convulsions in mice.

Group	Treatment	Flexion (Duration in seconds)	Extension (Duration in seconds)	Clonus (Duration in seconds)	Stupor (Duration in seconds)	% Inhibition of convulsions
Control	Vehicle	8.9 ± 0.51	12.70 ± 0.561	17.71 ± 1.311	86.02 ± 4.051	0
Standard	Phenytoin (25mg/kg)	0.00	0.00	0.00	0.00	100
Dose-1	ZOEE (150mg/kg)	1.95 ± 0.355*	9.89 ± 0.587*	13.12 ± 0.561*	47.21 ± 2.11*	28.41
Dose-2	ZOEE (300mg/kg)	0.95 ± 0.254**	7.21 ± 1.256**	10.24 ± 2.644**	39.45 ± 2.54**	43.22

All the results are expressed in term of Mean ± SEM n=6 animals in each group; Statistical Significance was determined by ANOVA followed by Dunnett's test. *P< 0.05, **P<0.01, statistically significant compared to control group.

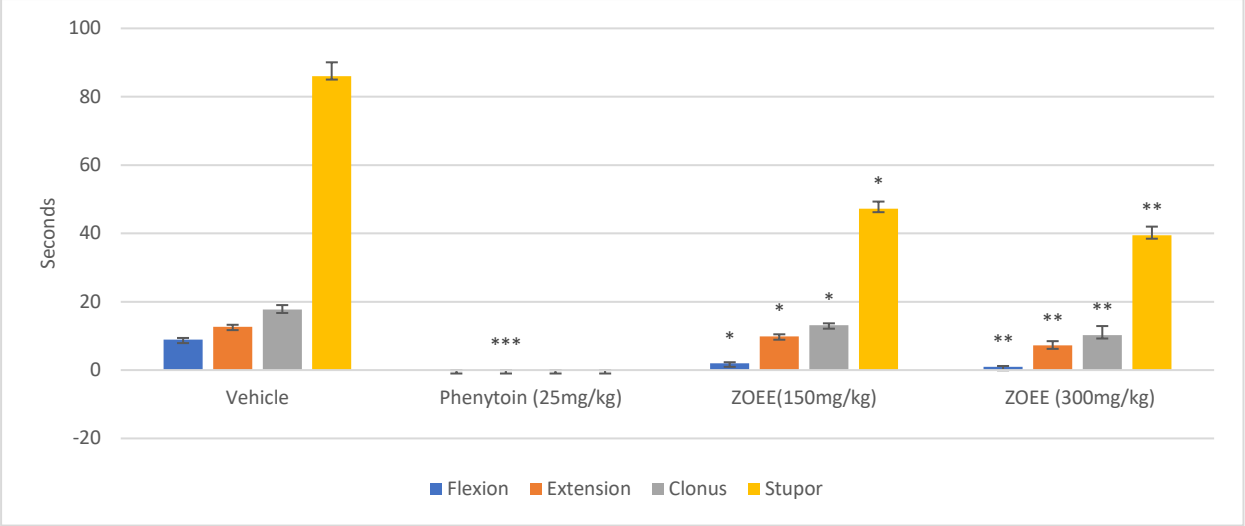

Fig.No.1: Effect of ZOEE on onset of convulsions in MES induced convulsions in mice

PTZ Model

The ZOEE of 150mg/kg and 300mg/kg (p.o.) doses and vehicle were given for 14 days respectively and the standard Diazepam (4mg/kg, i.p.) was given on the 14th day 30min prior to PTZ (80mg/kg, i.p.) administration. On the 14th day 30min after drug administration and 45min after treatment with the extracts the animals were induced with Pentylenetetrazole 80mg/kg intraperitoneally. The effects ethanolic extract of *Zizyphus oenoplia* in PTZ induced seizure model is shown in Table No. 2

A delay in the onset of convulsions following PTZ induced seizures was observed in both the standard group and the test groups (ZOEE,150 and 300 mg/kg). The extract at a dose of 150 mg/kg showed a moderate significant delay ($P<0.05$), while the 300 mg/kg dose demonstrated a significant delay ($P<0.01$) in the onset of convulsions when compared to the control group treated with distilled water. Additionally, reduction in the duration of convulsions after PTZ administration was noted in the test groups. The ethanolic extract of *Zizyphus oenoplia* at 150 mg/kg showed a moderate significant decrease ($P<0.05$), and (300 mg/kg) exhibited a significant decrease ($P<0.01$) in the duration of the convulsion period compared to the control group treated with the vehicle. In contrast, the standard group treated with Diazepam (4 mg/kg) completely protected the mice against PTZ-induced convulsions.

Table No.2: Effect of ethanolic extract of *Zizyphus oenoplia* in PTZinduced convulsions in mice.

Group	**Treatment**	**Onset time of convulsion (sec)**	**Duration of convulsion (sec)**	**% of Mortality**
Control	Vehicle	42.0 ± 3.246	33.822 ± 2.613	66.66 %
Standard	Diazepam(4mg/kg)	0^{***}	0^{***}	100 %
Dose-1	ZOEE (150mg/kg)	$61.8 \pm 2.133^{*}$	$25.966 \pm 1.233^{*}$	50 %
Dose-2	ZOEE (300mg/kg)	$73.244 \pm 3.566^{**}$	$22.277 \pm 1.212^{**}$	33.33 %

All the results are expressed in term of Mean ± SEM n=6 animals in each group; Statistical Significance was determined by ANOVA followed by Dunnett's test. *P< 0.05 and **P<0.01, statistically significant compared to control group.

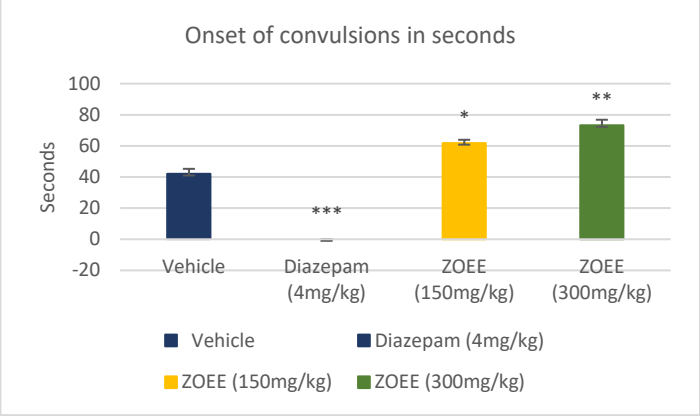

Fig. 2: Effect of ethanolic extract of *Zizyphus oenoplia* on onset of convulsions in PTZ induced seizures

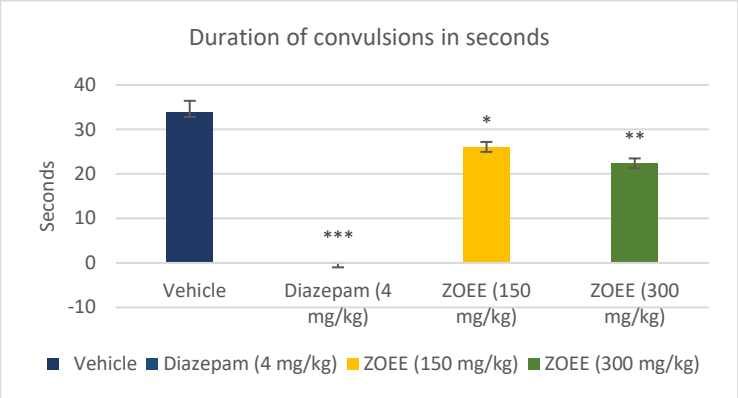

Fig. 3: Effect of ethanolic extract of *Zizyphus oenoplia* on duration of convulsions in PTZ induced seizures

Discussion :

Epilepsy ranks as the second most prevalent neurological disorder globally, affecting over 50 million individuals, with 40% being women. Defined by unprovoked, recurrent seizures due to abnormal cortical neuronal activity, epilepsy can present as convulsive or non-convulsive episodes, with violent, uncontrolled muscle contractions in some cases. While many epilepsy cases are idiopathic, some result from brain injuries, strokes, genetic mutations, or external factors. Antiepileptic drugs (AEDs) face challenges like limited availability, high cost, varying efficacy, and side effects, leading to a renewed focus on herbal treatments, which are especially popular in regions like Africa and Asia due to their tolerability and fewer side effects. [21,22]

This study examines the anticonvulsant effects of *Zizyphus oenoplia* ethanolic root extract on seizures induced by Maximal Electroshock (MES) and Pentylenetetrazole (PTZ) in mice. The MES model replicates generalized tonic-clonic seizures, while PTZ-induced convulsions model clonic-type seizures. In the MES model, electrical stimulation via ear-clip electrodes activates the brainstem, triggering tonic convulsions. Drugs like phenytoin, carbamazepine, and lamotrigine, which block voltage-gated sodium channels, effectively prevent MES-induced seizures, mirroring their clinical efficacy in treating tonic-clonic seizures. While effective, phenytoin carries risks of adverse reactions, including rash, neuropathy, cardiovascular effects, and more. [23,24]

In contrast, the PTZ model simulates petit mal or absence seizures by acting on the $GABA_A$ receptor. PTZ inhibits GABA, a key inhibitory neurotransmitter, leading to convulsions. Standard treatments like diazepam enhance GABA activity, though with possible adverse effects like respiratory depression and dependency.[25]

The study administered *Zizyphus oenoplia* root extract (150 mg/kg and 300 mg/kg) over 14 days, observing a significant delay in the hind limb tonic extension (HLTE) phase in MES-induced seizures, suggesting sodium channel blockade similar to phenytoin. For PTZ-induced seizures, the extract delayed seizure onset and reduced duration, likely due to GABAA receptor modulation, which boosts GABAergic neurotransmission. Phytochemical screening of the extract revealed flavonoids, alkaloids, saponins, and tannins, with flavonoids noted for benzodiazepine-like effects on GABAA receptors. Overall, the extract showed a dose-dependent antiepileptic effect in both MES and PTZ models, supporting its potential as an alternative treatment for epilepsy.

Conclusion :

Many herbal medicines have been traditionally recommended for treating epilepsy. This study explored the anticonvulsant potential of *Zizyphus oenoplia* root extract in mouse models, demonstrating significant activity in both Maximal electroshock (MES) and Pentylenetetrazole (PTZ) induced seizure models.

The MES model is designed to simulate generalized tonic-clonic (grand mal) seizures through high-frequency electrical stimulation, activating voltage-gated sodium channels. It is a widely used method for screening anti-seizure drugs, particularly those targeting sodium channels to prevent excessive neuronal firing and the spread of seizures. Phenytoin, a standard drug used in the MES model, works by stabilizing neuronal membranes and inhibiting the spread of electrical discharges across the brain.

In this study, the ethanolic extract of *Zizyphus oenoplia* roots exhibited a dose-dependent reduction in seizure severity, with the highest dose (300 mg/kg) producing effects comparable to Phenytoin. This suggests that the root extract may influence sodium channels similarly, reducing neuronal hyperexcitability and preventing the propagation of seizures, aligning with the mechanism of many existing anticonvulsant drugs.

In the PTZ-induced seizure model, which is often used to study absence and myoclonic seizures, seizures are triggered through the intraperitoneal administration of PTZ, a GABAA receptor antagonist. By inhibiting GABAergic transmission, the *Zizyphus oenoplia* root extract also showed significant anticonvulsant activity in this model, with the 300 mg/kg dose effectively reducing PTZ-induced convulsions. This suggests that the root extract may enhance GABAergic neurotransmission, potentially interacting with GABAA receptor complexes in a manner similar to Diazepam, and restoring the inhibitory balance in the brain.

Chemical analysis of the *Zizyphus oenoplia* root extract revealed the presence of several bioactive compounds, including flavonoids, alkaloids, saponins, tannins, proteins, phenols, and carbohydrates. Among these, flavonoids are thought to have benzodiazepine-like effects, possibly contributing to enhanced GABAergic transmission and playing a key role in the extract's anticonvulsant properties. Alkaloids and terpenoids likely play a complementary role by stabilizing ion channels, which is crucial for reducing neuronal excitability and preventing seizures.

The study's findings suggest that *Zizyphus oenoplia* root extract is effective in both MES and PTZ seizure models, indicating its potential to treat various types of seizures. The broad spectrum of phytochemicals present in the root extract therefore offers strong anticonvulsant properties.

Based on this study, it can be concluded that the ethanolic extract of *Zizyphus oenoplia* root possesses notable antiepileptic potential. Despite the promising results, further research is required to isolate the bioactive compounds, understand the exact mechanism of action, and evaluate the safety profile of the plant for its potential as a natural remedy for epileptic disorders.

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