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EVALUATION OF ANTICONVULSANT ACTIVITY OF APIUM GRAVEOLENS ON DIFFERENT INDUCING MODELS IN MICE

[1]P. Vinay Kumar, [2]M. Meena Kumari
SSJ College of pharmacy, Gandipet, Hyderabad, Telangana, India.

Abstract:
Epilepsy is a chronic CNS disorder characterized by brief episodesof seizures andexcessive EEG discharge. The selection of this plant, Apium graveolens was made on the basis of its High therapeutic value, Easy availability, Degree of research work which is not done. Apium graveolens contained appreciable amount of tannins, flavonoids, steroids, saponins, however, terpenoids content was almost negligible. The Ethanol extract of Apium graveolens delayed the onset and reducedthe duration of convulsion in MES and PTZ induced convulsion models and can be used as an adjuvant therapy against cognitive deficit in convulsions. The extract also shows significant decrease in lipid peroxidation level and increase in reduced glutathione level, indicates that EAG possess good antioxidant activity. Also, EAG significantly increased the level of inhibitory neurotransmitter GABA and also showed increase in DA, NA and 5-HT levels. Hence it can be concluded that the EAG possesses good anticonvulsant activity. Further studies are needed to explore the mechanism as well as the active principle responsible for the anticonvulsant activity of Apium graveolens.

Key words: *Anticonvulsant activity, Apium Graveolens, Mice.*

Corresponding author:
M. Meena Kumari
Associate Professor, Dept. of pharmacology, SSJ College of pharmacy, Gandipet, Hyderabad, Telangana, India.
E-mail: vinaypulmaddi@gmail.com

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INTRODUCTION:

Epilepsy has been recorded throughout ancient history, and was considered as a spiritual condition [1], the word epilepsy is itself derived from as Latin term meaning to seize, possess or afflict [2]. It is a group of neurological diseases mostly with unknown reasons, some patients may develop epilepsy due to infection in brain such as meningitis, viral encephalitis, birth defects, stroke, injury or tumours in brain and brain stem [3,4]. It is a chronic disorder characterised by recurrent seizures due to decreased resistance of excitatory neurons to fire and down regulation of inhibitory neurons. This occurs in a particular region known as 'seizure focus' and the excessive, abnormal neuronal firing results in to a wave of depolarization which is termed as paroxysmal deploring shift 5. Epilepsy is incurable but modern medicine can help control most cases of seizures but several conditions such as nonresponsive cases need to opt for surgery, neurostimulation or lifestyle changes [6,7]. This situation can also be improved with the help of traditional and local medicines obtained from the natural flora of the region. A proper identification of medicinal properties and their scientific evaluation provides with much superior relief then the contemporary practice of medicine.

Apium graveolens Linn. (A. graveolens) is an annual herb belonging to family Apiaceae with green blanched leaf stalks. It is found in North and South Americas, Southern Europe, Africa and Asia. Its major active constituents are l-3-n-butylphthalide, sedanolide, linoleic acid, flavonoids, phenolic compounds and volatile oil, which are extracted from its various part including roots, leaves and seeds [8,9,10]. Several studies have reported its pharmacological activity on antimicrobial, anti-inflammatory, anti-arthritis, antiulcerogenic, antihyperlipidemia and antihypertension [11,12].

In recent year there has been a tremendous increase in demand for herbal drugs due to its safety, efficacy and better therapeutic results and also due to its economic pricing as compared to synthetic or allopathic drugs, which have several therapeutic complications.

The selection of this plant, *Apium graveolens* was made on the basis of its High therapeutic value, Easy availability, Degree of research work which is not done. Very less pharmacological studies have been carried out on the seeds of *Apium graveolens*. Hence, I have decided to choose *Apium graveolens* on which detailed studies on Preliminary Phytochemical and Pharmacological actions such as Anti-convulsant is done.

MATERIALS AND METHODS:

Plant collection and authentication:

The seeds of the Celery (Apium graveolens) plant were purchased from the local market of Hyderabad. Seeds were dried at room temperature (25ºC) under shade and grinded by tissue homogenizer to fine powder (Infinigen™ Tissue Mixer Mill, ACT Gene. These powdered samples were sealed in plastic bags and stored at 4ºC until analyzed.

Preparation of plant extract:

The powdered plants samples were macerated in aqueous. methanol, ethanol, hexane and methylated spirit (Sigma- Aldrich) and kept at room temperature for 7 days. The solution was stirred three times a day during this period for thorough mixing and was then filtered (WhatmanTM Whatman UK). One litre each of fresh solvents were added to the seed material and filtered again through Wattman filter paper and this process was repeated thrice. The filtered solution was evaporated with the help of a rotary evaporator (Rotavapor R -R 210/R215; BUCHIL Labortechnik AG).

Phytochemical Test:

Chemical tests performed in the screening and identification of phytochemical constituents in the tested medicinal plants were carried out in extracts as well as powder specimens using the standard procedures [14].

Maeyer's reagent:

0.355 g of mercuric chloride was dissolved in 60 ml of distilled water. 5.0g of potassium iodide was dissolved in 20 ml of distilled water. Both solutions were mixed and volume was raised to 100 ml with distilled water. Dragendorff's reagent

Solution A: 1.7 g of basic bismuth nitrate and 20 g of tartaric acid were dissolved in 80 ml of distilled water. Solution B: 16 g of potassium iodide was dissolved in 40 ml of distilled water. Both solutions (A and B) were mixed in1:1 ratio.

Test for alkaloids:

About 0.5 to 0.6 g of the methanolic plant extract was mixed in 8 ml of 1% HCl, warmed and filtered. 2 ml of the filtrate were treated separately with both reagents (Maeyer's and Dragendorff's).

Test for steroids

About 0.5 g of the methanolic extract fraction of each

plant was mixed with 2 ml of acetic anhydride followed by 2 ml of sulphuric acid.

Test for terpenoids

An aliquot 0.5 ml of methanolic extract was mixed with 2 ml of CHCl3 in a test tube. 3 ml of concentrated H2SO4 was carefully added to the mixture to form a layer.

Test for flavonoids

To the substance in alcohol, a few magnesium turnings and few drops of concentrated Hydrochloric acid were added and boiled for five minutes.

Test for tannins

The 0.5 g of powdered sample of each medicinal plant leaves was boiled in 20 ml of distilled water in a test tube and then filtered. The filtration method used here was the normal.

Test for Phytosterol

The extract (2 mg) was dissolved in 2 ml of acetic anhydride, heated toboiling, cooled and then 1 ml of concentrated sulfuric acid was added along the sideof the test tube.

Test for Phytosterol

Foam Test: 5 ml of the test solution taken in a test tube was shaken well forfive minutes.

Test for glycosides

Keller -Killiani test: Added 0.4 ml of glacial acetic acid and a few drops of 5% ferric chloride solution to a little of dry extract. Further 0.5 ml of concentrated sulfuric acid was added along the side of the test tube carefully.

Experimental Animals

The present study was conducted after obtained approval from the Institutional Animal Ethics Committee, the protocol met the requirements of national guidelines of CPCSEA (PROPOSAL NO: CPCSEA/IAEC/JLS/17/03/22/31).

ANTI CONVULSANT STUDY:

ANIMALS AND MANAGEMENT:

Healthy adult Wistar albino Mice of either sex weighing 180-250g will be selected. The animals will be housed in large, spacious, hygienic cages during the course of experimental period. The animal house will be well maintained and the animals will have12 1 hour day and night schedule with a temperature [64-79°F] maintained at standard experimental condition. The animals will be fed with standard rodent pellet feed and water *ad libitum*. The animals will be fasted 12 hours prior to the experiment with free access to only water [13].

ACUTE TOXICITY STUDY:

Mice were kept overnight fasting prior to drug administration. A total of five animals were used which received a single oral dose (2000mg/kg) of Ethanol extract of the root of *Apium graveolens.* After administration of the test extract, food was withheld further 3–4hr. Animals were observed individually at least once during the first 30min after dosing, periodically during the first 24hr (with special attention during the first 4hr) and daily thereafter for a period of 14days. Once daily, cage side observations included changes in skin and fur, eyes and mucous membrane (nasal) and also respiratory rate, circulatory (heart rate and blood pressure), autonomic (salivation, lacrimation, perspiration, piloerection, urinary incontinence, and defecation) and central nervous system (ptosis, drowsiness, gait, tremors and convulsion) changes. Mortality, if any, was determined over a period of 2 weeks. LD50 was done as per OECD guidelines for fixing the dose for biological evaluation [14].

EVALUATION OF ANTIEPILEPTIC ACTIVITY OF EAG:

Maximal electroshock seizure [MES] model

Experimental design:

Wistar albino Mice weighed around 150-250g were used for the study. Mice were divided into four groups of 5 animals each.

Table No. 1: Maximal electroshock seizure model

Model I: Maximal electroshock seizure [MES] Model	
Group 1:	*Vehicle control* [Equivalent normal saline i.p]
Group 2:	*Standard* [Diphenylhydantoin 25 mg/Kg BW i.p]
Group 3:	*Apium graveolens low* dose (75 mg/kg) orally
Group 4:	*Apium graveolens high* dose (150 mg/kg) orally

Procedure

Animals in the control group [Group 1] will be administered equivalent volumeof normal saline by i.p route. Animals in Group 2 will be administered standard drug Diphenylhydantoin. In Groups 3 and 4 *Apium graveolens low* dose and high dose will be administered by oral route in 1% Sodium lauryl sulphate solution respectively. After 30 minutes of administration of above drugs, all the Mice will be given electroshock with electro convulsiometer through ear electrodes [after moistening the ear of animals with drop of normal saline] at intensity of 150 mA, 60Hz for 0.2 seconds. There after various parameters will be recorded.

A. Pentylenetetrazol [PTZ] model Experimental design

Wistar albino Mice weighed around 150-250g were used for the study. Mice were dividedinto four groups of 5 animals each.

Table No 2: Pentylenetetrazole model

Model II: **Pentylenetetrazole Model**	
Group 1:	*Vehicle control* [Equivalent normal saline i.p]
Group 2:	*Standard* Sodium valproate (150 mg/Kg BW i.p)
Group 3:	*Apium graveolens low* dose (75 mg/kg) orally
Group 4:	*Apium graveolens high* dose (150 mg/kg) orally

Procedure

Animals in the control group [Group 1] will be administered equivalent volume of normal saline by i.p route. Animals in Group 2 will be administered standard drug Sodium Valproate. . In Groups 3 and 4 *Apium graveolens low* dose and high dose will be administered by oral route in 1% Sodium lauryl sulphate solution respectively. After 30 minutes of administration of above drugs, all the animals will be given Pentylenetetrazol [PTZ] and the various parameters will be recorded.

STATISTICAL ANALYSIS

The datas of all the parameters were analyzed using the software Graph pad Prism 5. Analysis of variance (ANOVA); one way ANOVA followed by Dunnet's test was performed. The values were expressed as Mean ± SEM.

RESULTS AND DISCUSSION

Phytochemical Analysis

Table No.3: Phyochemical Analysis

Phytochemicals	**Inference**
Tannins	+
Flavonoids	+
Steroids	+
Phytosterol	+
Terpenoids	-
Saponin	+

+, Presence of the compound

-, Absent

Apium graveolens contained appreciable amount of tannins, flavonoids, steroids, saponins, however, terpenoids content was almost negligible**.**

ACUTE TOXICITY STUDY:

The acute toxicity test was performed by using the Ethanol extract at concentrations 2000 mg/kg, 1000 mg/kg, 900 mg/kg, 850 mg/kg, 800 mg/kg and 750 mg/kg. As it is a natural substance and is not expected to be particularly toxic. Hence 2000 mg/kg of the test animal was administered orally. And 3 animals were died. As mortality was observed after administration of 2gm/kg body weight, then a lower dose of 1000 mg/kg and 900 mg/kg was given. And mortality was observed for all animals for both doses. Hence a lower dose of 850 mg/kg was given. Two animals died and one animal survived after administration of 850 mg/kg. Hence a lower dose of 800 mg/kg was given. Two animals survived and one animal died for 800 mg/kg. Then a dose of 750 mg/kg was given. All animals survived for 750 mg/kg. and no signs of toxicity was observed following administration of 750 mg/kg. Hence *Apium graveolens w a s* found to be safe at 750 mg/kg.

Table No 4: Acute toxicity study of *Apium graveolens*

No. of animals used	Dose (mg/kg)	No.of animals survived
3	2000	0
3	1000	0
3	900	0
3	850	1
3	800	2
3	750	3

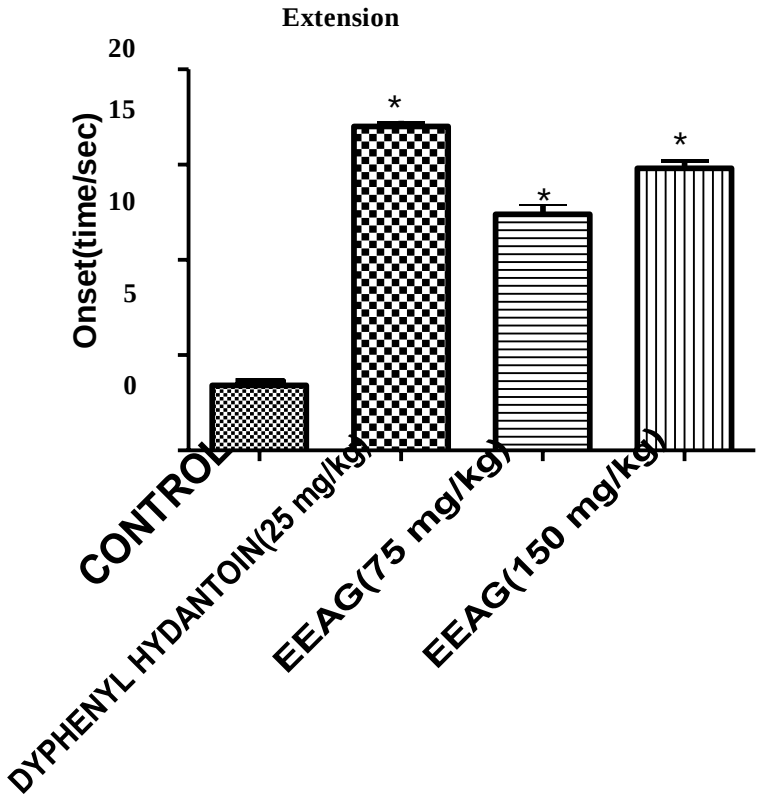
EVALUATION OF ANTIEPILEPTIC ACTIVITY:

Table No 5: Effect of Ethanol extract of *Apium graveolens on* onset of hind limb extension in MES induced seizures models

Groups	**Onset time (sec)**		**Recovery/ Mortality**
	Extension	**Clonus**	
Control	3.40± 0.24	33.20± 1.15	Recovery
Diphenylhydantoin (25mg/kg)	17.00±0.31 *	0***	Recovery
EAG(75 mg/kg)	12.40± 0.50*	0***	Recovery
EAG(150mg/kg)	14.80± 0.37*	0***	Recovery

Statistical comparison: One way ANOVA, followed by Dunett's multiple comparison test. Standard, EAG (low dose) and EAG (High dose) are compared with control ($p<0.05$-* , $p<0.01^{**}$, $p<0.001^{***}$)

Figure No 1: Effect of Ethanol extract of *Apium graveolens on* onset of hindlimb extension in MES induced seizures models



Statistical comparison: One way ANOVA, followed by Dunett's multiple comparison test. Standard, EAG (low dose) and EAG (High dose) are compared with control ($p<0.05$-*, $p<0.01^{**}$, $p<0.001^{***}$)

Table No 6: Effect of Ethanol extract of *Apium graveolens on* MES induced seizures models

Groups	Flexion	Extension	Clonus	Stupor	Recovery/ Mortality
Control	5.60±0.4	18.6±0.5	24±1.68	50.40±1.77	Recovery
Diphenylhydantoin (25 mg/kg)	2.20±0.20***	4±1.04***	0***	11.00±0.44***	Recovery
EAG (75 mg/kg)	3.60±0.24***	6±0.66***	0***	19.40±0.60***	Recovery
EAG (150 mg/kg)	2.80±0.20***	5.4±1.50***	0***	14.40±0.67***	Recovery

Statistical comparison: One way ANOVA, followed by Dunett's multiple comparison test. Standard, EAG (low dose) and EAG (HIGH DOSE) are compared with control ($p<0.05$-*, $p<0.001^{**}$, $p<0.0001^{***}$)

Figure No 2: Effect of EAG on duration of flexion after MES

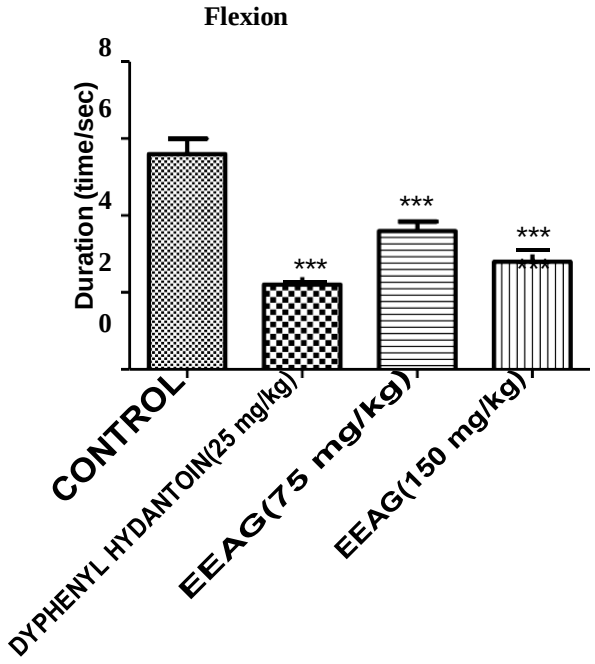


Figure No 3: Effect of EAG on duration of extension after MES

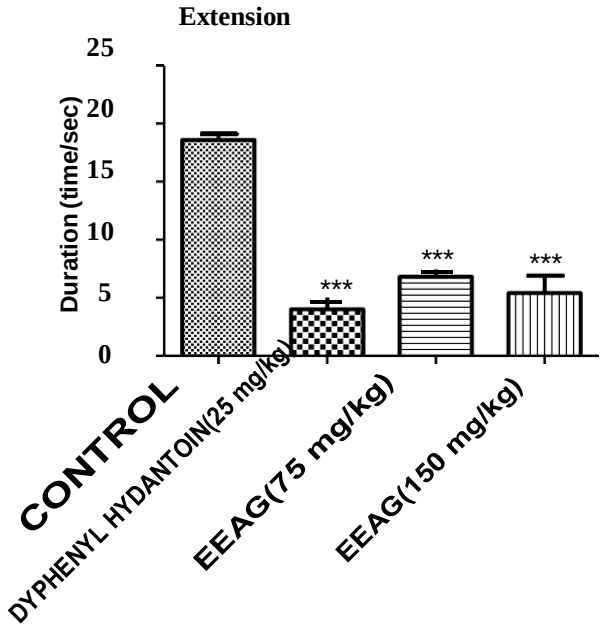
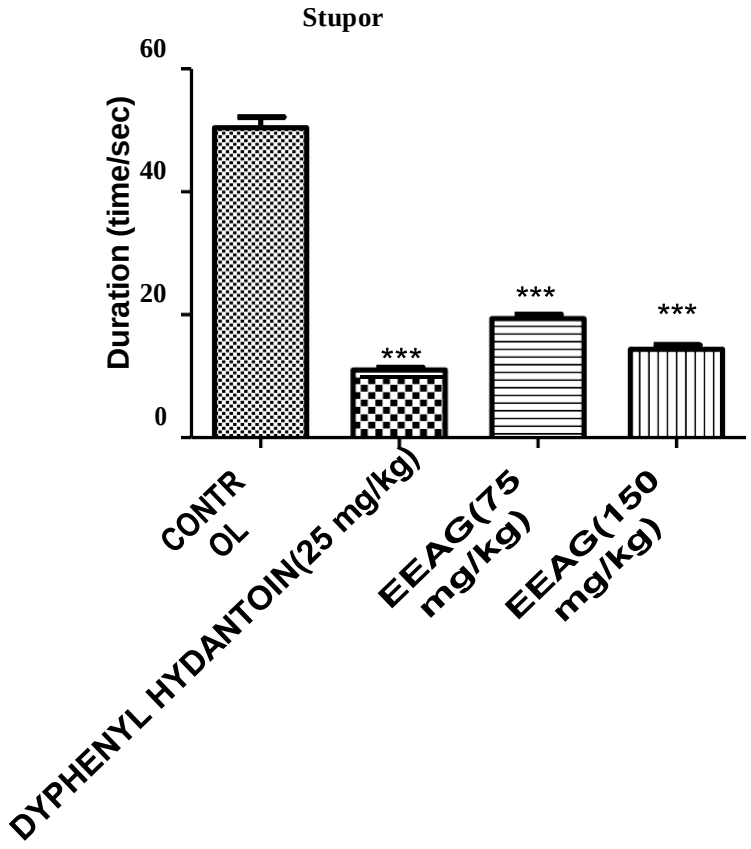


Figure No 4: Effect of EAG on duration of stupor after MES



Statistical comparison: One way ANOVA, followed by Dunett's multiple comparison test. Standard, EAG (low dose) and EAG (HIGH DOSE) are compared with control ($p<0.05$-* , $p<0.001^{**}$, $p<0.0001^{***}$)

Table No 7: Effect of Ethanol extract of *Apium graveolens* on PTZ induced seizures models

Groups	Onset of convulsion (sec)	Duration of convulsion (sec)	Recover/ Mortality
Control	107.40 ±1.32	74.00 ±1.41	Mortality
Sodium valproate(150mg/kg)	680.60 ±1.28***	11.20 ±0.37***	Recovery
EAG (75 mg/kg)	384.40 ±2.29***	27.40 ±0.67***	Mortatility
EAG (150 mg/kg)	478.80 ±1.35***	45.80 ±0.73***	Recovery

Statistical comparison: One way ANOVA, followed by Dunett's multiple comparison test. Standard, EAG (low dose) and EAG (HIGH DOSE) are compared with control ($p<0.05$-* , $p<0.001^{**}$, $p<0.0001^{***}$)

Figure No 5: Effect of Ethanol extract of *Apium graveolens on* onset ofconvulsion in PTZ induced seizure models

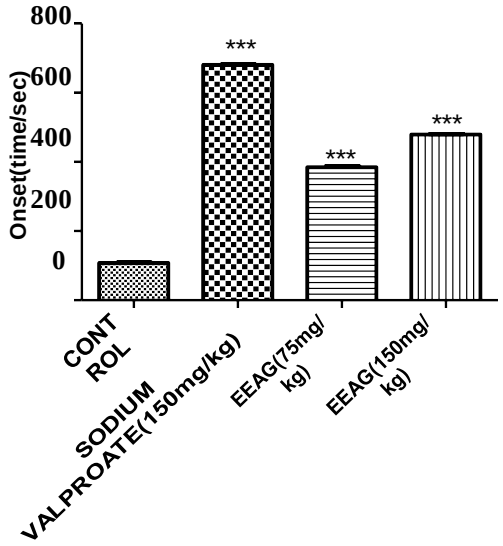
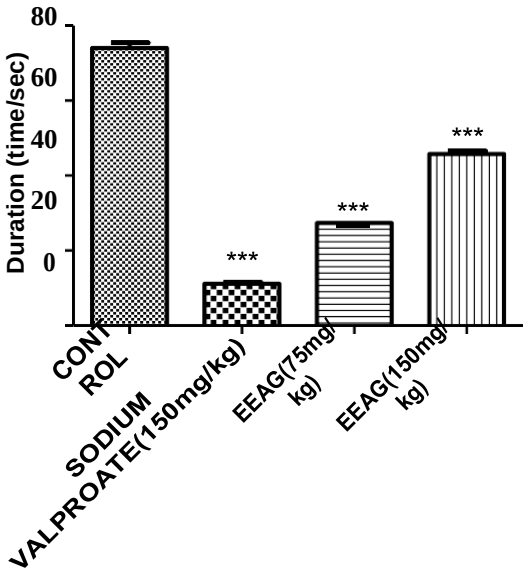


Figure No 6: Effect of Ethanol extract of *Apium graveolens on* duration ofconvulsion in PTZ induced seizure models



INVIVO ANTIOXIDANT ACTIVITY:

Table No 7: Effect of EAG on brain antioxidant GSH, Total protein, LPO in MES induced seizure models

Groups	Total protein (mg/dl)	GSH(mM/mg of tissue extract)	LPO (nMoles of MDA released/ mg protein)
Control	61.8± 0.80	35.2± 0.37	57.8± 0.42
Diphenylhydantoin (25mg/kg)	13.4 ±0.40***	92.8± 0.33***	14.2 ±0.37***
EAG (75 mg/kg)	32.80 ±0.86***	73.8± 0.37***	28.8± 0.33***
EAG (150 mg/kg)	24.0± 0.44***	80.2± 0.80***	23.8± 0.40***

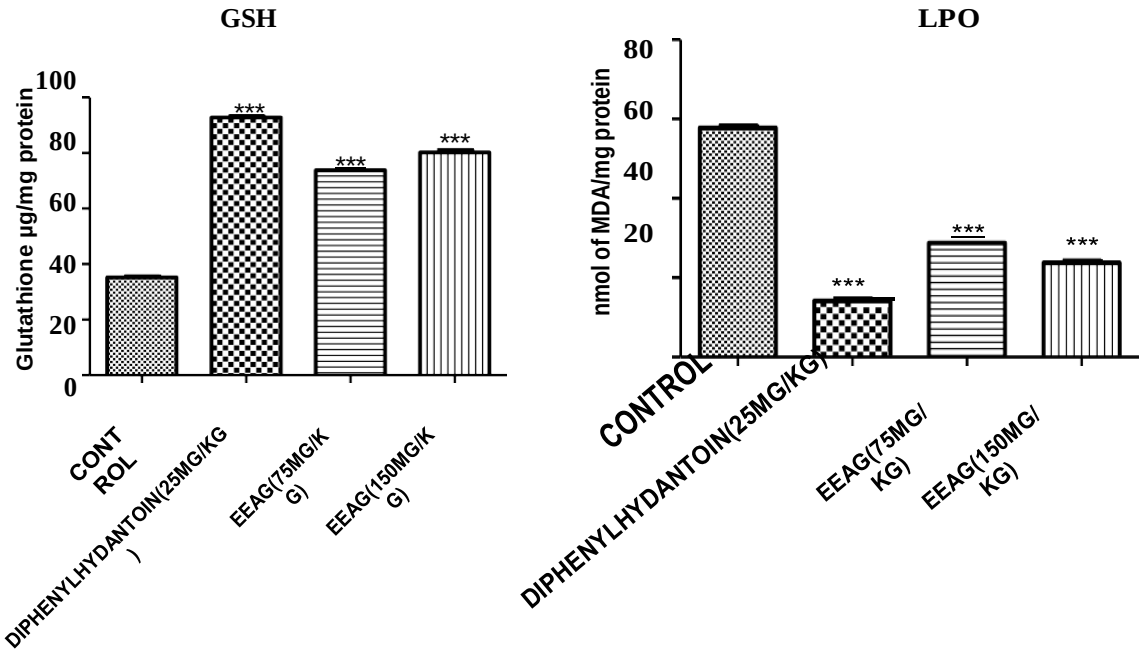
Statistical comparison: One way ANOVA, followed by Dunett's multiple comparison test. Standard, EAG (low dose) and EAG (high dose) are compared with control ($p<0.05$-*, $p<0.001$**, $p<0.0001$***)

Table No 8: Effect of EAG on brain antioxidant GSH, Total protein, LPO in PTZ induced seizure model

Groups	Total protein (mg/dl)	GSH (mM/ mg of tissue protein)	LPO (nMoles of MDA released/ mg protein)
Control	21.8± 0.33	98.0± 0.40	96.6± 0.40
Sodium Valproate (150 mg/kg)	99.2± 0.37***	42.4± 0.24***	58.8± 0.58***
EAG (75 mg/kg)	76.0± 0.44***	57.0± 0.31***	53.8± 0.37***
EAG (150 mg/kg)	86.2± 0.37***	52.0± 0.54***	55.0± 0.31***

Statistical comparison: One way ANOVA, followed by Dunett's multiple comparison test. Standard, EAG (low dose) and EAG (HIGH DOSE) are compared with control ($p<0.05$-*, $p<0.001$**, $p<0.0001$***

Figure No 9: Effect of EAG on brain antioxidant GSH, Total protein, LPO in MESinduced seizure models



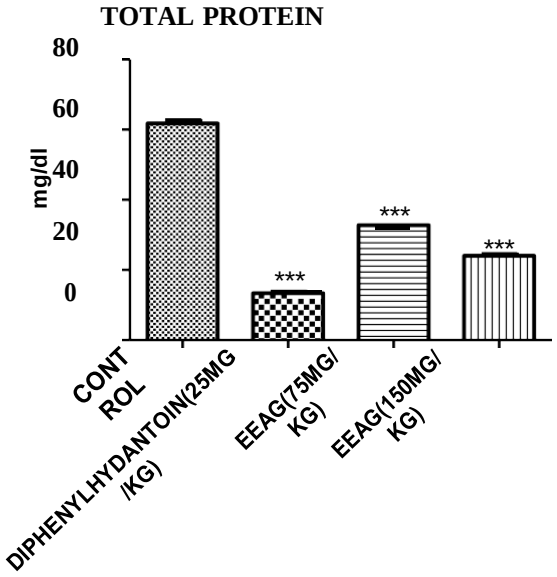
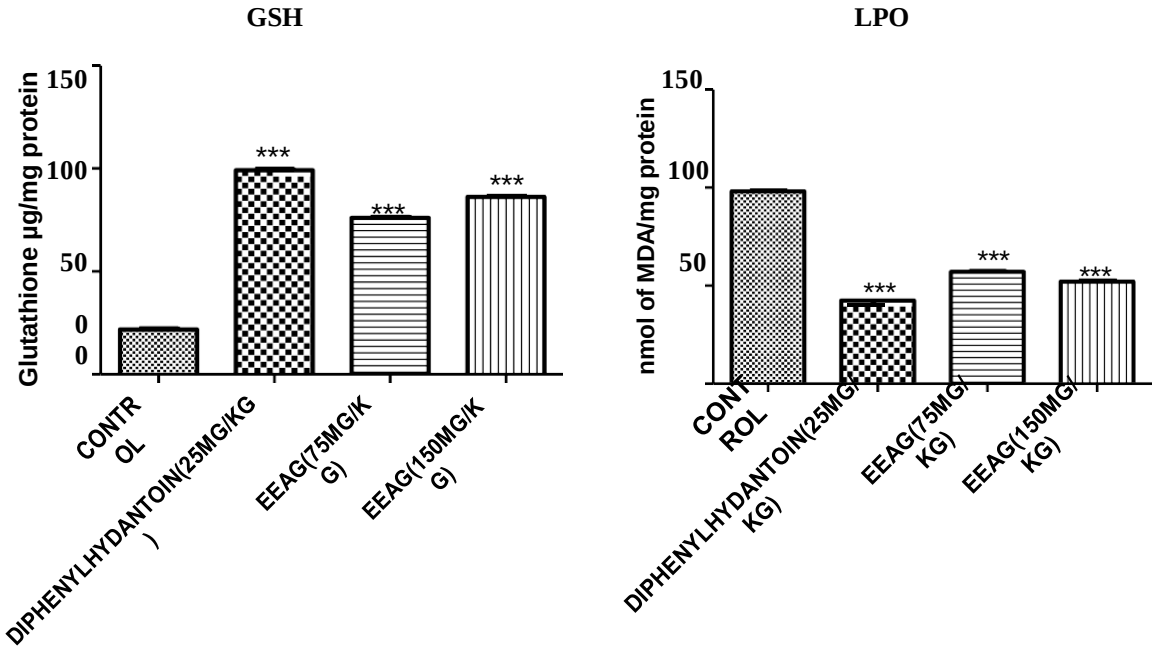
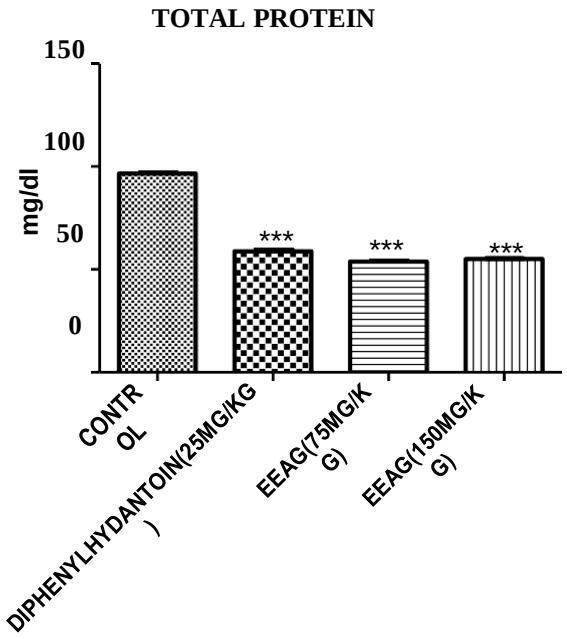


Figure No 10: Effect of EAG on brain antioxidant GSH, Total protein, LPO in PTZinduced seizure model





EFFECT OF EAG ON BRAIN NEUROTRANSMITTERS

Table No 11: Effect of EAG on neurotransmitters levels in rat brain after MES induced epilepsy

Groups	Nor adrenaline (µg/g tissue)	Dopamine (µg/g tissue)	Serotonin (µg/g tissue)	GABA (µg/g tissue)
Control	431.60±1.86	444.00±2.21	73.60±1.72	218.00±3.04
Diphenylhydantoin (25mg/kg)	584.20±1.35***	741.20±2.55***	136.80±1.65***	292.80±2.22***
EAG(75mg/kg)	530.80±2.08***	575.40±2.27***	95.80±1.28***	251.60±2.33***
EAG(150mg/kg)	545.60±2.58***	645.60±2.06***	114.60±1.77***	271.20±1.88***

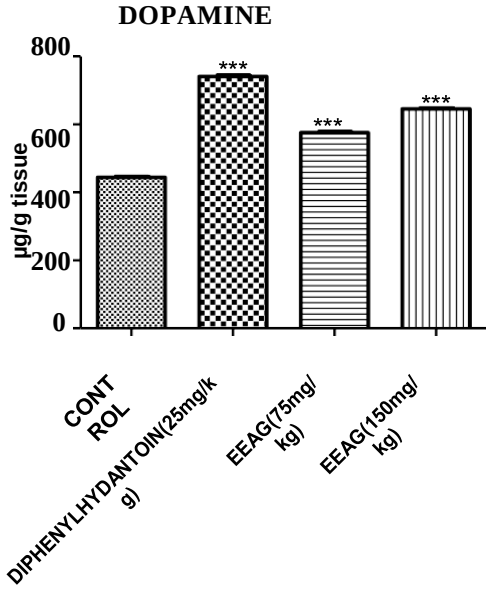
Statistical comparison: One way ANOVA, followed by Dunett's multiple comparison test. Standard, EAG (low dose) and EAG (HIGH DOSE) are compared with control ($p<0.05$-* , $p<0.001^{**}$, $p<0.0001^{***}$)

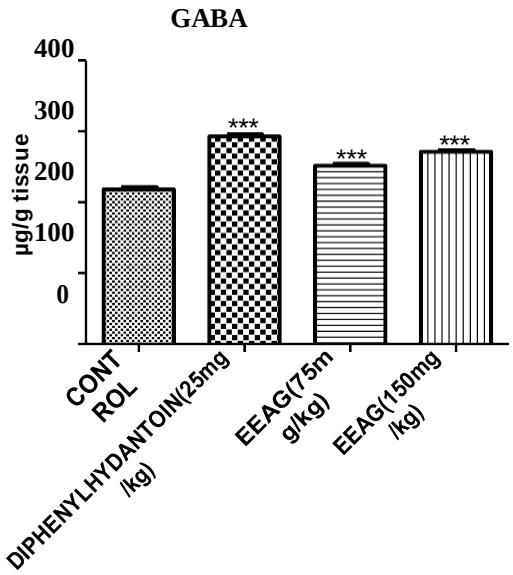
Table No 12: Effect of EAG on neurotransmitters level in rat brain after PTZinduced epilepsy

Groups	Nor adrenaline (µg/g tissue)	Dopamine (µg/g tissue)	Serotonin (µg/g tissue)	GABA (µg/g tissue)
Control	524.00±1.51	212.80±2.08	93.00±1.78	205.40±1.07
Diphenylhydantoin (25mg/kg)	790.40±1.63***	292.20±1.85***	134.80±1.98***	293.20±1.82***
EAG(75mg/kg)	682.80±1.93***	252.80±2.51***	112.20±1.98***	254.00±1.41***
EAG(150mg/kg)	749.40±1.56***	273.20±1.71***	123.20±1.01***	273.20±1.85***

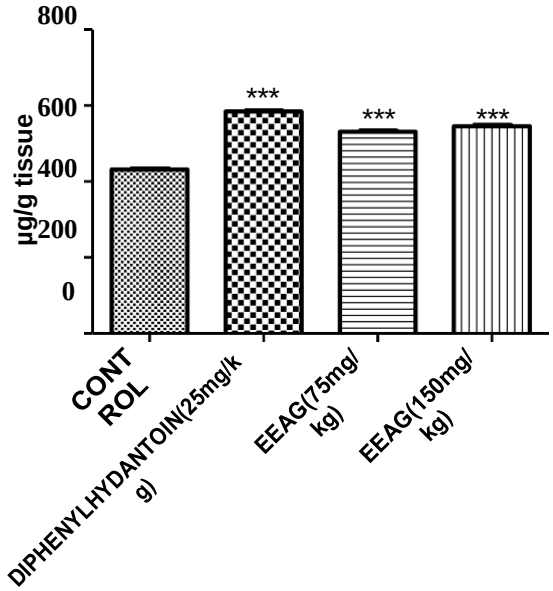
Statistical comparison: One way ANOVA, followed by Dunett's multiple comparison test. Standard, EAG (low dose) and EAG (HIGH DOSE) are compared with control ($p<0.05$-*, $p<0.001$**, $p<0.0001$***)

Figure No 11: Effect of EAG on neurotransmitters levels in rat brain after MES induced epilepsy





Effect of EAG on neurotransmitters levels in rat brain after MES inducedepilepsy



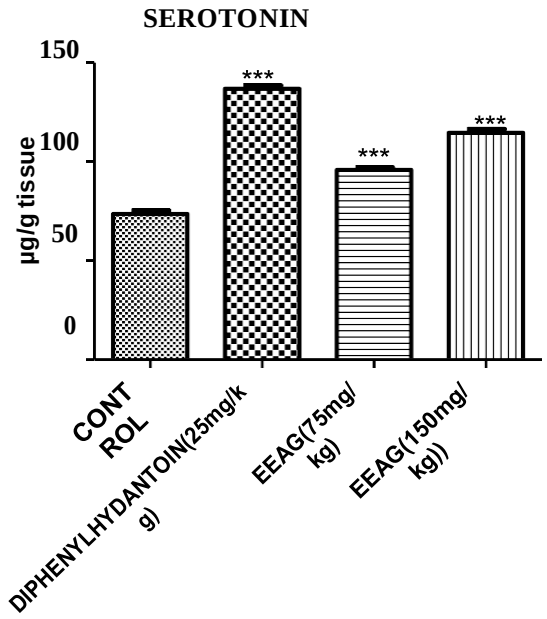
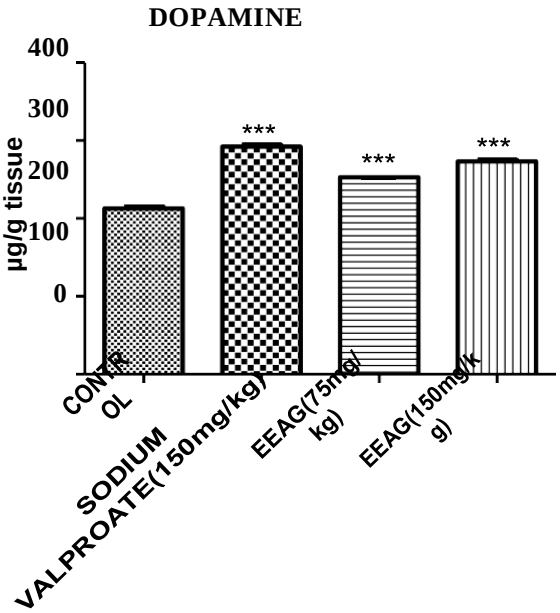


Figure No 12: Effect of EAG on neurotransmitters level in rat brain after PTZinduced epilepsy



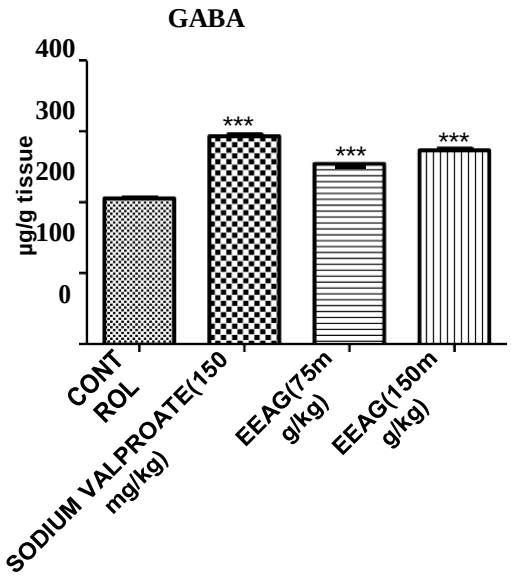
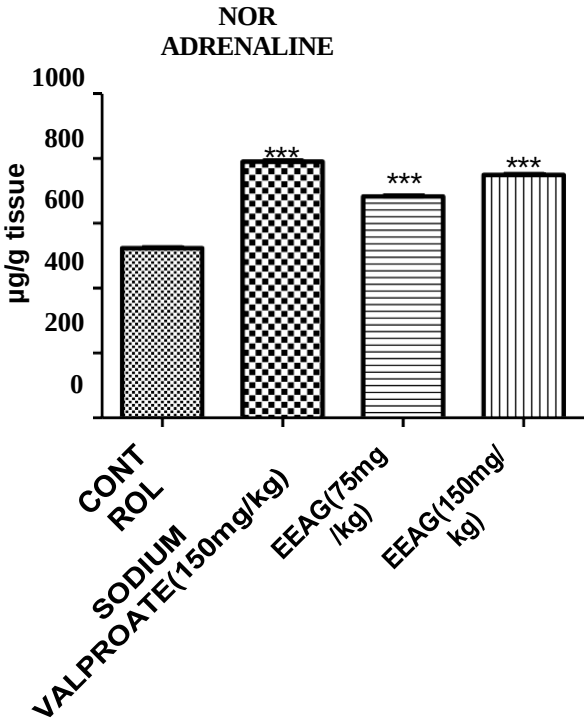
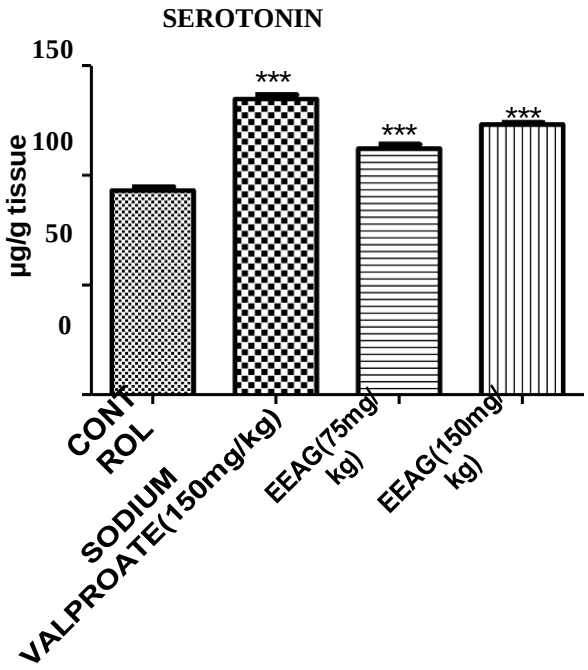


Figure No 13: Effect of EAG on neurotransmitters level in rat brain after PTZ induced epilepsy

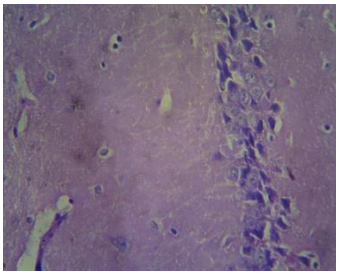




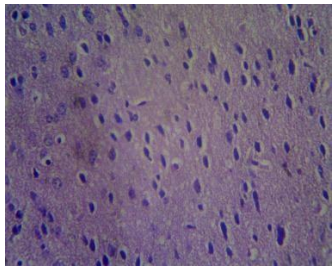
HISTOPATHOLOGICAL EVALUATION

Histopathological evaluation of MES model

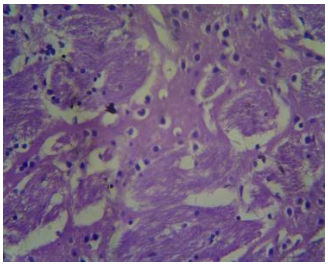
Figure No 14: Group 1: ONLY MES TREATED GROUP



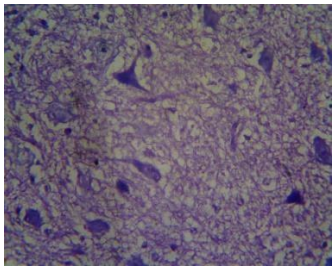
Normal hippocampus



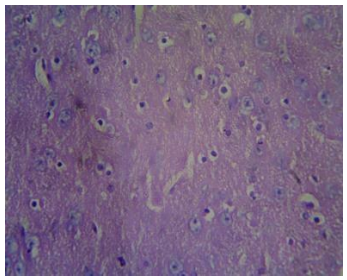
Normal thalamus



Normal corpus striatum



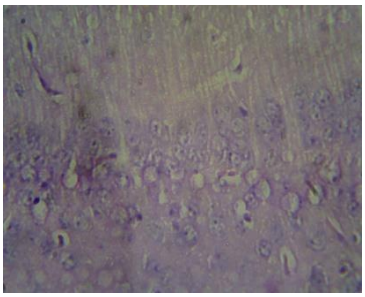
Normal substantia nigra



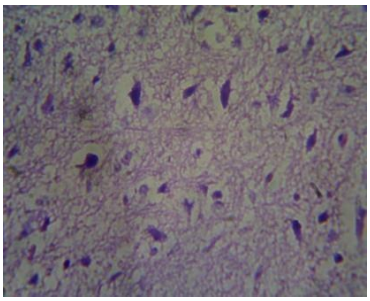
cerebral cortex with neuronal loss

From the results the rat brain shows normal hippocampus (dentate gyrus), thalamus, corpus striatum and substantia nigra and globus pallidus. Cerebral cortex shows neuronalloss.

Figure No 15: Group 2: MES + Standard PHENYTOIN TREATED GROUP



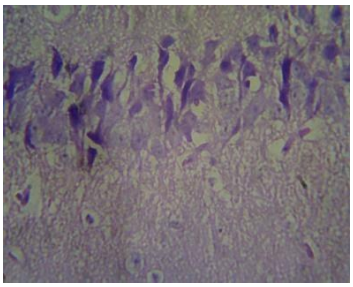
Degenerated hippocampus



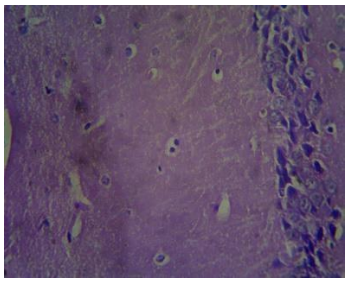
Substantia nigra with edema

From the result rat brain shows hippocampus with degeneration, Substantia nigra shows with edema.

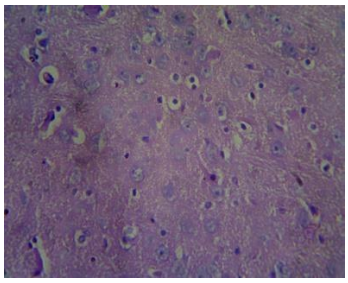
Figure No 16: Group 3: MES + EAG (75 mg/kg) TREATED GROUPS



Hippocampus degeneration



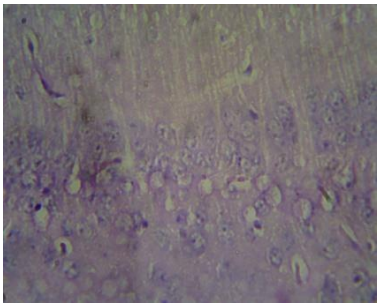
Hippocampus sclerosis



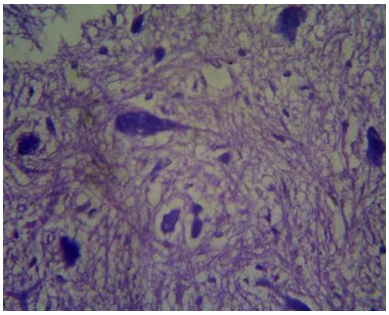
cerebral cortex with edema

From the results the rat brain shows hippocampus showing sclerosis and degeneration,cerebral cortex with edema.

Figure No 17: Group 4: MES + EAG (150 mg/kg) TREATED GROUP



Hippocampus degeneration

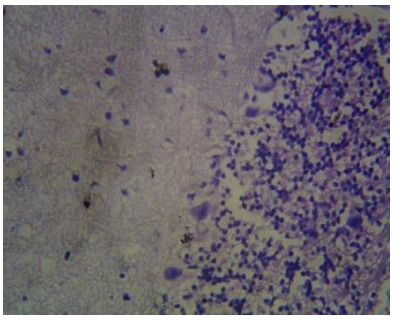


Substantia nigra with edema

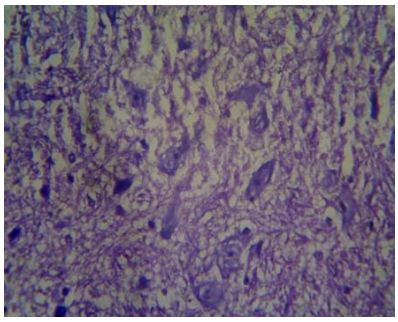
From the result rat brain shows hippocampus showing degeneration. Substantia nigra,shows neuronal loss with sclerosis.

Histopathological evaluation of PTZ model

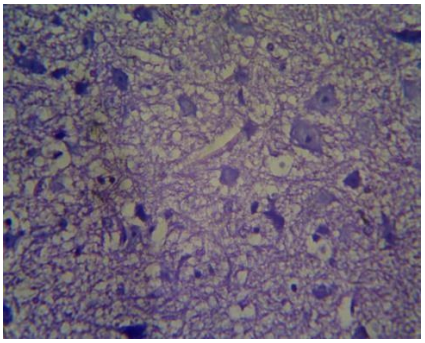
Figure No 18: Group 1: ONLY PTZ TREATED GROUP



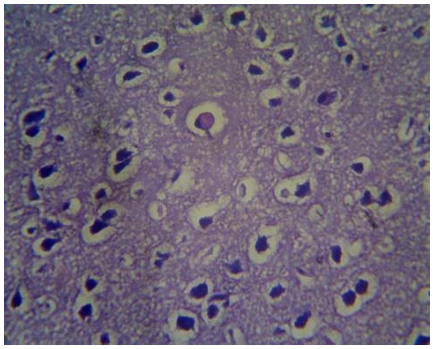
Normal cerebellum with lossmolecular purkinji cell layer



Cerebrum shows neuronal

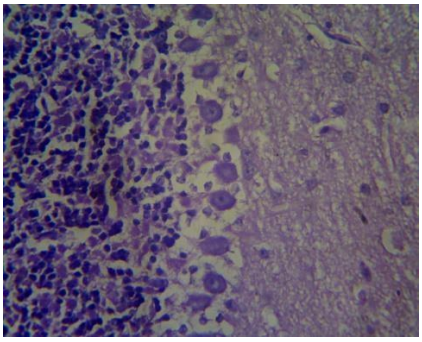


Cerebral cortex shows edema



Cerebral cortex shows piknosis

From the result rat brain shows normal cerebellum with molecular purkinji layer. Thecerebrum shows neuronal loss. Cerebral cortex shows edema and piknosis.



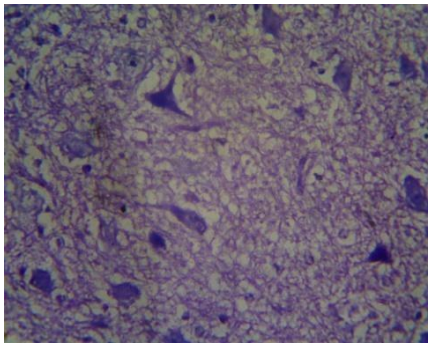


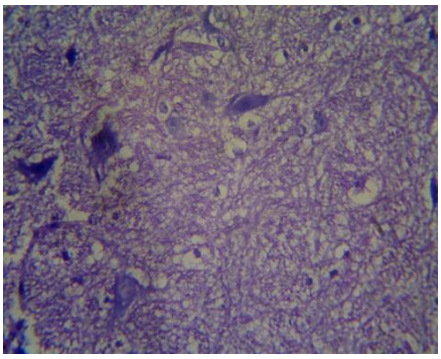
Figure No 19: Group 2: PTZ + SODIUM VALPROATE TREATED GROUP

Cerebellum shows normal purkinji with molecular layer

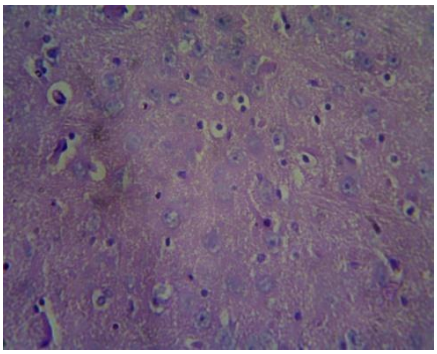
Substantia nigra with edemacells

From the result rat brain shows normal cerebellum shows normal purkinjiec cells with molecular layer and white matter. The substantia nigra shows neuronal loss and edema.

Figure No 20: Group 3: PTZ + EAG (75 mg/kg) TREATED GROUP



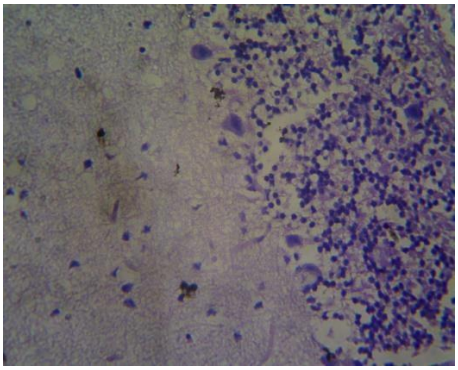
Cerebellum with normal purkinji cells cerebral cortexand molecular layer



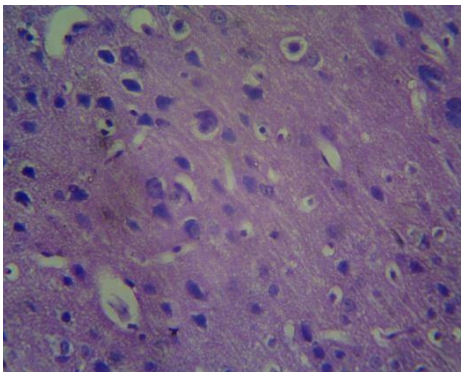
Normal

From the result rat brain shows cerebellum with normal purkinjiec cells and molecularlayer and white matter shows atrophy and gliosis. The cerebral cortex shows normal.

Figure No 21: PTZ + EAG (150 mg/kg) TREATED GROUPS



Normal cerebellum shows purkinji cells sclerosiswith molecular layer



Cerebral cortex shows

From the result rat brain shows normal cerebellum shows purkinji cells with molecularlayer and white matter shows sclerosis and gliosis. The cerebral cortex shows sclerosis.

DISCUSSION:

Epilepsy is a chronic disorder of the brain that affect people worldwide. Nearly about 50-80% of the patients with epilepsy are controlled with currently available antiepileptic drugs. But these drugs cannot able to control seizures effectively in about 10-20% of the patients. The treatment of epilepsy still remains inadequate even though new anticonvulsants are being developed. Furthermore, the current therapy of epilepsy with modern antiepileptic drugs is associated with side effects, dose related and chronic toxicity as well as teratogenic effects.

Traditional systems of medicines are popular in developing countries and upto 80% of the population relies on traditional medicines/ folk remedies for their primary health care need. Hence, there is a need to discover an alternative agent from natural sources.

Apium graveolens used as a herbal medicine and is well known for its traditional uses such as expectorants, diuretics, laxative etc. Various studies shows that the active principle diterpene alkaloids having a crucial role in treatment of epilepsy. *Apium graveolens is* rich in diterpene alkaloids. Since *Apium graveolens have* not been studied for its antiepileptic activity, the present study was aimed to evaluate the antiepileptic activity of Ethanol extract of *Apium graveolens*

The maximal electroshock induced convulsion in animals represents grand mal type of epilepsy. The

tonic extensor phase is selectively abolished by the drugs effective in generalized tonic clonic seizure. The result of the present study shows that the Ethanol extract of *Apium graveolens at* doses 75 and 150 mg/kg significantly delayed the onset of HTLE and reduced the duration of HTLE. And also both doses completely abolished the phase of convulsion in MES induced convulsion models.

In case of PTZ induced convulsion, the result of the present study shows that the Ethanol extract of *Apium graveolens* , at doses 75 and 150 mg/kg significantly reduced the duration and also delayed the onset of convulsion when compared to control group. PTZ may be exerting convulsant effect by inhibiting the activity of GABA at $GABA_A$ receptors. The results revealed that the EAG possess anticonvulsant activity.

Oxidative stress was described as an imbalance between generation and elimination of reactive oxygen species and reactive nitrogen species. The brain is particularly susceptible to oxidative stress because it utilizes the highest amount of oxygen than other body organs. It has been postulated that lipid peroxidation may be casually associated with certain types of epilepsy. A decrease in free radical scavenging activity may lead to an increased risk of seizure recurrence.[The effect of EAG on oxidative stress in MES and PTZ induced convulsion was evaluated. EAG at doses 75 and 150 mg/kg dose showed significant decrease in LPO level.

Glutathione reductase is an important free radical scavenging compound that prevents membrane lipid peroxidation. The decreased level of reduced glutathione in control group seen in the present study indicates that there was an increased generation of free radicals and that the reduced glutathione was depleted during process of combating oxidative stress.[61] EAG at doses 75 and 150 mg/kg dose showed significant increase in the GSH levels in brain tissue. The decrease in lipid peroxidation level and increase in the glutathione level in PTZ and MES induced convulsion models indicates that EAG exhibit good antioxidant activity.

Epilepsy may develop because of an imbalance of nerve signaling chemicals called neurotransmitters. In case of epilepsy, there may be abnormally high level of excitatory neurotransmitters(glutamate) that increase neuronal activity, while abnormally low level of inhibitory neurotransmitters(GABA) that increase neuronal activity in the brain. Hence, GABA hypoactivity and glutamate hyperactivity can enhance an epileptic seizure. In epileptic foci, GABA hypoactivity, which reduces the activity of dopaminergic neurons through a presynaptic effect through GABAA receptors. At low doses, NA can enhance an epileptic seizures, whereas at high doses, it has a protective effect on seizures. Glutamate hyperactivity is exerted through presynaptic N-methyl- D- aspartate receptors, which strongly inhibit serotoninergic neurons and through post synaptic ionotropic glutaminergic receptors, which can induce epileptic seizures. The result of the present study shows that EAG significantly increased the level of inhibitory neurotransmitter GABA and also showed significant increase in the levels of DA, NA and 5-HT when compared to control group. The histopathological study shows alteration in neuronal activity in only MES and PTZ treated groups compared to standard, EAG low dose and high dose. Hence, the result indicates that EAG have good anticonvulsant activity.

CONCLUSION:

The Ethanol extract of *Apium graveolens delayed* the onset and reducedthe duration of convulsion in MES and PTZ induced convulsion models and can be used as an adjuvant therapy against cognitive deficit in convulsions. The extract also shows significant decrease in lipid peroxidation level and increase in reduced glutathione level, indicates that EAG possess good antioxidant activity. Also, EAG significantly increased the level of inhibitory neurotransmitter GABA and also showed increase in DA, NA and 5-HT levels. Hence it can be concluded that the EAG possesses good anticonvulsant activity. Further studies are needed to explore the mechanism as well as the active principle responsible for the anticonvulsant activity of *Apium graveolens.*

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