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Evaluation of Antiepileptic Activity of Ethanolic Extract of *Tinospora Cordifolia Stem* Using Maximal Electricshocks Induced Seizure (MES) Method in Albino Mice

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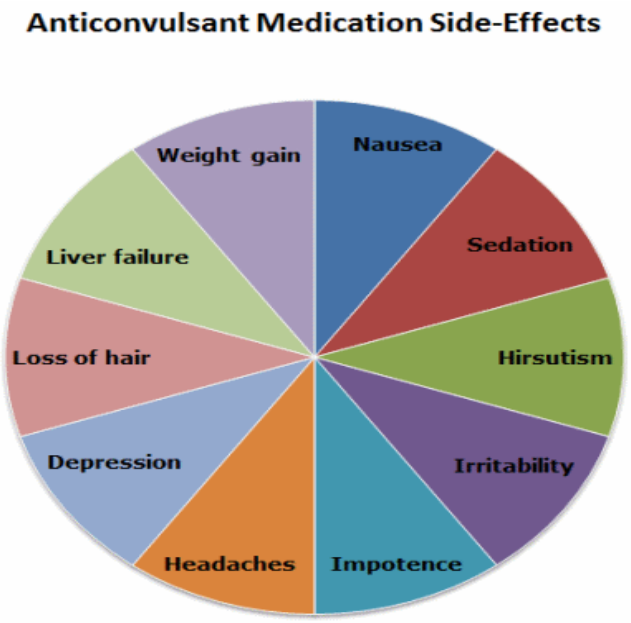
ABSTRACT

There is no particular formula to choice which seizure medicine to use for a particular patient. No one medicine dominates for effectiveness and all have various side effects. AEDs are chosen after considering which side effects can be avoided for particular patient. In that situation herbal Anti-epileptic drugs are also good option for patients. Because they have no side effect and less toxicity in patients. Tinospora cardifolia (Giloy) plant having a lot of medicinal properties. Stem extract of Tinospora cardifolia with Anti-epileptic activity in this study. In the present study, for the screening of aqueous & ethanolic extract of Tinospora cardifolia stem for anticonvulsant activity was carried out using standard methods namely, Maximal Electricshock Induced Seizure Method [MES]. On the basis of present study. it can be concluded that the ethanolic extract of Tinospora cardifolia stem possesses significant anticonvulsant activity against MES.

Keywords: *Antiepileptic Activity, Tinospora cardifolia, Maximal Electricshock Induced Seizure Method [MES].*

INTRODUCTION

Worldwide about 40 million people were affected by the disease epilepsy (1,2). Epilepsy is a condition, which causes seizures to happen. It is most common chronic disease affecting human beings. The risk of having epilepsy at some point in the average life span of any individual varies between 2% to 5% (2). Currently available Anti-epileptic drugs (AEDs) do not provide cure nor prevent relapse but are effective in controlling seizures in about 70% of patients (3,4) and They often associated with serious side effects like teratogenicity, chronic toxicity and adverse effects on cognitive function (3). Afraction of the antiepileptic population resistant to all



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available drugs. Single therapy is often not responsive in treating most of the epileptic patients, so combination of drugs is given, which lead to more severe side effects. (5)

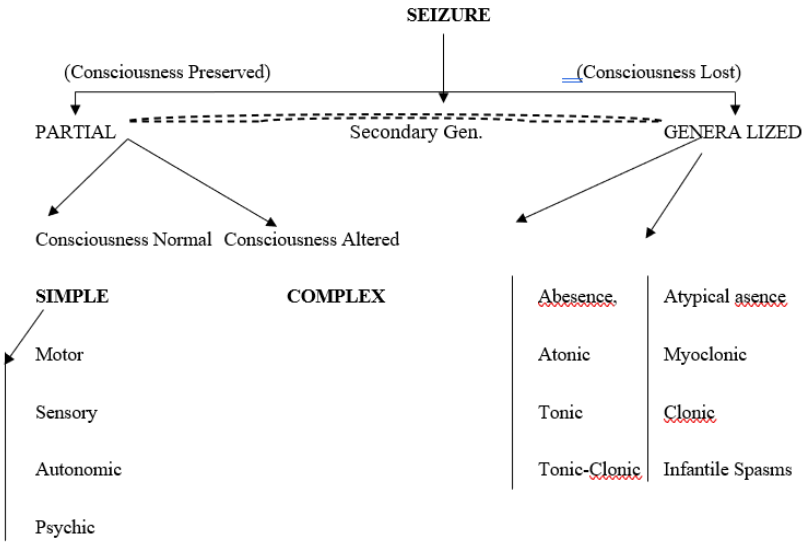
Side Effects of Commonly Used Conventional Drugs(A)

DRUGS	SIDE EFFECTS
Diazepam	Sedation, thromboflebitis, lowering of blood pressure, respiratory depression
Carbamazepine (Iminostilbene)	Dizziness, ataxia, drowsiness, hallucinations, dermatologic sweating, abdominal pain, genitourinary albuminaria, hypotension, liver dysfunction, urticaria, diplopia etc.
Phenobarbitone, Mephobarbitone	Dizziness, lethargy, hypotension, apnoea, megaloblastic anemia, Liver damage, ataxia, hypoventilation etc.
Phenytoin, Ethotoin	Nausea, skin rashes blood dyscarasias, hyperglycemia, cardiac arrhythmias, Steven Johnson syndrome,
Gabapentin	Mild sedation, tiredness, dizziness and unsteadiness

Medicinal plants have been useful in the development of new drugs and continue to play an invaluable role in the drug discovery process (4). Plants are medicinally used in different countries and these are the source of potent and powerful drugs. A wide range of medicinal plants and their parts are used as raw drugs as they possess varied medicinal properties thus herbal drugs constitute a major part in all traditional system of medicines. In many countries the use of medicinal plants ranges from 4 to 20 %. About 2500 species of medicinal plants are being trade globally (6).

According to WHO more than 80 % population of the developing countries of world's relies on traditional herbal medicine for their primary health care. Cucurbits are an excellent fruits in nature having composition of all the essential constituents required for good health in human (6, 7,8). The Manual of Antiepileptic Drug Therapy has been written annually since 1999 as a practical source of clinical information about drugs for the treatment of epilepsy. It is intended for physicians who care for patients with epilepsy.The Manual is updated annually as new information is available.(9)

Flowchart of Modified ILAE seizure classification-(9)



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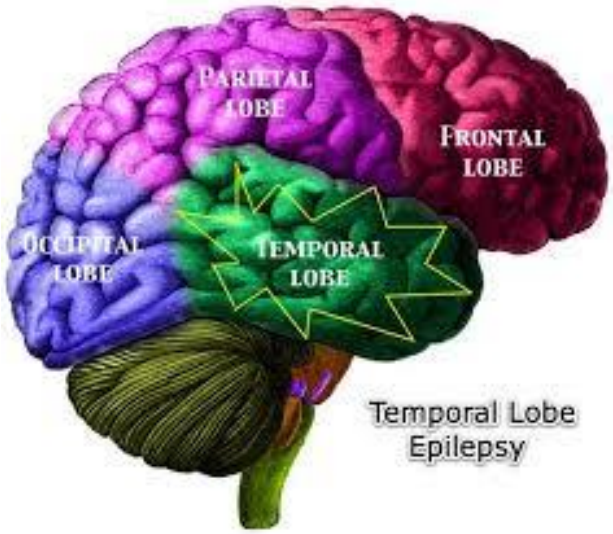
Epilepsy as a group of disorders characterized by excessive and paroxysmal neural discharge causing sudden alteration in neurologic function (10), resulting in recurrent spontaneous seizures. Thus, the seizure is the event and epilepsy is the disorder. One seizure does not make epilepsy. Thus, seizures must be spontaneous and recurrent to represent epilepsy. Seizures results from anelectrochemical disorder in the brain (11) prevailing



Around 1 in 20 of us will have a single seizure at some point in our lives,but this does not mean we have epilepsy.The reason could be a high temperature or Head injury.Most epileptic seizures stop by themselves.(12)

Seizures- Billions of brain cells pass messages to each other and these control what we say and do.A seizure can happen if the brain,s electrical activity is disrupted and these message get mixed up.Seizures usually last for short duration of time and the brain work normally between seizure.Epilepsy is very individual condition so seizures can happen often or raely.(12)

Seizures can vary widely in their clinical presentation, depending on site, extent and mode of propagation of the paroxysmal discharge and hence now looked at as spectrum of clinically

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different varieties rather than a single disease. Many different types of seizures can be identified on the basic of their clinical phenomenon. (13)
In many cases a cause cannot be identified; however, factors that are associated include brain trauma, strokes, brain tumor, ischemic brain damage and drug and alcohol misuse among others.

Up to 5 % or more of the population may have at least one seizure from any cause in their lifetime. Anyone can get epilepsy, from young babies to old men and women.

Possible Precipitating Factors For Seizures(14)

CONDITIONS	FACTORS
Physical	Overexertion,Sleep deprivation,recent Head Trauma,Fever,Concurrent illness/infections,Alteration in bowel elimination,Over-hydration,Excesses in caffeine,sugar,and other foods
Psychosocial/emotional	Stress,Depression,Anxiety,Psychosis,Anger
Metabolic and Electrolyte Imbalance	Low blood glucose,Low sodium,Low calcium,Low Magnesium,Dehydration,Hyperventilation
Medication or Chemical	Reduction or inadequate treatments of AEDs, Withdrawal of alcohol or other sedative agents Administration of Drugs with Proconvulsant properties Toxins Most dopamine blocking agents Antidepressants especially buproprion
Hormonal variations	Menstruation,Ovulation,Pregnancy
Environmental	Particular odor,Flashing lights,Certain types of music

Causes of Seizures

Neonates	-	Intracranial Hemorrhage, Metabolic Disturbances
Infants & Children	-	Febrile Seizures (up to 12yrs), Genetic Disorders
Adolescents	-	Trauma, Genetic, Infection
Older Adults	-	CVS Disease, Tumor

Diagnosis for Epilepsy
The most important diagnostic test in epilepsy is a careful history, taking detailed information on the nature of the patient, episodes followed by-

- Electroencephalogram(EEG) of the brain
- X-Ray of the brain
- CT Scan of the brain
- Magnetic Resonance Imaging(MRI) of brain
- Blood Test (Low blood sugar, Low blood calcium, Low oxygen, Kidney failure, Liver Failure, or drugs or toxins in the blood.

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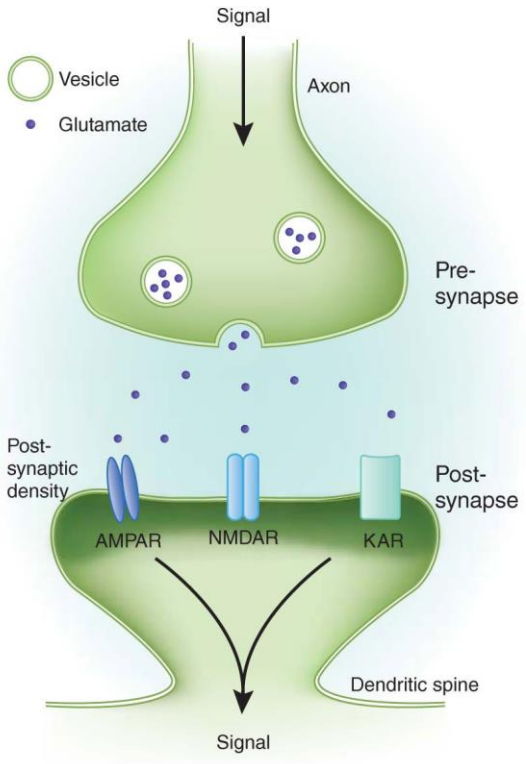
Basic Mechanism Underlying Seizures and Epilepsy

Epilepsy is a disorder of the central nervous system characterized by recurrent seizures unprovoked by an acute systemic or neurological insult. Epileptogenesis is the sequence of events that turns a normal neuronal network into a hyper excitable network. Basic mechanism of neuronal excitability is the action potential; a hyper excitable state can result from increased excitatory synaptic neurotransmission, decreased inhibitory neurotransmission, an alteration in voltage-gated ion channels, or an alteration of intra- or extra-cellular ion concentrations in favor of membrane depolarization. Action potentials occur due to depolarization of the neuronal membrane, with membrane depolarization propagating down the axon to induce neurotransmitter release at the axon terminal. Membrane potential thus varies with activation of ligand- gated channels, whose conductance is affected by binding to neurotransmitters, or with activation of voltage-gated channels, whose conductance is affected by changes in transmembrane potential, or with changes in intracellular ion compartmentalization.

Neurotransmitters are substances that are released by the presynaptic nerve terminal at a synapse and subsequently bind to specific postsynaptic receptors for that ligand. The major neurotransmitter in the brain is glutamate, gamma-amino-butyric acid (GABA), acetylcholine (ACh), nor epinephrine, dopamine, serotonin, and histamine.

Relevant to epilepsy, glutamate and GABA both require active reuptake to be cleared from the synaptic cleft. Transporters for both glutamate and GABA exist on both neurons and glia (primarily astrocytes). Interference with transporter function has also been shown to activate or suppress epileptiformactivity in animal models, depending on which transporter is being blocked(15).



Pathophysiology of Seizures

The hyper synchronous discharges that occur during a seizure may begin in a very discrete

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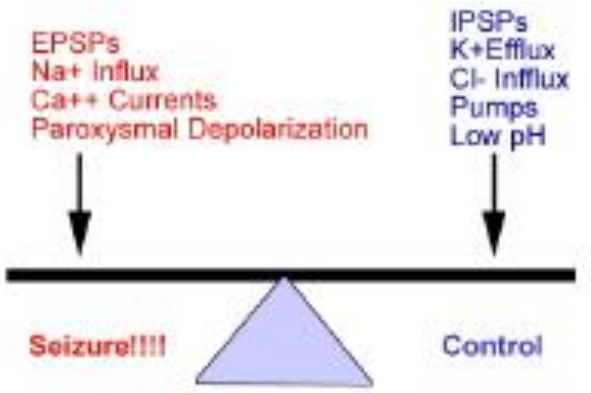
region of cortex and then spread to neighboring regions. Seizure initiation is characterized by two concurrent events:

- High-frequency bursts of action potentials
- Hyper synchronization of a neuronal population

Seizure propagation, the process by which a partial seizure spreads within the brain, occurs when there is sufficient activation to recruit surrounding neurons. This leads to a loss of surround inhibition and spread of seizure activity into contiguous areas via local cortical connections, and to more distant areas via long association pathways such as the corpus callosum.

The propagation of bursting activity is normally prevented by intact hyper polarization and a region of surrounding inhibition created by inhibitory neurons. With sufficient activation there are recruitment ofsurrounding neurons via a number of mechanisms. Repetitive discharges causes to increase in extracellular K^+, accumulation of Ca^{++} in presynaptic nerve terminal, which lead to enhance neurotransmitter release and depolarization induced activation of the NMDA subtype of the excitatory amino acid receptor, which causes more Ca^{++} influx and neuronal activation (15).



Seizures Phases or Stages

There are different major phases or stages of Seizures (16).

- Preictal or Prodrome
- Ictal
- Interictal
- Co/Interictal

1) **Preictal or Prodrome –** This is the time before the seizures occurs. It can last from few minutes to days and make people act feel differently.
2) **Ictal –**This is the actual seizure. In this phase there will be actual physical changes in the person's body.
3) **Interictal –**This is the time between seizures. People with epilepsy, including more than half of all people with temporal lobe epilepsy, suffer emotional disturbance between seizures. This disturbance ranges from mild fear to pathological levels of anxiety and depression.
4) **Co/Interictal –**This is the final phase; It is very slow recovery period after a seizure. This can finish from minutes to hours and very quiet a bit, partly depending on the type of seizure experienced the intensity of it, and how long it lasted.

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Types of Seizures –There are different types of seizures. These are categorizes by on the basis of brain part involved in seizures. People may experience one or more than one type seizure.

There are four Sub-Categories of seizures:

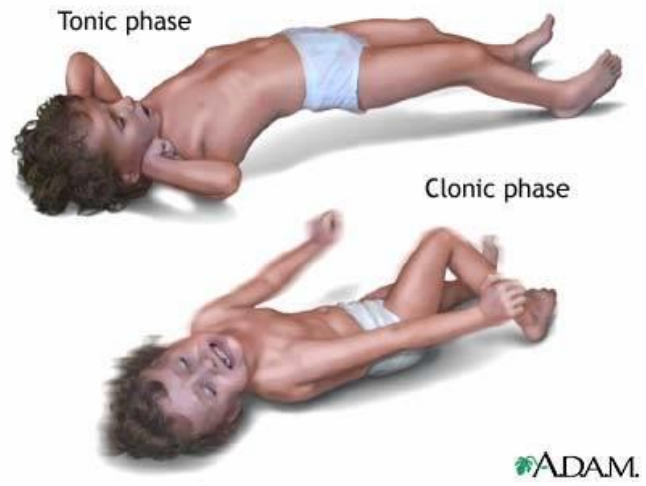
- Generalized Seizures
- Partial Seizures
- Non-Epileptic Seizures
- Status Epileptics

1) Partial Seizures - Partial seizures are those in which the discharge begins locally and often remains localized. The symptoms depend upon brain region or region involved and include involuntary muscle contractions, abnormal sensory experience or autonomic discharge or effects on mood and behavior, often termed as psychomotor epilepsy.
There are two main types of partial seizures: -

- **Simple Partial Seizures:** Person having simple partial seizure will often stay awake and aware throughout the seizure but unable to speak after knowing everything happening until the seizure is over.
- **Complex Partial Seizures:** These seizures affect a greater part of the brain than simple partial seizures and they also affect consciousness. They can affect any part of the brain.

2) Generalized Seizures -Generalized Seizures involved the whole brain, including the reticular system, thus producing abnormal electrical activity throughout the both hemisphere, Immediate loss of consciousness is characteristic of Generalized Seizures. It is of following types namely: -

Tonic-Clonic Seizures: These are also called as Grand mal Seizures. It is consisting of strong contraction of whole musculature, causing a rigid extensor spasm and an involuntary cry. Respiration stops and defecation, micturition and salivation often occur. This tonic phase lasts for about one minute, during which the face is suffused and becomes blue and is followed by a series of violent, synchronous jerk that gradually die out in 2-4 minutes. The patient stays unconscious for a few more minute and then gradually recovers, feeling ill and confused. Injury may occur during convulsive episodes.



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Absence Seizures
It is also called petit mal seizure and often occurs in children. They are much less dramatic but may occur more frequently than tonic-clonic seizures. The patient abruptly ceases whatever he or she was doing, sometimes stopping speaking in mid-sentence and scares vacantly for a few seconds with little or no motor disturbance. Patient is unaware of their surroundings and recovers abruptly with no after effects

Myoclonic Seizures
These seizures cause parts of a person's body to jerk for instance, his or her arm or leg might suddenly twitch..

Atonic Seizures
It is also known as drop attacks, or astatic or akinetic Seizures. These seizures make a part, or all, of a person's body suddenly go limp. In this Condition people's head might suddenly drop, or he or she calls slump down or even totally collapse, suddenly dropping to the floor.

Seizures Unique to Childhood

Neonatal Seizures: -These seizures are difficult to recognize. Neonatal seizures can stimulate normal jitteriness of newborn. These seizures can consist of tonic deviations of head, neck, oral buccal movements, opisthotonic posturing, or multifocal myoclonic movements.

Infantile Spasms: -Infantile spasms are seizures beginning in children between 3 and 12 months of age. The child may have shown previous neurologic signs or may have been previously normal. Infantile spasms consist of sudden brief flexor spasms of head, neck, trunk, and extremities that cause the child to double up or jack-knife.

Febrile Seizures: -This seizure initially develops between the age of 6 months to 4yrs of age. It consists of brief episodes of generalized major motor seizures occurring as child initially develops febrile response. This child usually has only brief postical depression and no facal neurologic deficit, and interictal ECG is normal (10).

Non-Epileptic (Dissociative)Seizures-
Non-epileptic seizure is not accompanied by abnormal electrical discharges. They have been previously called pseudo seizures, but that term is misleading. These seizures are quite real, and people who have them do not have conscious, voluntary control over them. Non epileptic seizures have no identifiable physical cause, but they are believed to be physical reactions to psychological stresses. Non-epileptic seizures resemble epileptic seizures in outward appearance, even though their cause is very different. Non epileptic seizures may appear to be generalized convulsions, similar to grand mal epileptic seizures, characterized by falling and shaking. They also may resemble petit mal epileptic seizures, or complex partial seizures, characterized by temporary loss of attention, staring into space or dozing off. (17)

Types of Non-Epileptic Seizures-

Non-epileptic seizures (NES) can be divided into two types. (18)

- Organic non –epileptic seizures
- Psychogenic seizures

Organic Non-Epileptic Seizures-
These seizures have a physical cause (relating to the body). They include fainting (syncope)

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and seizures with metabolic causes such as diabetes. Because organic NES have a physical cause, they may be relatively easy to diagnose and the underlying cause can be found.

Psychogenic Seizures- Some NES have a psychological cause and are called 'psychogenic seizures' because they are caused by the impact of thoughts and feelings on the way that the brain works.

Psychogenic seizures include-
Dissociative seizures are involuntary and happen unconsciously. The person has no control over them and they are not 'put on'. This is the most common type of NES.

Panic attacks are a psychiatric condition. They can happen in frightening situations, when remembering previous frightening experiences or in a situation that the person expects to be frightening. Panic attacks can cause sweating, palpitations (being able to feel your heartbeat), trembling and difficulty breathing. The person may also lose consciousness and may shake (convulse).

Factitious seizures happen under some conscious control. An example of this is when seizures form part of Münchausen's Syndrome, a rare psychiatric condition where a person is driven by a need to have medical investigations and treatments.

Status Epilepticus-
Status epilepticus is ,when a person has a prolong seizure,lasting more than 30 minutes or a person has one seizure after another with no return to normal breathing and consciousness between the seizures for more than 30 minutes.Status epilepticus is ver rare.and it is always a medical imergency.It can be life threatening and cause permanent damage to the brain.(D)

Management of Epilepsy

Drug Therapy:- About 40 % of the patients the seizures will remain resistant to treatment. The success f the medical treatment depends on the number of seizures before treatment. The selection of the AEDs depends on the seizures type, syndrome diagnosis, half time and the effect of the AED on metabolism.

Ictogenesis in focal epilepsy decisively depends on the intrinsic paroxysmal depolarization of the nerve cell. Anti-Epileptic drugs (AEDs) aim at the prevention of repetitive action potential by natrium flow at the cell membrane, by augmentation of deficient GABAergic inhibitory processes, or by reduction of pathological glutamatergic excitation. In idiopathic generalized epilepsies, AEDs aim at receptor ion –channels (T-Calcium channels, GABA A/B receptors), Which are causative for synchronized bursts.

There are a lot of medicines available in the market for the treatment of epilepsy like Phenytoin, Carbamazepine, Valproate, Ethosuximide, Phenobarbital, Benzodiazapines, Vigabatrin.

Side Effects: Confusion, Gum-hyperplasia, Skin rashes, Anemia, Teratogenesis Sedation, Ataxia, Mental Disturbance, Water Retention, Drowsiness Nausea, Anorexia, Dizziness, Lethargy, Hyper sensitivity reactions etc.

Surgery: It can be very successful treatment option for patient with focal symptomatic

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epilepsies. Surgery is recommended when patients are pharmacoresisitant, and they have a resettable epiletogenic region, and when surgey in the effected brain structure will not lead to any serious negative side effects.

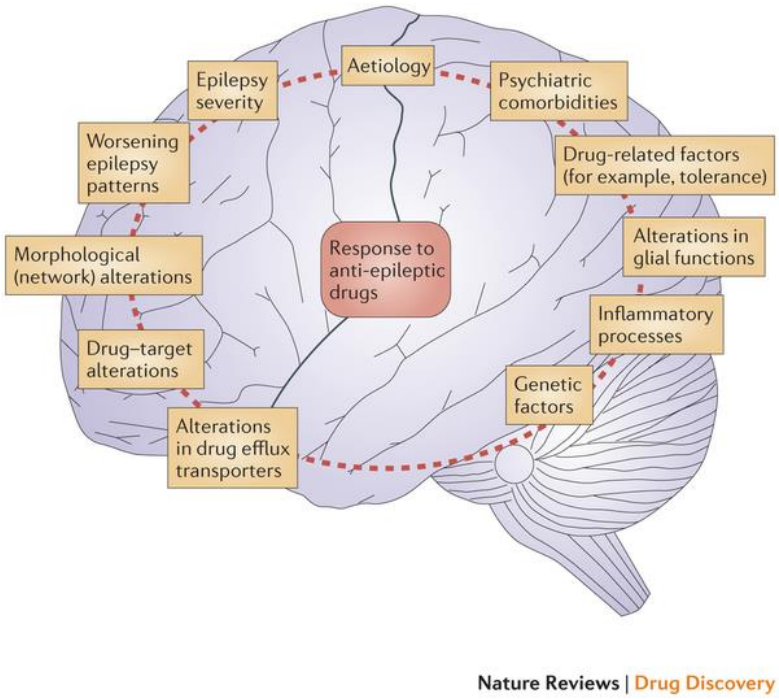
Vagal Nerve Stimulation: The electrical stimulation of vagal nerve (VNS) has turned out to be something like a third way for treating pharmacoresistant epilepsies. It is other than medical and surgical treatment in patients (19).

Behavioral Therapy: Behavior modification and neurofeedback are treatment options, which mainly arose from three observations:

- Seizures in reflex epilepsies can be suppressed by sensory stimulation;
- Seizures often start with an aura as a first sign of an evolving seizure. This can be taken as a warning sign;
- The EEG can be taken to visualize pathological and no pathological brain activity.

Management with Ketogenic Diet: Patients with seizures are prescribed a ketogenic diet for treatment and control of seizures. The ketogenic diet is designed to induced and maintain a state of ketosis which has been found to metabolically improve seizure control in certain cases. the diet is high in fat (80 -90%) and low in carbohydrate and proteins,Ketogenic diet carefully calculated and require daily monitoring to maintain ketosis.

Despite of extensive research in medical field, no drug in the modern system of medicine can be claimed to cure epilepsy completely, which may be fatal many times. We have as yet no effective remedy which can effectively cure epilepsy(20).



Nature Reviews | Drug Discovery

Mode of Action of Antiepileptic Drugs: Majority of antiepileptic drugs possesses more than one mechanism of action. The proposed classification of antiepileptic drugs based upon different mechanisms. First group consists of antiepileptics (f.e. carbamazepine, gabapentin,

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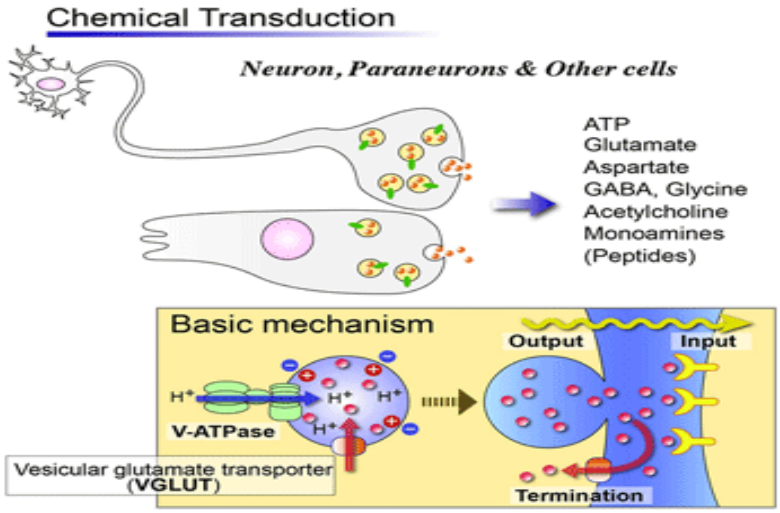
lamotrigine, oxcarbazepine, phenobarbital, phenytoin, topiramate, valproate) which block sustained repetitive firing in individual neurons, this effect being mainly due to the blockade of voltage-dependent sodium or calcium channels. These drugs are effective against generalized tonic-clonic and partial seizures. The second group includes drugs enhancing inhibitory events mediated by g-amino butyric acid (GABA): benzodiazepines, gabapentin, phenobarbital, tiagabine, topiramate, vigabatrin, and valproate. Some of these drugs may be used in all seizure types (absence, generalized tonic-clonic, and partial seizures) – see below. The third group practically consists of one drug – ethosuximide which blocks T-type calcium channels and is active against absences. Recent evidence suggests that also zonisamide may be a T-type calcium channel inhibitor. A separate category of drugs may be also suggested – these antiepileptic drugs reduce events mediated by excitatory amino acids (f.e.: glutamate) and at present three anti-epileptics meet these criteria: felbamate, phenobarbital, and topiramate (21)



Mechanisms of Action of Conventional and New Antiepileptic Drugs (AEDs).(21)

AED	Enhancement of GABA- mediated excitation	Blockade of sodium channels	Blockade of Calcium channels	Blockade of calcium channels	Other
Benzodiazepines	+	+			
Carbamazepine		+			
Ethosuximide			+ (T-Type)		
Phenobarbital	+	+		+	
Phenytoin		+			
Valproate	+	+			+
Gabapentin			+ (L-Type)		
Felbamate	+	+		+	
Lamotrigine		+	+(L-Type)		
Levetiracetam					+
Oxcarbazepine		+	+ (L-Type)		
Tiagabine	+				
Topiramate	+	+	+ (L-Type)	+	+
Vigabatrin	+				
Zonisamide		+	+ (T-Type)	+	+

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Future prospectus for diagnosis and treatment of epilepsy-(22)

It is quite pertinent that commonly available synthetic anticonvulsants do not adequately meet patient treatment demands.

1) Ketogenic diet- A highly fat, low carbohydrate diet developed with the advent of effective anticonvulsants. The mechanism of action is unknown. It is used mainly in the treatment of children with severe, medically intractable epilepsies.
2) Electrical stimulation- A currently approved device is vagus nerve stimulation. Investigational devices include the responsive neurostimulation system and deep brain stimulation.
3) Vagus nerve stimulation-The device stimulates the vagus nerve at pre-set intervals and intensities of current. Efficacy has been tested in patients with localization-related epilepsies.
4) Responsive neurostimulator system (RNS)-It consists of a computerized electrical device implanted in the skull with electrodes implanted in presumed epileptic foci within the brain. The brain electrodes send EEG signal to the device which contains seizure detection software. When certain seizure criteria are met, the device delivers a small electrical charge to other electrodes near the epileptic focus and disrupt the seizure.
5) Deep brain stimulation-Consists of computerized electrical device implanted in the chest in a manner similar to the VNS.
6) Non-invasive therapy- Use of Gamma knife device is used in neurosurgery are currently being investigated as alternatives to traditional open surgery in patients who would otherwise qualify for anterior emporal lobectomy.
7) Avoidance therapy- Avoiding therapy consists of minimizing or eliminating triggers in patients whose seizures are particularly susceptible to seizure participants.

Herbs in Epilepsy

Traditional medicinal practices have remained as a component of health care system of many societies in spite of the availability of well-established alternatives. But today management shifted towards the herbal uses in the management of seizures because herbal drugs do not possess serious adverse effects and fit to the culture of people with less contradiction.(2)

Traditional Herbs are very useful and indispensable in the struggle for seizure management and future AED development. Therefore alternative therapy including herbal drugs and complementary medicine is becoming increasingly popular.(13)

There are a lot of Antiepileptic Herbs available in the world.(2,13)

S.NO.	Plant Name	Part Used
1	Citrus Sinesis	Leaves,Flower,Barksand Roots
2	Datura Stromonium	Fruits,Leaves
3	Ricinus Communis	Leaves ,Flower
4	Terminalia Glaucescens	Bark, Fruits,Roots
5	Tetra Pleura Tetraptera	Bark, Fruit,Leaves
6	Senna Singuena	Leaves,Flower,Bark,Root
7	Jatropha Gossypiifolia	Leaves,Root
8	Mentha Cardifolia	Leaves
9	Brahmi Ghrita	A Poly Herbal Formulation
10	Cissus Sicyoides	Aerial Part

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11	Passion Flower	Leaves ,Flowre
12	Rosa Domescana	Flower
13	Argyreia Speciosa	Leaves
14	Drosera Burmanni	Whole Plant
15	Glycerrhiza Glabra	Root
16	Oscimum Sanctum	Leaves
17	Pongamia Pinnata	Leaves
18	Berberis Vulgeris	Plant
19	Clerodendrum Infortunatum	Leaves
20	Echium Amoenum	Flower
21	Butea Monosperma	Flower
22	Valeriana Officinalis	Root
23	Saussurea Lappa	Root
24	Cymbopogon Winterianus	Leaves
25	Taxux Wallichiana	Plant
26	Dorstenia Arifolia	Rhizome
27	Scuteellaria Lateriflora	Arial Part
28	Sutherlandia Frutescens	Shoot

MATERIALS AND METHODS

Identification, Collection and Authentication of Plant Stem

Plant was selected on the basis of traditional uses and extensive literature survey was done to ruled out similar work in past. The stem of *Tinospora cardifolia* were collected from Moradabad,U.P.India. The plant material was identified & authenticated by Principal Scientist Dr. (Mrs.) Anjula Pandey National Bureu of Plant Genetic Research (NBGPR)Pusa Campus,New Delhi- vide voucher no.NHCP/NBPGR/2014-15, deposited to TMCP,TMU MORADABAD for future reference.\

PREPARATION OF EXTRACT

Grinding of selected plant material (33): The plant material was dried at room temperature.Exposure to sunlight was avoided to prevent the loss of active constituents.After drying the plant material was cut into small pieces and then grinded to form the course powder.The powdered plant material was taken for extraction procedure. The powderes material was then packed in soxhlet extractor and then defated with petroleum ether to remove any greasy material present.

Preparation of Ethanolic Extract of Tinospora cordifolia stem (34): For the preparation of ethanolic extract, the dried coarse powder was packed in Soxhlet apparatus and extracted with 95% ethanol. The appearances of colourless solvent in the tube was taken as the termination of extraction. The extract was transfer into a previously weighed empty beaker, and then it was kept on a water bath maintained at 500 C and evaporated to a thick paste. The extract was thoroughly air dried to remove all trace of the solvent. For the preparation of test sample, the weighed amount of extract was dissolved in normal saline.

Preparation of aqueous extract of Tinospora cordifolia stem (34): About 500 gm of **Tinospora cordifolia stem** powder was taken in a round bottom flask (2000 ml) and macerated with about 500 ml of distilled water and 10 ml of chloroform (preservative) for 24 hrs with shaking (for every hour in a closed vessel). Then the marc was removed by filtering

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the extract, and then it was concentrated on a water bath at 50°C to get a semi solid mass. The extract was stored in an airtight container in a refrigerator below 10°C

Phytochemical Screening of Ethanolic and Aqueous Extracts of Tinospora cordifolia stem :- (35, 36,37)

A preliminary phytochemical screening of Tinospora cordifolia extracts was performed for the determination of phytoconstituents like Alkaloids, Glycosides, Carbohydrates, Flavonoids, Saponins, Sterols, Terpenes and Tannins.

Detection of Alkaloids: Extracts were dissolved individually in dilute hydrochloric acid and filtered. The filtrates were used to test for the presence of alkaloids.

- **Mayer's Test:** Filtrates were treated with Mayer's reagent (saturated solution of potassium mercuric iodide). The formation of a yellow cream precipitate indicates the presence of alkaloids.
- **Dragendorff's Test:** Filtrates were treated with Dragendorff's reagent (saturated solution of potassium bismuth iodide). The formation of red precipitate indicates the presence of alkaloids.
- **Wagner's Test:** Filtrates were treated with Wagner's reagent (iodine potassium iodide solution). The formation of reddish brown precipitate indicates the presence of alkaloids.
- **Hager's Test:** Filtrates were treated with Hager's reagent (saturated solution of picric acid solution). The formation of yellow precipitate indicates the presence of alkaloids.

Detection of carbohydrates

Extracts were dissolved individually in 5 ml distilled water and filtered. The filtrates were used to test for the presence of carbohydrates.

- **Molisch's Test:** Filterates were treated with 2 drops of alcoholic α-naphthol solution in a test tube and 2 ml of conc. sulphuric acid was added carefully along the sides of the test tube. The formation of violet ring at the junction and the two layered indicates the presence of carbohydrates.
- **Benedict's Test:** Filterates were treated with Benedict's reagent and heated on water bath. The formation of orange red precipitate indicates the presence of reducing sugars.
- **Fehling's Test:** Filterates were hydrolysed with dilute hydrochloric acid, neutralized with alkali and heated with Fehling's A and B solutions. The formation of red precipitate indicates the presence of reducing sugars. Detection of Saponins
- **Foam Test:** Small amount of extract was shaken with little quantity of water. If foam produced persists for 10 min. that indicates the presence of saponins.

Detection of Glycosides: Extracts were hydrolysed with dilute hydrochloric acid, and then subjected to test for glycosides.

- **Modified Borntrager's Test:** Extracts were treated with ferric chloride solution and immersed in boiling water for about 5 min. The mixture was cooled and shaken with an equal volume of benzene. The benzene layer was separated and treated with ammonia solution. The formation of rose-pink colour in the ammonical layer indicates the presence of glycosides.
- **Legal's Test:** Extracts were treated with sodium nitroprusside in pyridine and methanolic alkali. The formation of pink to blood red colour indicates the presence of cardiac glycosides.

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Detection of Proteins and Amino Acids

- **Millon's Test:** The extracts were treated with 2 ml of Millon's reagent. Formation of white ppt. indicates the presence of amino acid.
- **Ninhydrin Test:** To the extract, Ninhydrin reagent (0.25% in alcohol) was added and boiled for few min. The formation of blue colour indicated the presence of amino acids.
- **Biuret Test:** The extracts were treated with 1 ml of 10% sodium hydroxide solution and heated. To this a drop of 0.7% copper sulphate solution was added. The formation of purplish violet colour indicates the presence of proteins.

Detection of Tannins

- **Gelatin Test:** To the extract, gelatin solution (1%) containing sodium chloride was added. The formation of white precipitate indicates the presence of tannins.

Detection of Flavonoids

- **Shinoda Test:** To the test solution added few magnesium ribbon and concentrated HCl (dropwise), pink, scarlet, crimson red or occasionally green to blue colour after few minutes indicates presence of flavonoids.

- **Alkaline Reagent Test:** To the test solution added few drops of sodium hydroxide solution, intense yellow colour formation which turns to colourless on addition of few drops of dilute acid indicates the presence of flavonoids.
- **Zinc Hydrochloric Acid Reduction Test:** To the alcoholic solution of extracts, a pinch of zinc dust and conc. HCl was added. Appearance of magenta colour after few minutes indicates the presence of flavonoids.
- **Lead Acetate Test:** Extracts were treated with few drops of lead acetate solution. The formation of yellow colour precipitate indicates the presence of flavonoids.

Detection of Terpenoids

The terpenoids have a common biosynthetic origin. The terpenoids includes essential oils diterpenoids and gibberlines triterpenoids etc.

- **Lebermann-Burchard reaction:** The extract was treated with acetic anhydride and concentrated H2SO4, gives purple red color.
- **Salkowski test:** Chloroform solution of the extract when shaken with concentrated sulphuric acid, lower layer turns to yellow on standing.

Detection of Steroids

- **Salkowski Tests:** Chloroform solution of the extract when shaken with concentrated sulphuric acid and on standing yields red colour.
- **Lieberman Burchardt tests:** Chloroform solution of the extract with few drops of acetic anhydride and one ml of concentrated sulphuric acid from the sides gives reddish ring at the junction of 2 layers.

PHARMACOLOGICAL SCREENING

Experimental Animals

Albino mice weighing between 25-30g were used for the study.The animals were procured two weeks prior to the study and maintained in institutional animal house, so that animals could acclimatize to the new environment.

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Identification

Number of animals/group-For the study six groups are made.Each group of animals contain six-six animals.

Selection of dose- The selection of dose of the test plant Tinospora cardifolia stem was done on the basis of the previous work of vipin kumar et al 2013, B.T.Kavitha et al 2011 and Javeed ahmed et al 2011. The animals were kept fasting for overnight providing only water, after which the extract was administered orally at doses of 100, 200 and 300mg/kg b.w. and observed for toxic symptoms up to 72 h. 200 mg/kg b.w was taken as the therapeutic oral dose for all the extracts.(B.T.Kavitha et al)(38) The aqueous extract of *T. cordifolia* was administrated orally in increasing dose up to 800 mg/kg. The rats were observed continuously for 14 h for behavioural, neurological, and autonomic profiles and after 24 and 72 h for any lethality.(vipin kumar et al 2013).(39).As per the studies dose were selected 200mg/kd body weight as therapeutic dose and 400mg as increasing dose. (Javeed ahmed et al 2011).(35) so we selected 200mg/kg and 400mg/kg body weight for our study.

Environmental condition-. A semi natural light cycle of 12:12 or 10:14 has light: dark was followed during the experiment. A room temperature range for mouse housing between 20 and 26 0C is recommended.

Accommodation- Cage temperature was 24-26 0C. A relative humidity at the level of 55 percent ± 15 percent (40-70) was maintained.

Diet-Animals had free access to food and fresh water provided *ad libitum* unless special permission has been obtained from Animal Ethics Committee. However, food but not water was withdrawn 8h before and during the experiments

Approval-The Institutional Animal Ethics Committee permission was obtained **(Ref no..awaited)** before starting the experiments on the animals. Animals had free access to food and fresh water provided *ad libitum* unless special permission has been obtained from Animal Ethics Committee. However, food but not water was withdrawn 8h before and during the experiments

Evaluation of Anticonvulsant Activity

The anticonvulsant potential of Tinospora cordifolia stem extract was screened using the following two models: Maximal electroshocks induced Seizure (MES) method

Experimental Design

Animals were randomly divided into six groups; each group having six animals.

MES Method: The mice of test groups were administered with extracts for seven days last day of dosing i.e.seventh day; test was started 60 min after administration of extracts and 30 min after standard drug (Phenytoin 50 mg/kg p.o.*(43*). The electroshock was applied via ear-clip electrodes separately to each mouse. The stimulus duration was 0.2 s and the current frequency was 50 mA (60 Hz). The animals were observed for the occurrence of tonic hind limb flexion, tonic hind limb extension, clonus and stupor and mortality for duration of 15 minutes, with following design:

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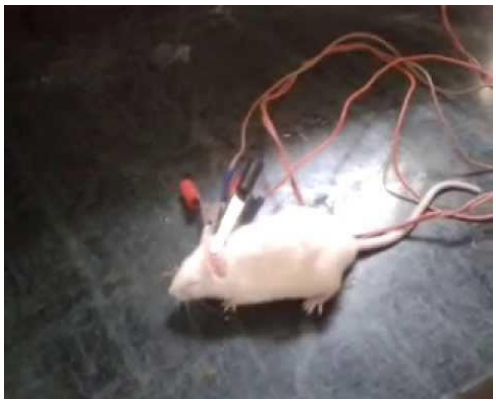
Electroconvulsiometer



Induction of seizures by electroshock in mice

1) **Group I (Negative control);** given distilled water (0.25 ml p.o.).
2) **Group II (Positive control);** received phenytoin (50 mg/kg p.o.).
3) **Group III (Test, T1);** received aqueous extract (200 mg/kg p.o.).
4) **Group 1V (Test, T2);** received aqueous extract (400 mg/kg p.o.).
5) **Group V (Test, T3);** received ethanolic extract (200 mg/kg p.o).
6) **Group VI (Test, T4);** received ethanolic extract (400 mg/kg p.o).

STATISTICAL ANALYSIS

All results were expressed as mean± standard error of mean (Mean±SEM). Results were analyzed by student't' test. Significance was established when probability value (p value) is less than 0.05. P values are denoted as * $p<0.05$ as significant, ** $p<0.01$ as highly significant and *** $p<0.001$ as very extremely significant.

RESULTS AND DISCUSSION

Phytochemical Screening of Extracts: The preliminary phytochemical screening of the ethanolic and aqueous extract of Tinospora cardifolia stem extract revealed the presence of flavonoids, Triterpenoids, Saponins, Tannins, carbohydrates, Alkaloids, steroids, protein & Amino acids.

Phytoconstituents present in ethanolic and aqueous stem extract of *Tinospora cardifoia*.

S.No.	Phytochemical Constituents	Test	Ethanolic Extract	Aqueous Extract
1	Alakaloids	**Mayer's Test**	+	+
		Dragendorff's Test	+	+
		Wagner's Test	+	+
		Hager's Test	+	+
2	Glycosides	**Modified Borntrager's Test**	+	+
		Legal's Test	+	+
3	Flavonoids	**Shinoda Test**	+	+
		Alkaline Reagent Test	+	+
		Zinc Hydrochloric Acid Reduction Test	+	+
		Lead Acetate Test	+	_

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4	Terpenoids	**Lebermann-Burchard reaction**	+	_
		Salkowski Test	+	_
5	Saponins	**Foam Test**	+	+
6	Tannins	**Gelatin Test**	+	+
7	Carbohydrate	**Molisch's Test**	+	+
		Benedict's Test	+	+
		Fehling's Test	+	+
8	Steroids	**Lebermann-Burchard reaction**	+	+
		Salkowski Test	+	_
9	Protein & Amino acid	**Millon's Test**	+	+
		Ninhydrin Test	+	+
		Biuret Test	+	+

Note: '+ve' sign indicates presence and '-ve' sign indicate absence

ANTICONVULSANT ACTIVITY OF EXTRACTS

Maximal Electroshock (MES) Method:- The mice were subjected to maximal electroshock convulsions with a current of 50 mA for 0.2 second via ear electrodes. The electrodes were moistened with saline solution before application. The resultant seizure passes through various phases: phase of tonic limb flexion, tonic limb extension, clonus, and stupor. The mouse was considered as protected if the drug prevented the appearance of hind limb tonic extensor component of the seizure.

Tonic hind limb flexion:- A comparison of mean duration of tonic hind limb flexion of control group with other groups indicates that there is a decrease in mean time of tonic hind limb flexion of groups III, IV, V & VI *i.e.* extracts exhibited dose dependent significant anticonvulsant activity. In group II (Standard), there is complete abolition of flexor phase, and 100 % protection of animal which is statistically significant. The EETC (400 mg/kg) and EETC (200mg/kg) showed 100 % protection of animal comparable with reference drug phenytoin (50 mg/kg p.o.) while AETC (400mg/kg) showed 100% protection of animal and AETC (200mg/kg) showed only 33.33% protection of animal comparable with reference drug phenyto in (50 mg/kg p.o.) for anticonvulsant activity.

Tonic hind limb extension:- A comparison of mean duration of tonic hind limb extension revealed that there is statistically significant decrease in mean duration of III, IV, V and VI groups when compared to that of control group. In group II (standard), there is complete abolition of tonic hind limb extension a manifestation of complete protection of animals. Also, the decrease in mean time of hind limb extension by the extracts of *Tinospora cardifolia* stem indicates their ability to inhibit or prevent seizures.

Clonus :- Analysis of results suggests that when compared with control group there is statistically significant decrease in mean duration of clonus in groups III, IV, V and VI. In group II no clonus activity is observed and there is complete abolition of clonus phase.

Stupor : There is a significant decrease in the mean duration of stupor phase in groups III, IV, V and VI, when compared to that of control group.

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Effect of vehicle (0.25 ml) on various phases of MES induced convulsions in experimental mice of Group I

Parameters (in seconds)	Serial no. of animals						
	1	2	3	4	5	6	Mean
Tonic hind limb flexion	11	13	11	10	13	10	11.3
Tonic hind limb extension	21	20	19	17	18	21	19.3
Clonus	117	113	116	113	114	115	114.6
Stupor	161	158	164	155	153	154	157.6

Effect of Phenytoin (50 mg/kg) on various phases of MES induced convulsion in experimental mice of Group II

Parameters (in seconds)	Serial no. of animals						
	1	2	3	4	5	6	Mean
Tonic hind limb flexion	2	3	4	5	4	3	3.5
Tonic hind limb extension	--	--	--	--	--	--	--
Clonus	--	--	--	--	--	--	--
Stupor	13	14	9	11	10	11	11.33

Effect of aqueous extract of test d rug (200 mg/kg) on various phases of MES induced convulsion in experimental mice of Group III

Parameters (in seconds)	Serial no. of animals						
	1	2	3	4	5	6	Mean

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Tonic hind limb flexion	8	10	7	8	10	7	8.3
Tonic hind limb extension	12	13	12	10	13	10	11.6
Clonus	58	64	70	51	63	58	60.66
Stupor	120	125	117	127	112	115	119.3

Effect of aqueous extract of test d rug (400 mg/k g) on various phases of MES ind uced convulsion in exp erimen tal mice of Grou p IV

Parameters (in seconds)	**Serial no. of animals**						
	1	2	3	4	5	6	Mean
Tonic hind limb flexion	7	9	7	8	5	9	7.5
Tonic hind limb extension	12	9	8	10	12	13	10.6
Clonus	55	61	63	64	55	53	58.5
Stupor	88	78	95	90	83	90	87.3

Effect of ethanolic extract of test drug (200 mg/kg) on various phases of MES induced convulsion in experimental mice of Group V

Parameters (in seconds)	**Serial no. of Animals**						
	1	2	3	4	5	6	Mean
Tonic hind limb flexion	7	3	4	3	8	7	5.3
Tonic hind limb extension	9	8	7	12	9	7	8.6
Clonus	51	60	59	50	56	52	54.5
Stupor	73	75	82	69	85	75	76.5

Effect of ethanolic extract of test d rug (400 mg/kg) on various phases of MES induced convulsion in experimental mice of Grou p VI

Parameters (in seconds)	**Serial no. of animals**						
	1	2	3	4	5	6	**Mean**

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Tonic hind limb flexion	7	2	5	3	6	3	**4.3**
Tonic hind limb extension	8	5	4	8	9	4	**6.3**
Clonus	48	54	49	55	50	52	**51.33**
Stupor	**55**	**60**	**63**	**64**	**55**	**53**	**58.33**

Comparison of mean duration (in seconds) of various parameters of different groups with control in MES method	**Dose**	**Flexion (HLTF)**	**Extension (HLTE)**	**Clonus**	**Stupor**
Control (Negative control)	Vehicle (0.25 ml)	11.3±0.557	19.33±0.667	114.6±0.666	157.6±1.76
Standard (Phenytoin)	50 mg/kg	3.5±0.42**	---	---	11.33±0.76**
AETC	200 mg/kg	8.3±0.557*	11.6±0.544*	60.66±2.654*	119.3±2.37*
AETC	400 mg/kg	7.5±0.619*	10.6±0.820*	58.5±1.927*	87.3±2.44*
EETC	200 mg/kg	5.3±0.918*	8.6±0.760*	54.66±1.748*	76.5±2.418*
EETC	400 mg/kg	4.3±0.802**	6.3±0.918**	51.33±1.145**	58.33±1.89**

All values expressed as MEAN ± SEM; n=6 mice in each group, by one-way ANOVA followed by Dunnet's multiple comparison Test (compared with control group) *p<0.05 and **p<0.01 AETC= Aqueous extract of *Tinospora cardifolia* EETC= Ethanolic extract of *Tinospora cardifolia*

Percentage Mortality & Percentage Protection in MES Model

Groups	**% Mortality**	**% Protection**
Control	66.66%	33.34%
Standard	00.00%	100%
AETC (200 mg/kg)	33.33%	66.6%
AETC (400 mg/kg)	00.00%	100%
EETC (200 mg/kg)	00.00%	100%
EETC (400 mg/kg)	00.00%	100%

Note: Result were the percentage mortality & percentage protection

CONCLUSION

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The results of the present study shown the positive test for presence of flavonoids and saponins in *Tinospora cardifolia stem* extract and screening of extracts in experimental models clearly confirmed the anticonvulsant activity of ethanolic extract of *Tinospora cardifolia stem*. These moieties in the leaves extract of may be responsible for the exhibited anticonvulsant activity of the plant. Hence, it can be concluded that the ethanolic extract of *Tinospora cardifolia stem* possesses significant anticonvulsant activity against MES as compared to aqueous extracts. Identification and quantification of active constituents responsible for the activity can be done by using various modern analytical techniques. A marked mechanism of action of the isolated components can be identified. Various dosage forms can be formulated as the drug showed significant activity similar to Phenytoin.

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