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Evaluation of Anticovulsant Activity of Jadwar *(Delphinium denudatum)* in Experimental Animals

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Keywords: Jadwar, PTZ, MES, Sara'a, seizure, *Delphinium denudatum*

ABSTRACT

Background: Convulsion is the disorder of the nervous system in which a sudden irregular involuntary contraction of voluntary muscles occurs.it is characterizes by recurrent seizures, which are brief episodes of involuntary movement that may involve a part of the body (partial seizures) or the entire body (generalized seizures). An estimated 7 million people in India suffer from epilepsy. The present study was planned to assess the anticonvulsant effect of Jadwar (*Delphinium denudatum*) in experimental animals and confirm its use as an anticonvulsant drug as stated in the Unani medicine framework. **Objective:** To assess and evaluate the effectiveness of JADWAR (*Delphinium denudatum*) in the management of Convulsions/Seizures due to central nervous system disorders. **Methods:** The anticonvulsant efficacy of hydro-alcoholic extract of Jadwar (*Delphinium denudatum*) (1.60 mg and 3.21 mg /kg, b/w orally) in rats was tested using the maximal electroshock convulsion (MES) test and the PTZ test. Rats were divided into four groups of six animals in each group. Group I was used as a negative control and distilled water was administered orally for 10 days. Group II was administered phenytoin 25 mg/kg bw on 10th day I.P as a standard group, group III and group IV animals were treated with hydro-alcoholic extract of Jadwar for 10 days. **Conclusion:** The study has shown that the research drug has important anticonvulsant efficacy against both pentylenetetrazol (PTZ) and MES mediated convulsions. The study validated the argument of Unani physicians to use Jadwar in patients of convulsion.

INTRODUCTION

Convulsion is the disorder of the nervous system in which a sudden irregular involuntary contraction of voluntary muscles occurs. it is characterizes by recurrent seizures, which are brief episodes of involuntary movement that may involve a part of the body (partial seizures) or the entire body (generalized seizures) and are sometimes accompanied by loss of consciousness and control of bowel or bladder function.

Seizure is one of the most common neurological disorder, which occur in many diseases like Hysterical seizure, infantile seizure, Traumatic seizure, Epilepsy seizure etc.

In Unani Medicine, Tashannuj (convulsion) is associated with Sara'a or Mirgi. According to Majusi "Sara'a is caused by a Sudda-e-Balghami (obstruction) or sudda-e-Saudavi within the brain and ventricles".

Accordant to Ibn Sina, Sara'a is a condition caused by an abnormal matter which impedes the Aza-e-nafsaniya's sensory and motor functions. The seizure is caused by incomplete obstruction in Butoon-e-dimagh (*Cerebral ventricles*); blockage may be responsible for even a very small amount of a balgham ghaleez madda.

Sara'a is graded as Sara'a Shirki and Sara'a Asli. (Jalinoos classified it as Sara'a asli, Sara'a shirki medi and Sara'a shirki atrafi, the other forms are named after the causes and names of the affected organs that also include the brain because of the musharikat of the nerves that supply them, namely Sara'a zarabi, Sara'a deedani, Sara'a lasai, Sara'a tehali, Sara'a meraqi, Sara'a kabidi and Sara'a rahmi.Hippocrates referred to the kaboos (*nightmare*) as Sara'a.

In recent years, laboratory studies have also used modern research techniques to test treatments of plant origin. Such research, focused on evidence-based medicine, increased the prospect of revival of conventional treatments.

Medicinal plants used for the treatment of epilepsy in the Unani System of Medicine have been clinically proven to possess positive anticonvulsant behaviors in animals. There are several single and compound medicines available, which are believed to be effective in treating such a disease.

The single drugs are: Jadwar *(delphanium denudatum*), Ajwain Khurasani (*Hyoscymus niger*), Aqer Qerha (*Anacyclus pyrethrum*), Brahmi (*Centella asiatica*), Hilteet (*Ferula*

asafoetida), Ood-e-saleeb (*Paeonia officinalis*), Ustokhuddus (*Lavandula stoechas*), Zabeeb (*Vitis vinifera*) and Zaravand mudahraj (*Aristolochia rotunda*) etc.

Compound drugs like Khamira Jadwar ood Saleeb wala, Majoon Zabeeb, Habb-e-jund and Habb-e-jadwar are used in Unani System of Medicine for the treatment of convulsion from ancient times.

Jadwar is an important drug that is recognized by a number of Unani physicians as being useful in many neurological disorders, Jadwar being muqawwi-e-dimagh (*brain tonic*) or mufatteh (*deobstruent*) has been use in convulsion. The drug "Jadwar" was selected for evaluation of its anticonvulsant properties.

MATERIALS AND METHODS

Collection Identification and authentication of Jadwar:

The Jadwar was procured from a local vendor of Unani Medicine "Faiz Dawa Saaz". Hyderabad. Telangana state, and cleaned from stones, dust and other plant matters. Dr. Mohd Kashif Hussain (Botanist) of Survey of Medicinal Plants Unit (SMPU) of NRIUMSD authenticated the jadwar (*Delphinium denudatum*), Hyderabad vide Voucher specimen number SMPU/CRI-Hyd 14100.

Preparation of extract:

The jadwar (*Delphinium denudatum*) was cleaned and pulverized with the help of electric grinder. 100 gm powder of drug was used for hydro-alcoholic extraction using Soxhlet apparatus. The extract was concentrated on water bath at 80 °C until it becomes semisolid in nature and then dried in air. The dried extracts was weighed and it was labeled and kept in airtight container in refrigerator for further use.

Drug and Chemicals: Pentylenetetrazol (PTZ) and phenytoin by abbott india Ltd. were used in this study.

Experimental animals

The study was carried out on Albino Wistar rats, each weighing 150-200 gm. The experimental protocol was approved by Institutional Animal Ethics Committee of Govt. Nizamia Tibbi College, Charminar, Hyderabad. Reg. No.1070/GO/Re/S/07/CPCSEA, dated 24.03.2018. All experimental procedures and animal care are in accordance to CPCSEA

guidelines for care and use of Animals in scientific research. The animals were housed in clean polypropylene cages with temperature (25 ± 2 C) and relative humidity of (60 ± 5%) under a 12 h light/dark cycle. Animals were fed with normal rat chow and water ad libitum throughout the study period. The animals were purchased from VAB Bio Sciences, CPCSEA No.282/PO/RcBt/S/2000/CPCSEA, #7-12 Medipally Village, Narapally, Ghatkesar Mandal, Medchal District, Hyderabad-500039.

Acute toxicity

Acute oral toxicity study was performed as per OECD guidelines 423. The dose of 2000mg/kg, P.O. of extract administered in the acute toxicity study. The animals were observed continuously for 2hrs for gross behavioral changes and intermittently once every 2hrs and finally at 24 and 72 hours to note any signs of toxicity including death. After this observation, no sign of toxicity or death was recorded.

Study Protocol/ Experimental design:

60 albino Wister rats of either sex, weighing150-200 gm, are taken for the study and study was divided into two phases.

(1) **Phase I - Maximal electric shock (MES)**

(2) **Phase ii - Pentylenetetrazol (PTZ)**

Phase I: Maximal electric shock (MES)

All the animals of this phase were divided into four groups, each group consisting of 6 animals (n=6).

Electrical stimulation was applied using ear electrodes. The electrodes were moistened with saline before application. All animals were stimulated with 150mA for 0.2 seconds, with constant voltage stimulators of 250 V (Vogel GH and Vogel WH 1997).

Group I served as negative group, animals of this group received standard pellet diet and purified water for 24 hours over a period of 10 days and were induced convulsion by MES method 150mA 0.2 sec, on 10^{th} day.

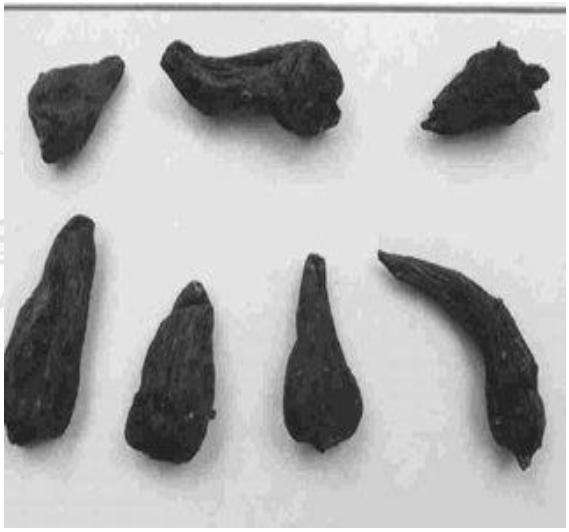
Group ll served as standard group, animals of this group received standard pellet diet and a phenytoin 25mg/kg ip on 10th day and after 60 minutes convulsion was induced by MES method 150mA 0.2 sec, on 10th day.

Group lll (Test drug low dose**)** Animals in this group received hydro alcoholic extract of Jadwar (HAJ) 1.60 mg/kg body weight (oral) for a period of 10 days. After 60 minutes convulsion was induced by MES method 150mA 0.2 sec, on 10th day.

Group lV (Test drug high dose**)** animals in this group received hydro alcoholic extract of Jadwar (HAJ) 3.21 mg/kg bw (oral) for a period of 10 days. After 60 minutes convulsion was induced by MES method 150mA 0.2 sec, on 10th day.

On 10th day, the test drug was given 1 hour prior to induction of convulsions. Suppression of tonic hind limb extension was taken as a measure of efficacy in this test.

MES METHOD



JADWAR (*Delphinium denudatum*)

Phase ii: Pentylenetetrazol (PTZ)

All the animals of this phase were divided into four groups, each group consisting of 6 animals (n=6). PTZ 60 mg/kg ip was administered to the experimental animals. The parameters of this phase were number of convulsions, onset of convulsion, onset of clonic convulsion, duration of clonic convulsion, onset of tonic convulsion and duration of tonic convulsions, number of death and percentage of protection. (Vogel GH and Vogel WH 1997).

Group I served as control group, animals of this group received standard pellet diet, purified water for 24 hours over a period of 10 days, and were given inducing drug PTZ on 10th day.

Group ll served as standard group, animals of this group received standard pellet diet and phenytoin 25mg/kg I.P on 10th day .and after 60 minutes were given inducing chemical PTZ 60mg/kg I.P.

Group lll (Test drug low dose**):** animals in this group received HAJ 1.60 mg/kg/b/w (oral) for a period of 10 days and after 60 minutes single dose of PTZ 60mg/kg bw was given intraperitoneal.

Group lV (Test drug high dose**):** animals in this group received HAJ 3.21 mg/kg bw (oral) for a period of 10 days and after 60 minutes single dose of PTZ 60mg/kg bw was given intraperitoneal.

On 10th day, the test drug was given 1 hour prior to induction of convulsions. Abolition of the convulsions was taken as a measure of efficacy in this test.

Statistical Analysis:

Results were expressed as Mean±SD. The different values determined were compared with each other and comparison was made using One-way ANOVA followed by Tukey's test. The difference of mean was considered significant at $p< 0.05$.

RESULT

MES: All the animals were pre-treated with the test drug from day 1st-9th day and on the 10th day, standard drug is given 30 minutes prior to induction of convulsion. One hour latter maximal electroshock was given for 0.2 sec of 150Am of current and immediately they are place on black paper under table and observe for hind limb extension, followed by recovery or death.

PTZ: All the animals were pre-treated with the test drug from day 1st-9th day and on the 10th day, standard drug is given 30 minutes prior to induction of convulsion. One hour latter PTZ 60mg/kg was dissolved in 2ml distilled water, given intra peritoneal and immediately they are place on black paper under table and observe The various parameters like onset of convulsion, No. of convulsions, onset of tonic convulsion, duration of tonic convulsion, onset

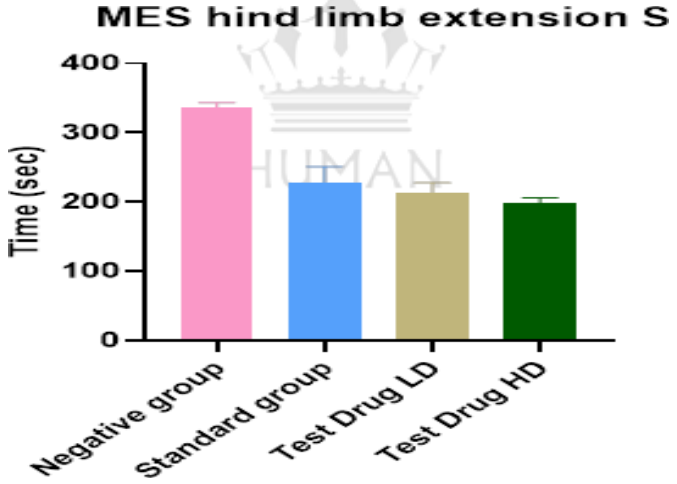
of clonic convulsion, duration of clonic convulsion, followed by recovery , no of death within 30 minute or percentage of protection for all the animals are taken to differentiate p value from each group of animals.

Results of the MES and PTZ induced activity are below in the form of tables and graphs.

Effect of MES was observed and mention according to groups as follows.

Effect of HAJ on MES induced seizure in rats

S. No.	Group	Duration of hind leg extension (Seconds)
1.	I. Negative Control	335±7.52
2.	II. Std (Phenytoin)	228.33±22.72***
3.	III. HAJ 2.5 mg/kg	213.17±14.80***, ns
4.	IV. HAJ 3.5 mg/kg	198.50±7.64***, $$, ns



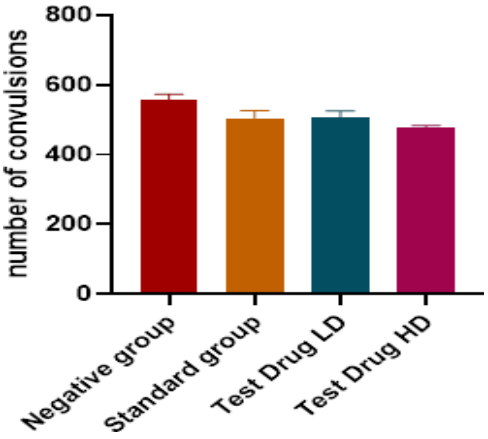
N=6, Mean ± SD, ns=Non significant

One-way ANOVA followed by Tukey's Test. P<0.01 is considered significant.

*Compared Negative control Vs. Std. and Test Drug Low Dose and High Dose Treatment Groups.

$Compared Standard Drug vs Test Drug Low Dose and High Dose Treatment Groups.

#Compared Test Drug Low Dose vs Test Drug High Dose Treatment Groups.



Effect of HAJ in PTZ-induced on number of convulsions in rats.

S. No.	Group	Effect of HAJ on Number of Convulsions
1.	I. Negative Control	557.83±15.37
2.	II. Std (Phenytoin)	504.50±22.12***
3.	III. HAJ 2.5mg/kg	505.50±19.77***, $$$
4.	IV. HAJ 3.5mg/kg	477.00±6.45***, $$$, ns

N=6, Mean ± SD, ns=Non significant

One-way ANOVA followed by Tukey's Test. P<0.01 is considered significant.

*Compared Negative control Vs. Std. and Test Drug Low Dose and High Dose Treatment Groups.

$Compared Standard Drug Vs. Test Drug Low Dose and High Dose Treatment Groups.

#Compared Test Drug Low Dose Vs. Test Drug High Dose Treatment Groups.

Duration of clonic convulsion S

S. No.	Group	Onset of Clonic Convulsions (Seconds)	Duration of Clonic Convulsions (Seconds)
1.	I. Negative Control	47.83±6.05	314.50±84.22
2.	II. Std (Phenytoin)	95.50+15.48**	165.33+19.92***
3.	III. HAJ 2.5 mg/kg	89.17±19.41*, ns	159.67±13.35***, ns
4.	IV. HAJ 3.5 mg/kg	143.83±33.38***, $$, ###	73.33±5.50***, $$, #

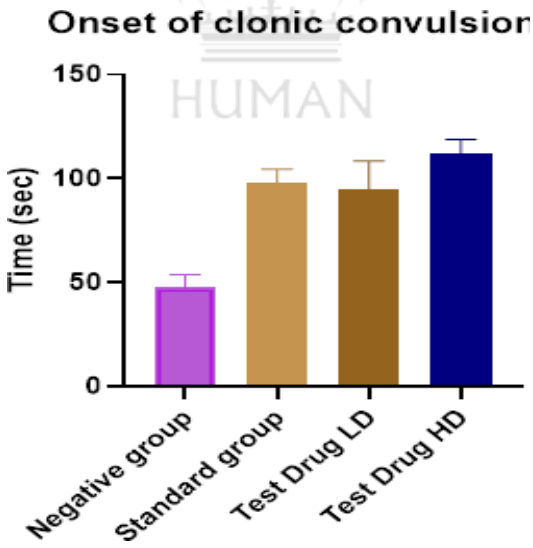
N=6, Mean ± SD, ns=Non significant

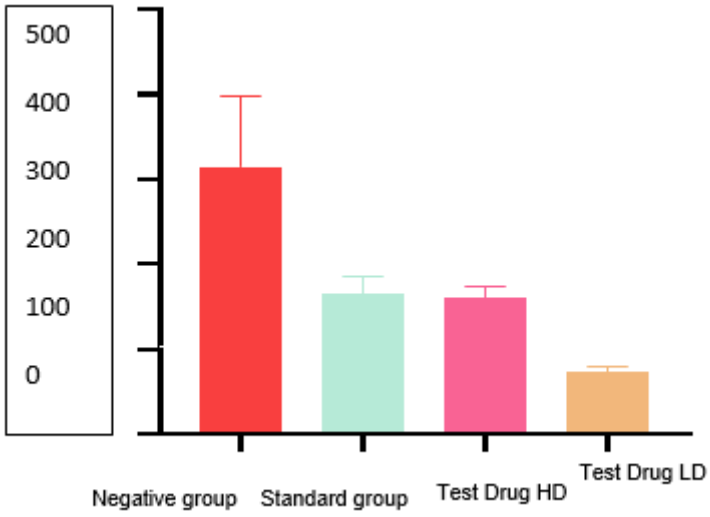
One-way ANOVA followed by Tukey's Test. P<0.01 is considered significant.

*Compared Negative control Vs. Std. and Test Drug Low Dose and High Dose Treatment Groups.

$Compared Standard Drug Vs. Test Drug Low Dose and High Dose Treatment Groups.

#Compared Test Drug Low Dose Vs. Test Drug High Dose Treatment Groups.





Effect of HAJ PTZ- induced tonic convulsion

S.No.	Group	Onset of Tonic Convulsions (Seconds)	Duration of Tonic Convulsions (Seconds)
1	I. Negative Control	16.33±14.77	13.17±2.40
2	II. Std (Phenytoin)	41.17+ 9.04**	8.00+2.10**
3	III. HAJ 2.5 mg/kg	36.83±5.95**, ns	8.67±2.16**, ns
4	IV. HAJ 3.5 mg/kg	57.67±4.55***, $, ##	4.67±1.03***, $, #

N=6, Mean ± SD, ns=Non significant

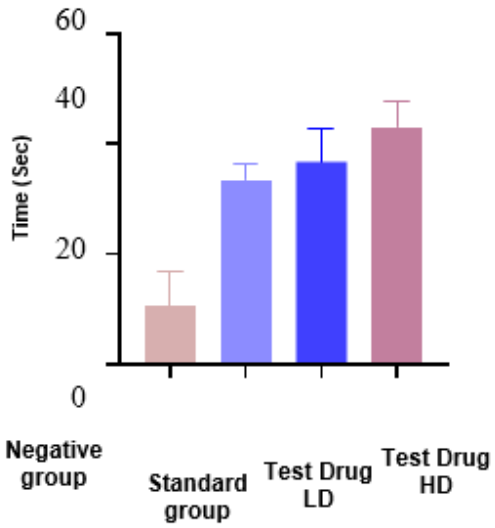
One-way ANOVA followed by Tukey's Test. P<0.01 is considered significant.

*Compared Negative control Vs. Std. and Test Drug Low Dose and High Dose Treatment Groups.

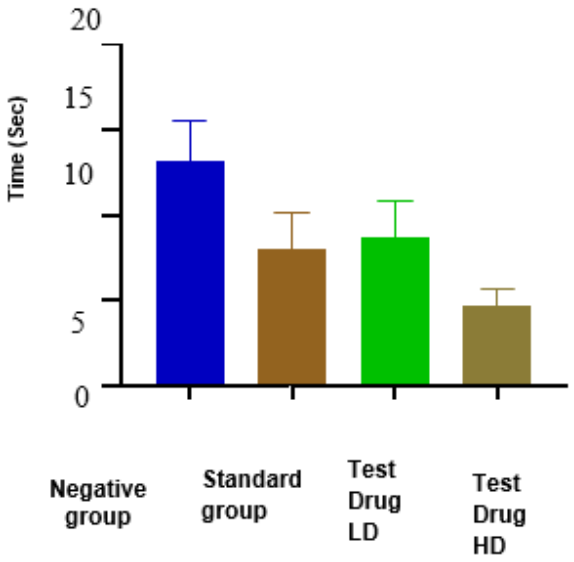
$Compared Standard Drug Vs. Test Drug Low Dose and High Dose Treatment Groups.

#Compared Test Drug Low Dose Vs. Test Drug High Dose Treatment Groups.

Onset of tonic convulsion (S)



Duration of tonic convulsion (S)



DISCUSSION

According to the concept of Unani system of medicine the action of daaf-e-tashannuj drugs is two types, one which decrease quwaa-e-muharrika and other which decrease quwat-e-inqebaaz or marakiz-e-aasaab and hence controlled the seizure. Jadwar come in second category, it works on marakiz-e-aasaab (centres of the nerves) and sedates them because of its musakkin (sedative) property. Its temperament is hot and dry; the seizure comes under cold and moist disease. It can be used with the theory of ilaaj biz-zid as tashannuj comes under balghami amraaz, and JADWAR is anti-phlegmatic in action.

It gives strength to the nerve as convulsions occur due to zoaf-e-aasaab, and JADWAR is muqawwi in action. Accordingly act as anticonvulsant drug. Delphinium denudatum is a source of high triterpenoid alkaloid concentration and is commonly used in the treatment of various neurological disorders such as Sara'a (*Epilepsy*), Irqun nisa (*Sciatica*), and Alzheimer's.

Many single drugs and compound formulations such as Jadwar (*Delphanium denudatum*) Ajwain Khurasani (*Hyoscyamus niger*), Aqer Qerha (*Anacyclus pyrethrum*), Brahmi (*Centella asiatica*), Hilteet (*Ferula asafoetida*), Ood-e-saleeb (*Paeonia officinalis*), Ustokhuddus (*Lavandula stoechas*), Zabeeb (*Vitis vinifera*), Zaravand mudahraj (*Aristolochia rotunda*), Amber, Mushk, Jund bedastar, Khamira Jadwar ood Saleeb wala, Majoon Zabeeb, Habb-e-jund and Habb-e-jadwar etc are used in Unani System of Medicine for the treatment

of Various neurological disorders and few of them have been investigated for an anticonvulsant effect. These studies have demonstrated great potential of Unani medicine to provide anticonvulsant drugs.

In view of the above *Jadwar* is an important drug of Unani system of medicine described to be Muqawwi-e-Asab *(Nervine tonic*), Mufatteh (*Deobstruent*), Musakkin (*Sedative*), mufrreh or muqavi-e-aazai rayeesa or tiryaq-e-sumoom and useful in various CNS disorders was selected for the evaluation of Anticonvulsant effect. Hydro-alcoholic extract of test drug was used for the study.

The Anticonvulsant effect was tested in experimental models subjected to convulsion by administration of PTZ and MES.

The convulsion was induced by the administration of PTZ in a dose of 60 mg/kg intraperitoneal on 10^{th} day as a single dose and considered as negative control group. The negative group when compared with standard control group the p value was ($P<0.001$) Hence there is significant difference in the P value.

when negative group was compared to test drug LD there was significant difference in the P value ($P<0.001$), while negative group was compared to test drug HD Hence, there is significant difference in the P value ($P<0.001$). The standard control group was compared to test drug LD hence there is no significant difference in the P value ($P>0.05$). when the standard control group was compared to test drug HD hence there is significant difference in the P value ($P<0.001$). The test drug Jadwar produced anticonvulsant effect against PTZ and MES induced convulsion. Thus, it can also be concluded that test drug can be used in the treatment of neurological disorders.

CONCLUSION

The present study has been carried out to screen JADWAR's anticonvulsant activity. The drug was given orally in the form of hydro alcoholic extract and the effect was observed in two doses (1.60 mg/kg body weight as low dose and 3.21 mg/kg body weight as high dose). The test drug is very effective orally in animals in both dosage. The drug showed significant anticonvulsant effect in convulsions induced by PTZ and MES. At the higher dose of the test drug, the anticonvulsant effect was more than lower dose.

The effect of JADWAR was found to be effective in a dose-dependent manner in the form of hydro alcoholic extract.

In view of above result, we can say that Jadwar not only reduces the duration of convulsion but also reduces the dose-dependent mortality rate.

Thus, the present study shows that Jadwar possesses anticonvulsant activity and it can be concluded that the Jadwar can be used in the treatment of neurological disorders.

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