"EVALUATION OF ANTI-EPILEPTIC ACTIVITY OF TUBEROUS ROOTS OF *Ipomoea batatas* Lam BY MAXIMAL ELECTROSHOCK AND ISONIAZID INDUCED CONVULSIONS IN WISTAR RATS"

A Dissertation Submitted to

THE TAMILNADU Dr. M.G.R MEDICAL UNIVERSITY
CHENNAI-600 032

In partial fulfillment of the requirements for the award of degree of

MASTER OF PHARMACY
IN

BRANCH-IV → PHARMACOLOGY

Submitted by

AISHWARYA. S
Register No: 261925001

Under the guidance of
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Professor, Department of Pharmacology

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DECLARATION

I, hereby declare that this dissertation entitled **"EVALUATION OF ANTI-EPILEPTIC ACTIVITY OF TUBEROUS ROOTS OF *Ipomoea batatas* Lam BY MAXIMAL ELECTROSHOCK AND ISONIAZID INDUCED CONVULSIONS IN WISTAR RATS"** was carried out by me under the guidance and supervision of **Dr. P. Amudha**, **M.Pharm., Ph.D.,** Professor in the Department of Pharmacology at **C.L. Baid Metha College of Pharmacy,** Chennai-600097 for the academic year 2020-2021.This work has not been submitted in any other degree at any other university

Date:

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LIST OF ABBREVATIONS

Ach	Acetylcholine
AED	Anti-epileptic drug
ALT	Alanine aminotransferase
ALP	Alkaline phosphatise
AMP	Adenosine monophosphate
ANOVA	Analysis of variance
AS	Audiogenic seizures
AST	Aspartate amino transferase
Ca^{+}	Calcium ion
CAT	Computerized axial tomography
CK	Creatine kinase
Cl^{-}	Chloride ion
CNS	Central nervous system
CPCSEA	Committee for the purpose of Control and Supervision of Experiments on Animals
CSF	Cerebrospinal fluid
CT	Computerized tomography
EEG	Electroencephalogram
EEIB	Ethanolic extract of *Ipomoea batatas*
E/I	Excitation / Inhibition
GABA	γ-amino butyric acid
GAT	GABA transporter

GAD	Glutamic acid decarboxylase
Glu	Glutamate
H_2O	Water
H_2O_2	Hydrogen Peroxide
HPLC	High performance liquid chromatography
HPTLC	High pressure thin layer chromatography
Hcl	Hydrochloric acid
i.p	Intraperitoneal
ILAE	International League Against Epilepsy
ICES	International Classification of Epileptic Seizures
IPSPs	Inhibitory postsynaptic potentials
Kg	Kilogram
KOH	Potassium hydroxide
K^+	Potassium ion
LDH	Lactate dehydrogenase
LD_{50}	Lethal Dose – 50%
mA	Milli ampere
MEG	Magenetoencephalography
MES	Maxiamal Electric shock
mmol/dl	milli mole per decilitre
mg	Milligram
mol. Wt	Molecular weight

MRI	Magnetic resonance imaging
mL	Milliliter
MSI	Magnetic source imaging
N	Normality
NAD+	Nicotinamide adenine dinucleotide
Nm	Nano meter
NMDA	*N*-methyl-D-aspartate
NMDAR	*N*-methyl-D-aspartate receptor
NO	Nitric oxide
O_2-	Superoxide
OECD	Organization for Economic Co-operation and Development
PET	Positron emission tomography
POD	Peroxidase
p.o	Per orally
PTX	Picrotoxin
SE	Status epilepticus
Sec	Seconds
SPECT	Single photon emission computed tomography
STR	Strychnine
TLC	Thin layer chromatography
TLE	Temporal lobe epilepsy
WHO	World Health Organization

%	Percentage
µ	Micro
µl	Microliter
ºC	Degree Celsius
ng	Nanogram
b.w	Body weight
Hz	Hertz
INH	Isoniazid

Introduction…

1.INTRODUCTION:

According to WHO, Epilepsy is a chronic non communicable disease of the brain that affects around 50 million people worldwide. It is characterized by recurrent seizures, which are brief episodes of involuntary movement that may involve a part of the body (partial) or the entire body (generalized) and are sometimes accompanied by loss of consciousness and control of bowel or bladder function. [1]

Seizure episodes are a result of excessive electrical discharges in a group of brain cells. Different parts of the brain can be the site of such discharges. Seizures can vary from the briefest lapses of attention or muscle jerks to severe and prolonged convulsions. Seizures can also vary in frequency, from less than 1 per year to several per day.

Nearly 80% of epilepsy patients live in low- and middle-income countries. Many people with epilepsy respond to treatment in about 70% of cases. In low and middle-income countries, almost three-quarters of epilepsy patients do not receive the proper treatment they require. [1]

Epilepsy is the second common neurological disorder in India. It affects 70 percent of the population, with a high prevalence of 0.8 percent in children, and it can impact one out of every 200 people. [2]

According to the WHO, people with epilepsy in developing countries are not receiving enough treatment. [3]

It is a neuropsychological disorder which occurs due to over discharge of neurotransmitter substance. Epilepsy is caused by a variety of factors, including a scared tendency, chemical and hormonal imbalances, tumors, and brain damage. It also includes brain's sensitivity and low threshold for seizures, which causes the epilepsy. It can affect persons of any age, gender, or race at any stage of life. [4]

The common cause of epilepsy is exactly not known. It may be due to various reasons including trauma during birth process, head injury, childhood fevers, brain tumors, meningitis or drug induced. Genetic inheritance of single gene defects account for epilepsy in a small percentage of patients.

If an Epilepsy developed after a particular identifiable event (e.g., asphyxia, head injury, meningitis), then it is called symptomatic epilepsy, or if it developed without any identifiable cause, then it is termed as idiopathic epilepsy.

A seizure normally lasts for few minutes, and the patient usually recovers rapidly. Despite receiving regular medication, 20-30% of epileptic patients continue to experience seizures, requiring treatment with two or more antiepileptic drugs. [5]

The alternative drug therapy for the management of this disease can be, by the use of medicinal plants and their active principles. Control to seizures numerous conventional drugs came into existence. Most of the epileptic patients need poly therapy of conventional anticonvulsants and still not 100% cured. [6]

Antiepileptic drug therapy is the mainstay of treatment for most patients with recurrent Seizures. The antiepileptic drugs act by three basic mechanisms,

- Increased activity of GABA
- Decreased glutamate activity and
- Modification of ionic conductance

Approximately one-third of the patients develop refractory epilepsy requiring treatment with a combination of two or more antiepileptic drugs. [7]

So now a day we are focusing herbal medicines to get relief with the symptoms of epilepsy. The medicinal plants for the study were selected in such a way that their availability is maximized in many parts of the world. [8]

According to the World Health Organization (WHO), 4 billion people or 80% of the world's population use herbal medicine for some aspect of primary health care. [9]

The literature reveals that plants contain a large diversity of natural products that have demonstrated anti-epilepsy are like *Erythrophleum ivorense*, *Hypericum perforatum*, *Piper methysticum, Actaea racemose.* [10-13]

The plant *Ipomoea batatas* Lam belongs to family Convolvulaceae. **It is commonly known as Sweet potato** is an extremely versatile and delicious vegetable that possesses high nutritional value. It is also a valuable medicinal plant having anti-cancer, antidiabetic, and anti-inflammatory activities. Sweet potato is now considered a valuable source of unique natural products including some that can be used in the development of medicines against various diseases such as, hypertension, dysentery, constipation, fatigue, arthritis, rheumatoid diseases, hydrocephaly, meningitis, and kidney ailments. [14]

2. EPILEPSY - LITERATURE REVIEW:

2.1 DEFINITION:

2.1.1. EPILEPSY:

The word "epilepsy" comes from the Greek and means to be taken, seized or attacked. Epilepsy is a condition characterized by repeated seizures due to a disorder of the brain cells. It is a life-long tendency, though the seizures may start at any time during life and occur sporadically or frequently.

Some of the epilepsies are confined to particular age groups. Some suffer from it their whole lives and others only for a few years. [15]

According to the International League against Epilepsy (ILAE), epilepsy is defined by any of the following conditions

- At least 2 unprovoked (or reflex) seizures occurring > 24 h apart.
- one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least60%) after 2 unprovoked seizures, occurring over the next 10 years.
- Diagnosis of an epilepsy syndrome. [22,23]

2.1.2 SEIZURE:

A seizure is a result of excessive nerve-cell discharges in the brain. It is seen as a sudden abnormal function of the body, often with loss of consciousness, an excess of muscular activity, or sometimes a loss of it, or an abnormal sensation.

The excessive nerve-cell discharges or excitation may remain in a small area of the brain (a localized lesion or focus) giving rise to partial (focal) seizures or start immediately in the whole brain or spread from the small area (focus) to the whole brain and spinal cord giving rise to generalized seizures.

Not only may these discharges vary in site, but also in severity and extent, therefore a wide variation of clinical forms is seen.

A seizure is also referred to as a convulsion, fit, or attack. However, the words "convulsion" or "fit" are usually used to refer to seizures with tonic-clonic muscle movements.[15]

2.2 EPIDEMIOLOGY:[16,17,18]

Epilepsy is one of the world's oldest recognized conditions, with written records dating back to 4000 BCE. Fear, misunderstanding, discrimination and social stigma have surrounded epilepsy for centuries. This stigma continues in many countries today and can impact on the quality of life for people with the disease and their families.

Epilepsy accounts for a significant proportion of the world's disease burden, affecting around 70 million people worldwide. The estimated proportion of the general population with active epilepsy (i.e., continuing seizures or with the need for treatment) at a given time is between 4 and 10 per 1000 people. [1]

INCIDENCE:

Incidence is a measure of the number of new cases of a medical condition that occur in the population during a measured amount of time, usually one year. There are approximately 2 lakhs new cases of seizures and epilepsy that occur each year. The lifetime incidence of seizures is about 5% to 10%. [16]

PREVALENCE:

Prevalence is the total number of existing cases of a disease in a specific population at a stated point in time. The overall lifetime prevalence of epilepsy was 7.60 per 1,000 population. [16]

INCIDENCE AND PREVALENCE OF EPILEPSY BASED UPON COUNTRIES:

In high-income countries, there are estimated to be 49 per 100 000 people diagnosed with epilepsy each year. In low- and middle-income countries, this figure can be as high as 139 per 100 000. This is likely due to the increased risk of endemic conditions such as malaria or neurocysticercosis; the higher incidence of road traffic injuries; birth-related injuries; and variations in medical infrastructure, the availability of preventive health programs and accessible care. Nearly 80% of people with epilepsy live in low- and middle-income countries. The prevalence of epilepsy is 2.7 million Americans of all ages. Approximately 10% of Americans will have a seizure in their lifetime. Every year about 300,000 people have the first seizure in their lifetime. [17]

INCIDENCE AND PREVALENCE OF EPILEPSY BASED UPON GENDER AND AGE:

Incidence and prevalence of epilepsy are slightly higher in men than in women. The difference might be explained by the different prevalence of the most common risk factors and the concealment of the condition in women for socio cultural reasons in certain regions.

The incidence of epilepsy is higher in the youngest and oldest age-groups, with estimates of 86 per 100,000 per year in a well-defined population in the first year of age, a trend to decrease to about 23–31 per 100,000 in people aged 30–59 years, and a subsequent increase up to180 per 100,000 in the over 85 age-group.In children, the incidence of epilepsy is highest in the first year of life and declines to adult levels by the end of 10 years of age. [16]

2.3 INTERNATIONAL CLASSIFICATION OF EPILEPSY: [15, 20,21,22,24]

2.3.1 INTERNATIONAL CLASSIFICATION OF EPILEPSY -1981 (OLD VERSION OF ILAE CLASSIFICATION):

The ILAE revised classification of epileptic seizures was published in 1981.

It divides seizures into two broad types: **Partial seizure and Generalized seizure**.

Seizures that begin in a focal or restricted part of the cortex are called partial seizures, whereas seizures that involve the entire cortex in a symmetric and synchronous fashion from the onset are called generalized seizures.

Outline of the International Classification of Epileptic Seizures:

PARTIAL SEIZURES:

a. Simple partial seizures (consciousness not impaired)

- With motor symptoms
- With sensory symptoms
- With autonomic symptoms
- With psychic symptoms

b. Complex partial seizures (with impaired consciousness)

- Simple partial seizures followed by impairment of consciousness
- With impairment of consciousness at seizure onset

c. Partial seizures evolving to secondarily generalized seizures

GENERALIZED SEIZURES:

a. Absence seizures (petit mal)
b. Myoclonic seizures
c. Clonic seizures
d. Tonic seizures
e. Tonic clonic seizures (grand mal)
f. Atonic seizures (drop attacks)

- Typical absences
- Atypical absences

2.3.1.1 PARTIAL SEIZURES:

The partial seizures are first divided into two groups, those where the consciousness is maintained, and where there is an impairment of the consciousness. Both these groups may develop into generalized seizures, then forming a third group.

TYPES OF PARTIAL SEIZURE: [15]

a. SIMPLE PARTIAL SEIZURES:

The patient does not lose consciousness, and therefore is able to tell what happened, but the experience may be so strange that they may not be able to express themself properly. Whatever happened dependents on the location of the affected area.

In *motor seizures***,** the focus is on the primary motor cortex. There are twitching's, starting in a distal part of the extremity, or in the face. The twitching may remain there or spread up the whole extremity and even become completely generalized.

The *sensory seizures*, have their focus in the post central gyrus (primary sensory cortex). There might be feelings of tingling, pins and needles, cold or heat, or numbness of a limb. Sometimes there may be strange feelings with visual signs or hearing or smelling sensations.

The *autonomic seizures* are associated with foci in the temporal lobe. There may be a sensation rising from the epigastrium to the throat, palpitations, sweating or flushing.

The *psychic symptoms* may consist of changes in mood, memory, or thought (thinking). There may be distorted perceptions (time, space, or person) or problems with language. Structured hallucinations could occur (music, scenes).

These simple partial seizures are usually only recognized as epileptic seizures when they develop into generalized seizures.

b. Complex partial seizures:

In this type of seizure, the patient has impaired consciousness, there is no complete loss of consciousness, they are slightly aware of what is going on, but they cannot respond to anything, neither can they change his behavior during an attack. There is an aura, a strange feeling in the stomach rising up to the throat and head, or a sensation of light, smell, sound or taste. The seizure may occur with changes in perception, e.g., of time (time seems to pass too slowly or too fast), of light or sound or space. The surroundings may suddenly seem completely strange and different in scale (things seem larger or smaller than usual), or there is déjà vu (a sensation of things having happened before). These feelings can cause the patient a great deal of anxiety.

Sometimes the seizure occurs with hallucinations or with psychomotor symptoms such as automatisms, automatic movements, e.g., pulling at the clothes, chewing, lip smacking, or repeated aimless movements. These automatisms may become very complex, the patient is able to perform difficult tasks, or travel somewhere, but later not remember having done such a thing. During an automatism the patient may become aggressive and violent when restrained. There is a slow recovery after a complex partial seizure, with a period of confusion. After the attack there is complete amnesia of it.

These seizures were previously called 'psychomotor seizures', and as the localization of the abnormal discharge is often in the temporal lobe, the epilepsy is often called 'temporal lobe epilepsy' (the focus might occur in the frontal lobe too).

c. PARTIAL SEIZURES SECONDARY GENERALIZED:

Both the simple partial seizures and the complex partial seizures may become generalized tonic-clonic seizures.

2.3.1.2 GENERALIZED SEIZURES:

Generalized seizures involve the whole brain, including the reticular system, thus producing abnormal electrical activity throughout both hemispheres. Immediate and complete loss of consciousness is characteristic of generalized seizures. It occurs suddenly and unexpectedly, and if the patients fall, they may injure themselves. The generalized seizures consist of six different seizure types, of which the primary generalized tonic- clonic seizure (GTCS) is the most common.

TYPES OF GENERALIZED SEIZURE:

a. Absence seizures:

Formerly known as **Petitmal seizure**. These are short periods of loss of consciousness lasting only a few seconds (not more than half a minute). Absence seizures occur in children, they are much less dramatic but may occur more frequently. There is a blank stare, an interruption of ongoing activity, sometimes they will stop speaking in mid-sentence, brief upward rotation of the eyes, and stares vacantly for a few seconds, with little or no motor disturbance. Patients are unaware of their surroundings and recover abruptly with no aftereffects. The EEG pattern shows a characteristic rhythmic discharge during the period of the seizure. The rhythmicity appears to be due to oscillatory feedback between the cortex and the thalamus, the special properties of the thalamic neurons being dependent on the T-type calcium channels.

Absence seizures with special features:

Eyelid myoclonia with associated interruption of awareness is the characteristic seizure type in Jeavon's syndrome. Myoclonic seizures (discussed below) can also be associated with momentary loss of awareness.

b. Myoclonic seizures:

These seizures consist of sudden, brief, shock-like muscle contractions, either occurring in one limb, or more widespread and bilateral. They may be single jerks, or jerks repeated over longer periods. They are often seen in combination with other seizure types occurring in special epileptic Syndromes.

c. Clonic seizures:

These seizures are generalized seizures, where the tonic component is not present, only repetitive clonic jerks (clonic jerks are repetitive rhythmic flexing and stretching of limbs). When the frequency diminishes the amplitude of the jerks do not.

d. Tonic seizures:

Tonic seizures are sudden sustained muscle contractions, fixing the limbs in some strained position. There is immediate loss of consciousness. Often there is a deviation of the eyes and head towards one side, sometimes rotation of the whole body. They are seen mainly in pediatric practice.

e. Generalized tonic clonic seizure:

This type of seizure formerly known as Grand mal seizures; also known as convulsions or convulsive seizures. The patient loses consciousness, falls down, sometimes with a scream, and develops a generalized stiffness (the tonic phase). Breathing stops, as all the muscles of the trunk are in spasm, and the patient becomes cyanotic, the head is retracted, the arms flexed, and the legs extended. After a while, this tonic phase is followed by the clonic phase, when the muscles alternately contract and relax, resulting in clonic movements. With this jerking the patient might bite his tongue, pass urine, or sometimes stool. The clonic phase may last several minutes. When all the jerking stops, and the patient regains consciousness and may feel very tired with a headache and confusion. Patient has no memory of what happened and may find themself on the floor in a strange position. Often, they fall into a deep sleep. These seizures are not as frequent as absence seizures. Their frequency may vary from one a day to one a month or once a year, or even once every few years.

f. Atonic seizures (astatic seizures):

There is a sudden loss of muscle tone causing the head or a limb to drop, and often the patient falls suddenly to the floor. They are therefore also called "drop attacks". There is loss of consciousness, a sudden onset and no post-ictal phase. The patient stands up and continues what they were doing. The seizure is very short, only seconds, but may occur several times a day. The patients often present with scars or fresh wounds on chin, cheek or forehead, or the back of the head. A protective helmet is recommended for these patients.

2.3.2 INTERNATIONAL CLASSIFICATION OF EPILEPSY -2017 (NEW VERSION OF ILAE CLASSIFICATION- 2017). [21]

2.3.2.1 BASIC VERSION OF ILAE CLASSIFICATION OF SEIZURE 2017

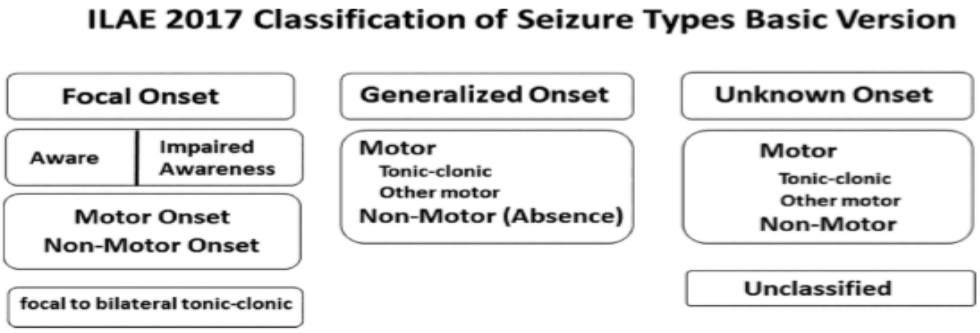


Figure:1 Basic version of ILAE classification

FOCAL SEIZURE:

The term partial seizure was replaced by the new term Focal seizure.

Based upon the level of awareness it was classified into Aware and impaired awareness.

- **Awareness:**

Awareness is defined as knowledge and understanding that something is occurring or exists.

- **Impaired awareness.**

The term simple partial seizure was replaced by Focal aware, and the term complex partial seizure was replaced by Focal impaired awareness

In basic classification, the next step after considering the level of awareness for a focal seizure entails defining the onset as "motor" or "non-motor."

GENERALIZED ONSET:

The term "generalized" seizure has been retained the same.

FOCAL TO BILATERAL TONIC-CLONIC SEIZURES:

Secondarily generalized seizures are now called as "focal to bilateral tonic-clonic seizures

2.3.2.2 EXPANDED VERSION OF ILAE CLASSIFICATION OF SEIZURE 2017

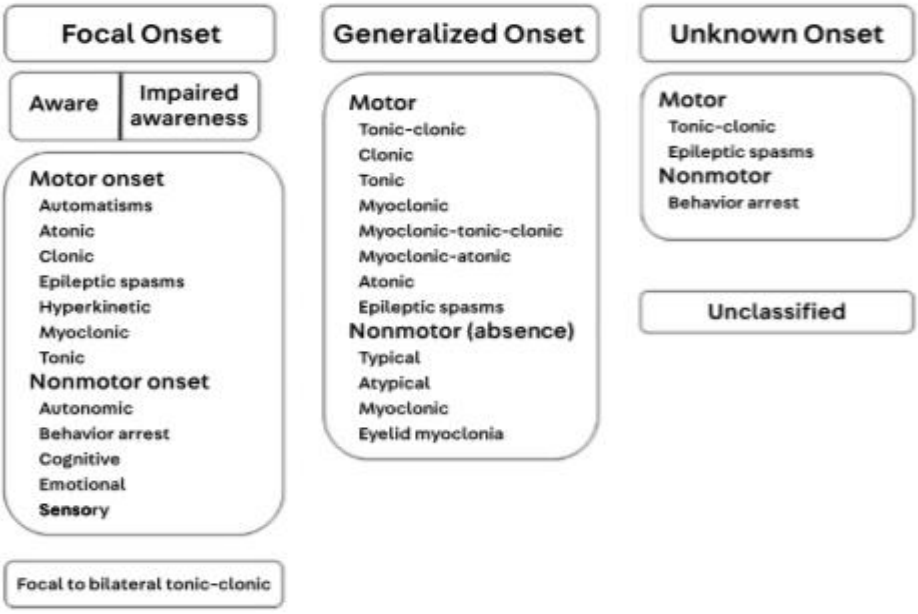


Figure: 2 Expanded version of ILAE classification of seizure 2017.

FOCAL MOTOR ONSET CLASSIFICATION:

- **Automatisms:**

  Automatisms are correlated, purposeless, redundant motor activities that might seem normal in different conditions. For examples oral automatisms, lip smacking and manual automatisms which includes tedious hand movements such as tapping.

- **Atonic seizure:**

  Atonic seizures are described by deficiency of tone in one body part.

- **Clonic seizure:**

  Clonic seizures are characterized by repeated, stereotypical jerking movements.

- **Epileptic spasm:**

  Epileptic spasms present in small kids with flexion of the abdomen and flexion or augmentation of the arms. If epileptic spasms occur in new-borns, then they are referred as infantile spasms.

- **Hyperkinetic seizure:**

  Hyperkinetic seizure includes thrashing or pedalling. It is also called as or excessive muscular movement seizures.

- **Myoclonic seizure:**

  Focal myoclonic seizures present with jerking, but the jerking is irregular, and they are not rhythmic.

- **Tonic seizure:**

  Tonic seizures are also referred as motor seizure with stiffening of neck, limbs, and increased tone.

FOCAL NONMOTOR ONSET CLASSIFICATION:

- **Autonomic:**

  Autonomic seizure involves changes in blood pressure, heart rate, skin tone, gastrointestinal sensations and piloerection.

- **Behavioural arrest:**

  Behavioural arrest seizures are portrayed by stopping of movement, clinical indications incorporate a blank stare and cessation from talking or moving.

- **Cognitive:**

  Patients with non-motor cognitive seizures can encounter changes in language capacity, thinking, or related higher cortical functions.eg- hallucination, jamaisvu and déjàvu

- **Emotional:**

  Emotional seizures are associated with emotional changes like anxiety, fear, dread, or pleasure.

- **Sensory:**

  Focal sensory seizures are classified by changes in sensory phenomena like vision, hearing, taste, smell, numbness, pain, or shivering.

FOCAL TO BILATERAL TONIC-CLONIC SEIZURE:

These seizures originate in one area of the brain and then spreads to both sides of the brain. This spread is typically clearly seen on EEG.

GENERALIZED MOTOR ONSET CLASSIFICATION:

- **Generalized tonic-clonic:**

  The duration of Generalized tonic-clonic seizures is 1to 3 minutes and result in prompt loss of consciousness or awareness.

- **Tonic phase:**

  The initial tonic phase is as hardening of all limbs. The patient might moan or cry at the outset as air is constrained past the vocal cords. The tongue may likewise be chomped during this stage.

- **Clonic phase:**

  The clonic phase seizure happens after the tonic phase and is portrayed by sustained repeated jerking of the limbs. Bladder or bowel Incontinence can occur. A patient with generalized tonic seizure will have stiffening of all limbs. A generalized clonic seizure is characterized by bilateral and sustained rhythmic jerking.

- **Generalized myoclonic seizures:**

  Generalized myoclonic seizures are related with unpredictable and not necessarily coordinated bilateral jerking of limbs, eyelids or eyes and face.

- **Myoclonic-tonic-clonic seizures:**

  Myoclonic-tonic-clonic seizures it's a new type of seizure followed by a tonic-clonic seizure; it usually begins with irregular jerking on both sides. Myoclonic-tonic-clonic seizures are common in juvenile myoclonic epilepsy.

- **Myoclonic-atonic seizures:**

  Myoclonic-atonic seizures it's also a new type of seizure are characterized by an initial irregular jerking followed by loss of tone on both sides. These seizures are common in epilepsy with myoclonic- atonic seizures (Doose syndrome).

- **Atonic seizures:**

  Atonic seizures brief and happen when there is respective deficiency of tone and the muscles become limp. The person will fall in ground for no obvious reason. This type of seizure is also called as drop attacks.

- **Epileptic spasms:**

  Epileptic spasms occur in clusters with flexion at the trunk and flexion or expansion of the limbs. As like focal epileptic spasms, an EEG might be expected to recognize whether the seizure is generalized.

GENERALIZED NONMOTOR CLASSIFICATION:

- **Typical absence:**

  Typical absence seizures present with an unexpected stopping of activities with eye fluttering, head gesturing, or different automatisms followed by immediate recovery.

- **Atypical absence:**

  Atypical absence seizures are like absence seizures however have different provisions including more slow beginning, delayed recovery and more articulated changes in tone.

- **Eyelid myoclonia:**

  A myoclonic absence seizure starts with a couple of sporadic jerks followed by an absence seizure. Eyelid myoclonia is characterized by jerks of the eyelids and up deviation of the eyes. Light and shutting the eyes can precipitate this generalized seizure. Eyelid myoclonia with absence seizures is seen in Jeavons syndrome.

UNKNOWN SEIZURES:

Unknown Seizures of unknown onset can be classified by motor or non-motor presentations. If information is inadequate or if the seizure cannot be categorized, then the seizure is considered unclassified.

2.4 PHASES IN SEIZURES: [15]

PRODROMAL PHASE:

This phase begins a few hours or even days before the actual seizure and should not be confused with the aura. Prodromal symptoms are headache, irritability, insomnia, bad temper, depression or increased activity.

AURA:

An aura precedes the seizure by seconds or a few minutes. It is the beginning of the seizure and signals the focal onset of the seizure. The symptoms depend on the location of this focus. The feelings of the aura are often vague and indescribable, leading to extreme fear. Strange epigastric sensations, dreamlike experiences, unpleasant smells, etc. may occur.

POST-ICTAL PHASE:

This phase may be absent, brief or may last several hours, and sometimes even days. There is usually a deep sleep and waking up with headache, tiredness, irritability, vomiting, confusion, muscular aches or ataxia. Transient paralysis of a part of the body, known as Todd's paresis may occur for a few hours or days. Altered speech or aphasia may occur when the dominant hemisphere of the brain has been involved. Altered behavior and emotional outbursts may occur, and if these are interfered with violent behavior

INTERICTAL:

This is the time between seizures. A lot of people with epilepsy, including more than half of all people with temporal lobe epilepsy, suffer emotional disturbances between seizures. These disturbances range from mild fear to pathological levels of anxiety and depression. However, anxiety and depression are by far the most common, and these interictal problems are often more incapacitating and difficult to control than the seizures themselves.

2.5 RISK FACTORS OF EPILEPSY: [15]

A risk factor is something that makes a person more likely to develop a certain disease or condition. Common risk factors for seizures and epilepsy are listed below. Sometimes, a person may have one of these risk factors, but they are not the cause of the seizures. In some cases, one or more risk factor may lead to a person developing seizures and epilepsy.

These are some common risk factors for epilepsy that are listed below:

PROBLEMS OR INJURIES ASSOCIATED WITH BRAIN:

- Abnormal blood vessels in the brain
- Serious brain injury
- Lack of oxygen to the brain
- Bleeding into the brain
- Infection in the brain, like meningitis, encephalitis,
- Brain tumor
- Inflammation of the brain

RISK FACTORS ASSOCIATED WITH MEDICAL HISTORY:

- Having seizures in the first month of life
- Having seizures within days after a head injury (called "early posttraumatic seizures")
- Fever-related (febrile) seizures that last longer than usual
- Long episodes of seizures or repeated seizures (called "status epilepticus")
- Family history of epilepsy or fever-related seizures
- Using illegal drugs, like cocaine

OTHER HEALTH CONDITIONS THAT MAKE EPILEPSY MORE LIKELY:

- Autism spectrum disorders
- Cerebral palsy
- Intellectual and developmental disabilities
- Stroke that is caused by blocked arteries (called an "ischemic stroke")
- Alzheimer's disease (late in the illness)

2.6 ETIOLOGY: [15,19]

Epilepsy is a condition with recurrent seizures. These may be idiopathic or symptomatic. Epilepsies can start at any age.

In approximately 60-75% of all cases, there is no known cause. Of the remaining cases, there are several frequently identified causes.

If an acute disturbance, a metabolic like hypocalcemia, or an infection such as meningitis, or a poisoning or any of the other causes mentioned below are recognized and treated adequately, epilepsy will not follow.

If the acute disorder was too severe, or not treated correctly, convulsions might have become prolonged and continuous, resulting in anoxia of the brain with subsequent brain damage followed by epilepsy.

In some infections, e.g., tuberculosis, toxoplasmosis, cysticercosis, the disease may leave calcified areas in the brain.

Some diseases—tuberous sclerosis, Sturge-Weber's syndrome—present with calcifications in the brain.

A hemorrhage, abscess or tumour may present with repeated seizures but when the blood, pus or tumour has been successfully removed surgically, no epilepsy needs to follow.

Any head injury, including birth trauma, may result in permanent changes of brain tissue, i.e., scar tissue.

Any area with abnormal brain tissue (calcifications, scars, or vascular abnormalities) may act as a focus from where abnormal activity of the neurons takes place causing "symptomatic epilepsy".

The causes mentioned below might lead to epilepsy:

METABOLIC CAUSES: [15]

- Hypoglycaemia
- Hypomagnesaemia
- Hypocalcaemia
- Electrolyte imbalance
- Pyridoxine deficiency
- Uraemia
- Phenylketonuria
- Porphyria
- Hyperbilirubinemia (kernicterus)

INFECTIONS:

INTRACRANIAL INFECTIONS:

- Meningitis
- Encephalitis
- AIDS
- Neurosyphilis
- Cerebral malaria
- Toxoplasmosis
- Rabies
- Cysticercosis
- Encephalopathy

EXTRACRANIAL INFECTIONS:

- Febrile illnesses
- Pertussis
- Tetanus.

TRAUMA:

- Birth trauma
- Head injury
- Hypothermia
- Cold injury

ANOXIA

- Birth asphyxia.

TOXIC:

- Alcohol and withdrawal from alcohol
- Carbon monoxide poisoning
- Drugs poisoning such as high doses of penicillin, strychnine, etc.
- Lead poisoning
- Organo-phosphorus insecticide poisoning.

SPACE-OCCUPYING LESIONS:

- Haemorrhage
- Tuberculoma
- Abscess
- Cysticercosis
- Tumor
- Toxoplasmosis

CIRCULATORY DISTURBANCES:

- Cerebro-vascular accident (stroke)
- Sickle-cell crisis
- Vascular anomalies

CEREBRAL OEDEMA:

- Hypertensive encephalopathy
- Eclampsia.

CONGENITAL:

- Malformations of the brain (hydrocephalus, microcephaly, etc.)
- Tuberous sclerosis (Bourneville disease)
- Neurofibromatosis (von Recklinghausen disease)
- Encephalo-trigeminal facial angiomatosis (Sturge-Weber's syndrome)

DEGENERATIVE DISEASES:

- Niemann-Pick disease
- Dementias
- Cerebromacular degeneration.

GENETIC FACTORS:

In many cases of epilepsies there is a genetic factor which influences the threshold for seizures Even in symptomatic epilepsy this factor plays a role, e.g., many people have had a head injury but only some develop epileptic seizures afterwards. If one parent has idiopathic epilepsy the risk of a child developing epilepsy is 4–6%, compared to a risk of 0.3-0.5% in the general population. If both parents have idiopathic epilepsy, the risk rises to 12–20%. In parents with symptomatic epilepsy, there is still a slight increase in the risk—up to 2% in European studies.

EFFECTS OF BRAIN MATURATION:

The resistance to seizures also depends on the maturation of the brain. The resistance in the first year of life (except during the newborn period) is very high, and therefore only a severe injury such as severe brain damage since birth, meningitis or tuberous sclerosis, will produce seizures. Between the ages of one and four the resistance to seizures is very low.

A simple febrile disease may precipitate seizures. After the age of four the resistance is again high, and seizures are mainly seen in already-brain damaged children. This resistance diminishes again from about the seventh year when the idiopathic epilepsies tend to appear.

OTHER PRECIPITATING FACTORS:

Apart from the condition and maturation of the brain and the genetic threshold, other factors may trigger a seizure. These factors may be different for each individual patient. Some patients learn which factors are important for them, and so they can modify their behaviour or activities to try to avoid seizures

The most common factors are mentioned below:

- Flashing lights (resulting in reflex epilepsy)
- Hyperventilation
- Lower alertness, sleep itself and lack of enough sleep
- Emotion
- Physical stress
- Special smells, sounds or sensations of touch
- Alcohol
- Hormonal changes, e.g., during menses
- High fever
- Overhydration

2.7 SYMPTOMS OF EPILEPSY:

Almost all seizures are relatively brief, lasting from a few seconds to a few minutes. Most seizures last from 1 to 2 minutes. When a seizure stops, people may have the below symptoms.

• Headache

• Numbness or tingling (pins and needles) in a specific body part

• Confusion

• Sore muscles

• Unusual sensations (taste, smell, etc.)

• Extreme tiredness

• Loss of bowel or bladder control (soiling or wetting). [34]

2.8 PATHOPHYSIOLOGY OF EPILEPSY[28,29,30,31]

The cerebral cortex of human consists of 3 to 6 layers of neurons.

The cortex consists of two classes of neurons. the principal neurons and interneurons. The function of principal neuron is to send information to neurons that are located in the distant area of brain. These principal neurons form excitatory synapses on post-synaptic neuron. interneurons influence the activity of nearby neurons, and these interneurons forms inhibitory synapses.

Basic Neurophysiology and Neurochemistry causing excitability:

The action potential is the basic mechanism of neuronal excitability; a hyperexcitable state can be caused by increased excitatory synaptic neurotransmission, decreased inhibitory neurotransmission, changes in voltage-gated ion channels, or changes in intra- or extracellular ion concentrations favoring membrane depolarization. When numerous syncs are activated at the same time, a hyperexcitable condition might develop.

The depolarization of the neuronal membrane causes action potentials, which propagate along the axon and cause neurotransmitter release at the axon terminal. As a result of local changes in membrane potential caused by net positive inward ion fluxes, the action potential happens in an all-or-none fashion. As a result of the activation of ligand-gated channels, membrane potential fluctuates.

NEUROTRANSMITTERS:

Neurotransmitters are chemicals that are released by a synapse's presynaptic nerve terminal and then bind to specific postsynaptic receptors for that ligand. The binding of ligands causes channel activation and ion flow into or out of the cells. Glutamate, gamma-amino-butyric acid (GABA), acetylcholine (ACh), norepinephrine, dopamine, and serotonin are the primary neurotransmitters in the brain.

GLUTAMATE AND ITS RECEPTORS:

The amino acid glutamate is the important excitatory neurotransmitter. Glutamate receptors are divided into numerous categories. Glutamate receptors have been detected postsynaptically on excitatory main cells as well as inhibitory interneurons, as well as on several types of glial cells.

GLUTAMATE IONOTROPIC RECEPTORS:

The ionotropic subclasses of glutamate receptors include AMPA, kainate receptor, NMDA receptor these allow influx of ions upon activation by glutamate. Na^+ and K^+ permeable to all ionotropic glutamate receptors, and the inflow of Na^+ and outflow of K^+ through these channels contribute to membrane depolarization and the production of the action potential. In resting state Mg^{2+} ions block the Ca^{2+} channel of NMDA receptors but during depolarization the

Mg^{2+} ions are displaced and the become permeable to $Ca^{2+,}$ this influx of Ca^{2+} leads to depolarization of the cell leading to neuronal injury in the condition of excessive neuronal activation leading to cell death, a process termed excitotoxicity.

GLUTAMATE METABOTROPIC RECEPTOR:

The metabotropic receptor, which acts through receptor-activated signal transduction involving membrane-associated G-proteins, is the other major kind of glutamate receptor. Metabotropic receptors are divided into at least three subgroups based on agonist potency, signal transduction mechanism, and pre- vs post-synaptic location.

GABA:

GABA, the most powerful inhibitory neurotransmitter, interacts with two different types of receptors: $GABA_A$ and $GABA_B$. $GABA_A$ receptors are located postsynaptically, whereas $GABA_B$ receptors are located presynaptically, and can thus control synaptic release.

$GABA_A$ RECEPTORS:

$GABA_A$ receptors are permeable to Cl^- ions in the adult brain; when activated, Cl^- inflow hyperpolarizes the membrane and suppresses action potentials. As a result, $GABA_A$ receptor agonists like barbiturates and benzodiazepines are widely known for their ability to reduce seizure activity.

$GABA_B$ RECEPTORS:

$GABA_B$ receptors are connected with second messenger systems rather than Cl^- channels, and their presynaptic placement causes attenuation of transmitter release.

The activation of K^+ channels by second messenger systems frequently results in a hyperpolarizing current. Certain $GABA_B$ agonists, like as baclofen, have been shown to aggravate hyper excitability and seizures in patients.

NETWORK ORGANIZATION INFLUENCING NEURONAL EXCITABILITY:

Neurons are linked in complex arrays to provide extra degrees of control over neural excitability. Changes in the function of one or more cells in a circuit can have a big impact on both nearby and far away neurons. The excitability of a network of linked neurons can be increased by sprouting excitatory axons to form new connections. Loss of inhibitory neurons, on the other hand, will increase the network's excitability. The loss of excitatory neurons that excite or "drive" the inhibitory neurons can also diminish inhibitory function.

MECHANISMS OF FOCAL SEIZURE INITIATION AND PROPAGATION:

During a seizure, hyper synchronous discharges may start in a small, isolated area of the cortex and subsequently spread to other areas.

Two events occur simultaneously during seizure initiation:

1) high-frequency bursts of action potentials, and

2) hyper synchronization of a neuronal population.

Epileptiform activity is defined as a continuous neuronal depolarization followed by a burst of action potentials, a plateau-like depolarization associated with the conclusion of the action potential burst, and then a fast repolarization followed by hyperpolarization at the level of single neurons. This sequence is called as paroxysmal depolarizing shift.

The influx of extracellular $Ca^{2+,}$ which leads to the activation of voltage-dependent Na^{+} channels, influx of Na^{+}, and formation of recurrent action potentials, causes the bursting activity that results from the relatively protracted depolarization of the neuronal membrane. Depending on the cell type, the subsequent hyperpolarizing after potential is mediated by GABA receptors and Cl^{-} influx, or by K^{+} efflux. Depending on the cell type, the subsequent hyperpolarizing afterpotential is mediated K^{+} by GABA receptors and Cl^{-} influx, or by K^{+} efflux.

When there is enough activity to attract adjacent neurons, seizure propagation, the process by which a partial seizure expands inside the brain, happens. This causes a loss of surround inhibition, allowing seizure activity to spread into nearby areas via local cortical connections and further away via long association pathways like the corpus callosum.

Intact hyper polarization and a zone of surrounding inhibition generated by inhibitory neurons generally prevent bursting activity from propagating.

Repetitive discharges result in:

1) an increase in extracellular K^{+}, which blunts the extent of hyperpolarizing outward K^{+} currents, tending to depolarize neighboring neurons.

2) Ca^{2+} buildup in presynaptic terminals, resulting in increased neurotransmitter release

3) depolarization-induced activation of the excitatory amino acid receptor subtype NMDA, resulting in increased Ca^{2+} influx and neuronal activity

CURRENT THEORIES AS TO HOW INHIBITION AND EXCITATION CAN BE ALTERED AT THE NETWORK LEVEL:

So far investigation has led to two theories of the cellular network changes that lead the hippocampus to become hyperexcitable, one of the most prevalent sites of partial seizures.

The first theory claims that a selective loss of interneurons reduces the normal feed-forward and feedback inhibition of the dentate granule cells, an important group of principal neurons.

The second theory proposes that synaptic remodeling occurs after injury, resulting in recurrent excitatory connections between nearby dentate granule cells via axonal "sprouting. "More recently, it has been postulated that the loss is due to excitatory neurons, rather than GABAergic inhibitory neurons, which ordinarily drive inhibitory interneurons, which inhibit the dentate granule cells.

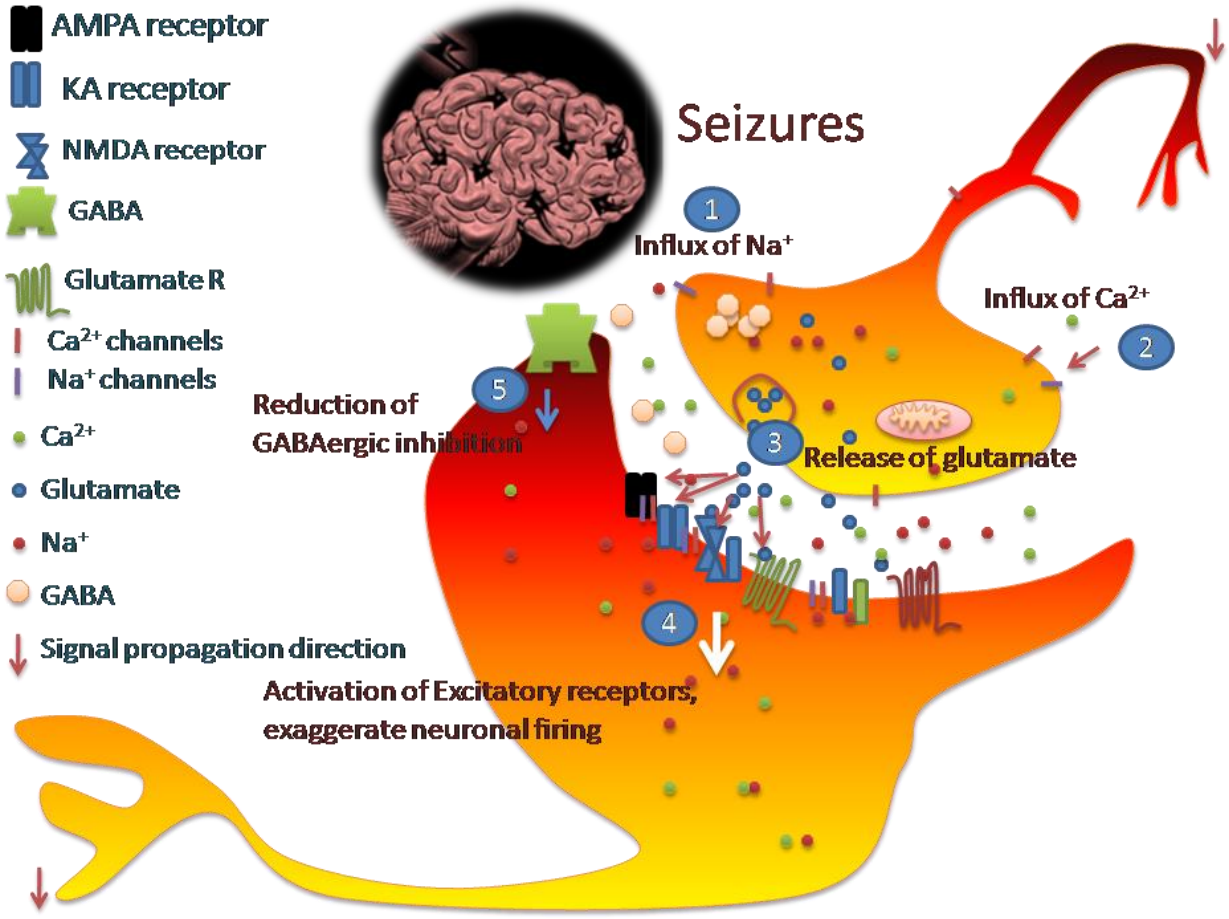


Figure:3 Mechanism of Seizure

2.9 DIAGNOSTIC METHODS OF EPILEPSY:

- CT scan
- EEG
- MEG/MSI
- MSRI
- PET
- MRI
- Functional MRI
- SPECT

2.9.1 COMPUTERIZED AXIAL TOMOGRAPHY (CT OR CAT) SCAN: [39]

CT scans use X-rays to take images of the brain. (CT scans are not suitable for a pregnant Patient because the X-rays could affect an unborn baby). Images from a CT scan are less detailed than those from MRI scans. During a CT scan patients lie on a couch which slides into the scanner. Unlike MRI scanners, CT scanners doesn't make loud noises. Some people may have a CT scan if they are not able to have an MRI scan. For example, if they have a heart pacemaker, if they might need to have an anesthetic to have an MRI, or if information is needed quickly about what might be causing their seizures.

2.9.2 MAGNETIC RESONANCE IMAGING (MRI): [38]

MRI is becoming the foremost important diagnosis and management of patients with epilepsy. The MRI plays an important role in locating and defining the probable anatomic epileptogenic lesions. MRI is more likely to point out an abnormality during a patient with focal seizures, abnormal neurologic findings, or focal discharges. MRI is more sensitive diagnostic method when compared to CT and is therefore preferred, especially for the detection of dysgenesis, malformation in the cortex, or hippocampal sclerosis treatment.

FUNCTIONAL MRI (FMRI):

A functional MRI measures the changes in blood flow that occur when specific parts of brain are working. fMRI may be used before surgery to identify the exact locations of critical functions, such as speech and movement, so that surgeons can avoid injuring those places while operating.

2.9.3 SINGLE-PHOTON EMISSION COMPUTERIZED TOMOGRAPHY (SPECT): [40]

This type of test is used primarily when the MRI and EEG doesn't pinpoint the exact location of brain where the seizures are originating. A SPECT test uses a small amount of low-dose radioactive material that's injected into a vein to create a detailed, 3D maps of the blood flow activity in brain during seizures. Areas of higher blood flow during a seizure may indicate where seizures occur.

2.9.4 ELECTROENCEPHALOGRAM (EEG): [35-37]

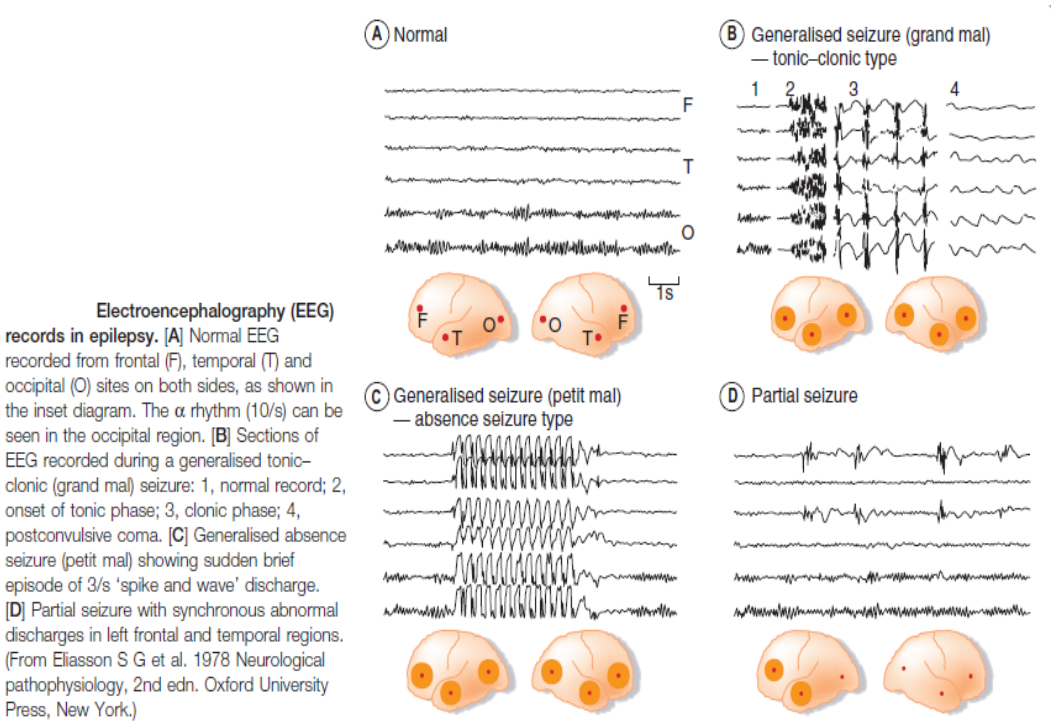
It is the most well-known demonstrative technique to determine epilepsy, in this strategy electrodes are connected to the scalp with a glue-like substance or cap. These electrodes will record the electrical movement of cerebrum and it will also distinguish the strange electrical action potential associated with brain. A normal EEG will ideally, include wakefulness, sluggishness, sleepiness that the predominance of epileptiform irregularities fluctuates in these conditions. The primary reason in getting EEG is to assess patients with known seizures is to allow an exact conclusion of the seizure type and epilepsy disorder so that treatment might be fittingly coordinated or to analyze obscure paroxysmal spells that may address seizures.

ROLE OF EEG IN DIAGNOSIS OF EPILEPSY:

Differential finding of paroxysmal neurological events, helps in Distinction between a focal and generalized seizure disorder**.**

ROLE OF EEG IN MANAGEMENT OF EPILEPSY:

In the assessment of risk recurrence after an unprovoked seizure**,** helps in appropriate selection of antiepileptic treatment**,** identification of epileptogenic region in epilepsy surgery persons helps to investigate the cognitive decline status if any, helps to detect the non-convulsive status, helps in Monitoring in convulsive status.



Electroencephalography (EEG) records in epilepsy. [A] Normal EEG recorded from frontal (F), temporal (T) and occipital (O) sites on both sides, as shown in the inset diagram. The α rhythm (10/s) can be seen in the occipital region. [B] Sections of EEG recorded during a generalised tonic–clonic (grand mal) seizure: 1, normal record; 2, onset of tonic phase; 3, clonic phase; 4, postconvulsive coma. [C] Generalised absence seizure (petit mal) showing sudden brief episode of 3/s 'spike and wave' discharge. [D] Partial seizure with synchronous abnormal discharges in left frontal and temporal regions. (From Eliasson S G et al. 1978 Neurological pathophysiology, 2nd edn. Oxford University Press, New York.)

Figure:4 EEG Records in Epilepsy

2.9.5 POSITRON EMISSION TOMOGRAPHY (PET SCAN) –

This scan uses a radioactive substance, called a tracer, to look for information about how the brain works. It can also show if there's a structural cause for the epilepsy.

PET scans use a small amount of low-dose radioactive material that's injected into a vein to help visualize metabolic activity of the brain and detect abnormalities. Areas of the brain with low metabolism may indicate where seizures occur.

2.10 FIRST AID FOR CONVULSIVE EPILEPTIC SEIZURES [41]

- Stay calm.
- Note the time.
- Prevent others from crowding round.
- Put something soft under the person's head like a jacket to prevent injury.
- Only move if they are in a dangerous place, such as in the road or at the top of stairs.
- Move things away from them if there is a risk of injury.
- Do not attempt to restrain the convulsive movements. Allow the seizure to take its course.
- Do not put anything in the person's mouth.

2.11 TREATMENT OF EPILEPSY:

ANTI-EPILEPTIC DRUGS: [37]

The first line of treatment for epilepsy is antiepileptic drugs (AED). Antiepileptic (sometimes known as anticonvulsant) drugs are used to treat epilepsy as well as non-epileptic convulsive disorders. Patients with epilepsy usually need to take drugs continuously for many years, so avoidance of side effects is particularly important. Nevertheless, some drugs that have considerable adverse effects are still quite widely used even though they are not drugs of choice for newly diagnosed patients.

HISTORY OF MEDICATIONS:

For more than 100 years, various kinds of medications have been used to treat seizure disorders.
1861 – Bromides the first medication used to control of seizures. Side effects were severe.
1912 – Phenobarbital Effective, but sedating.
1936 – Phenytoin Known as the "miracle drug" of its day.
Today – Many new medications are available, including a number approved since 1990.
Future – Research continues to be done in an effort to find a safe, effective anticonvulsant.

RATIONALISING THE USE OF ANTIEPILEPTIC DRUGS (AEDS):

Most people can have their epilepsy controlled by one or, at the most, two AEDs. If combination therapy is required, a second AED should be chosen which complements the first drug and attention should be paid to each one's influence on the other's metabolism.

Monotherapy with the most appropriate AED should be pursued as far as possible before changing to or adding other agents. Care should be taken to find the minimum effective dose for any AED and to cease drugs which are clearly non-efficacious.

A routine clinical review should be scheduled every three months for people using AEDs. A careful history and examination are more reliable in determining effectiveness and adverse effects of treatment than drug serum levels in most situations. The exception is phenytoin, which can reach toxic levels with small dose increases. Monitor for adverse effects, which might indicate the need for dose reduction. [33]

POSSIBLE ADVERSE EFFECTS:

- Ataxia
- Dysarthria
- Drowsiness
- Nausea and vomiting
- Skin rash

- Decline in cognition
- Agitation
- Other disturbed behaviours
- Rare cases of fatal liver failure have been linked to valproate.
- Vigabatrin and clonazepam may both stimulate aggression in people with developmental disabilities.
- Many people who have developmental disabilities find it difficult to co-operate with sampling for blood tests.
- Gingival hypertrophy (overgrowth of gums) occurs in approximately 30% of people who use phenytoin.

ANTI-EPILEPTIC DRUG CLASSIFICATION [42-45]

- Barbiturates-Phenobarbitone
- Deoxybarbiturate-Primidone
- Hydantoin-Phenytoin
- Iminostilbene- Carbamazepine
- Succinimide-Ethosuximide
- Aliphatic carboxylic acid- Valproic acid, Sodium valproate
- Benzodiapene- Clonaepam, Diazepam, Clobazam
- Phenyltriazine-Lamotrigine
- Cyclic GABA analogue- Gabapentin
- Newer drug- Vigabatrin, Topiramate, Tiagabine, Levetiracetam.

Table 1: Drug profile for Anti-Epileptic drugs

Drugs	**Mechanism of action**	**Uses**	**ADR**
Phenobarbitone	Enhancing the activation of GABA – A receptor and thus facilitating the GABA mediated opening of chloride ion channel	Generalized tonic – clonic, Simple and complex partial seizure, Status epilpticus	Behavioural abnormality Dimunation of Intelligence Impairment of Learning and memory Hyperactivity in chidren Rashes Megaloblastic anemia Osteomalacia.

Drugs	**Mechanism of action**	**Uses**	**ADR**
Primidone	Gets metabolized to phenobarbitone and phenyl ethyl malanomide	Generalized tonic –clonic Partial seizure	Anemia, Leucopenia, Lymph node enlargement Psychotic reaction
Phenytoin	Blocks the sodium channel in activated state Delays recovery of sodium channel from inactivation Blocks high frequency firing	Generalized tonic - clonic Simple and complex partial seizure. Trigeminal neuralgia	Gingival hyperplasia Hirsutism Hypersensitivity MegalobasticAnemia Osteomalacia Foetal hydantion syndrome. Hyper glycemia
Carbamazepine	Blocks the sodium channel	Complex partial seizure, Generalized tonic clonic. Simple partial seizure	Neurotoxicity Sedation Dizziness Vertigo Diplopia Ataxia
Ethosuximide	Reduces the low threshold calcium currents (T currents) in the thalamic neurons.	Used only in absence seizure	Tiredness, Mood swings Agitation, Drowsiness Hypersensitivity, Blood dyscrasias, Fatal bone marrow depression
Valproic acid	By increasing the level of GABA either by increasing its synthesis or by decreasing the metabolism of GABA, Blocks the sodium channel	Simple Partial seizure, Complex partial seizure, Absence seizure, Generalized tonic clonic attacks	Alopecia Curling of hair, Increased blood ammonia, Rashes, Thrombocytopenia, Rise in serum transaminase, Ataxia, Anorexia, Neural tube defects during pregnanc

Drugs	**Mechanism of action**	**Uses**	**ADR**
Clonazepam	It binds to the GABA A receptor present in the neurons of the CNS, it binds at a site which is different from GABA binding site and increases the affinity of GABA for the receptors which leads to increase in the frequency of chloride channel opening in response to GABA, leading to increased flow of chloride ions resulting in hyperpolarization	Absence seizure, Myoclonic and akinetic epilepsy, Infantile spasms	Sedation, Dullness Motor disturbances Ataxia Salivation Increased respiratory secretion Irritability.
Clobazam	Same MAO as of Clonazepam	Partial seizure, secondarily generalized tonic-clonic, absence seizure, myoclonic seizure, atonic seizure.	Dizziness, vertigo, ataxia, disorientation, amnesia, impairment of psychomotor skills.
Diazepam	Same MAO as of Clonazepam	Febrile convulsion in children's, status epilepticus, tetanus, eclampsia	Drowsiness, confusion, dizziness, amnesia, lethargy, blurred vision, weakness, disorientation, day time sedation.
Lamotrigine	Prolongs the inactivation of sodium channel, Inhibits the release of excitatory amino acids like glutamate.	Partial seizure, absence seizure, myoclonic seizure, generalized seizure.	Sleepiness, Dizziness Diplopia Ataxia, Vomiting,

Drugs	**Mechanism of action**	**Uses**	**ADR**
Gabapentin	Acts by increasing the release of GABA	Simple and complex partial seizure, pain due to diabetic neuropathy, postherpetic neuralgia.	Sedation, Tiredness, Dizziness and Unsteadiness
Vigabatrin	Inhibits the enzyme GABA transaminase thereby increasing the GABA level.	Kindled seizure, partial seizure.	Psychosis, Depression, Amnesia, Visual field contraction, Motor disturbance
Topiramate	Blocks sodium channel, increases GABA A receptor currents, blocks AMPA receptors.	Simple and complex partial seizure, Generalised tonic clonic seizure.	Ataxia, Sedation, Weight loss, Parasthesias Renal stones, Psychiatric symptoms, word finding difficulties.
Tiagabine	GABA mediated neuronal inhibition by depressing GABA transporter GAT 1which removes synaptically released GABA into neurons and Glial cells.	Kindled seizure	Mild sedation, Asthenia, Nervousness, Amnesia, Abdominal pain.
Levetiracetam	MAO not exactly known	Kindled seizure, Refractory partial seizure.	

RESPONSE TO MEDICATION:

On average, 70% of seizures are successfully controlled with one anti-epileptic medication. The remaining 30% of seizures are, thus far, resistant to medications.

2.12 OTHER TREATMENTS OF EPILEPSY:

2.12.1 SURGICAL INTERVENTION:

When antiepileptic medications fail to provide adequate control over seizures, surgery may be an option. Medically refractory epilepsy might affect up to 30% of epileptic patients. The patients suffering from continued seizures in spite of proper anti-epileptic drug treatment, then surgical intervention might be a choice to them. Surgical resection of the seizure focus brings about diminished recurrence or elimination of seizures with progress in quality of life, Seizure freedom is accomplished in up to 76% of patients after resection.

SURGICAL PROCEDURES TO TREAT EPILEPSY: [50-54]

Based upon the type of seizure (focal or generalized) the surgical procedure is determined. Complete resection of the epileptogenic focus prompts the best outcomes, that is freedom from seizures. In some patients the epileptogenic zone overlaps with eloquent cortex which results in neurologic deficits, where resection is impossible, hence in this type of scenario non resective procedures may be indicated**.**

Surgical procedures for epilepsy patients can be classified into three types.

a. Surgical resection or disconnection:

This is the most common surgical procedure. Surgical resection is the optimal procedure for patients who experience seizures with focal or regional onset. The eligibility for this method is, the epileptic zone is fairly circumscribed and restricted to a non-eloquent region that can be securely removed. The presence of a lesion on MRI increases the probability of surgical candidacy and of accomplishing freedom from seizures. if there is no lesion detected during the time of MRI ,then the seizure focus which needs to be resected is determined by intracranial ictal electroencephalography and through functional imaging such as SPECT (Single-photon emission computed tomography) and PET (Positron Emission Tomography).

b. Ablative procedures:

It is a less invasive medical procedure, advantage of this method is exact focusing of the seizure-delivering foci, and minimum disruption of healthy brain tissue. it is mostly used for well-delineated lesions causing epilepsy. The risk associated with this method is brain oedema and delayed benefit.

c. Therapeutic devices:

Randomized controlled trials of electrical stimulation of peripheral nerves, especially vagus stimulation, and stimulation of brain cortex or deep brain nuclei for the treatment of epilepsy are undertaken. Stimulation procedures show a better result in seizure frequency and are often reserved for patients who cannot undergo resective epilepsy surgery.

Adverse effects of surgery: [50,51]

Factors related with seizure freedom after surgical procedure incorporate, seizures without loss of awareness, complete or broad resection of the lesion, and delayed febrile seizures. Infection, Aseptic meningitis, Deep vein thrombosis or pulmonary embolus, Intracranial hematoma, Pneumonia, Cerebrospinal fluid leak, Hydrocephalus, Dysphasia, Hemiparesis, Psychiatric, Intracranial hematoma, Hydrocephalus, Minor visual field defect, Minor or temporary hemiparesis, Verbal memory decline.

2.12.2 KETOGENIC DIET:

The ketogenic diet, which is very high in fats and low in carbohydrates, was first developed almost 80 years ago. It makes the body burn fat for energy instead of glucose. It has a success rate of 75%, stopping seizures in 50% of individuals and further reducing seizures in 25% of cases. Side effects of a ketogenic diet may include dehydration, constipation, slowed growth because of nutritional deficiencies and a build-up of uric acid in the blood, which can cause kidney stones. These side effects are uncommon if the diet is properly and medically supervised.

2.13 RECENT ADVANCES IN EPILEPSY TREATMENT: [46,47,48]

2.13.1 LASER ABLATION:

In this ablation is done by MRI guided laser interstitial thermal therapy (MRgLITT). The visualize thermal therapy system is composed of 15W 980 nm diode laser with cooled laser application system along with an image processing workstation. In this method the applicator is inserted to the target by a stereotactic method, and laser treatment is applied in the MR scanner, along with MR thermal imaging to visualize the thermal ablation. MRgLITT is a stereotactic surgical procedure. Previously it has been used in the treatment of brain metastases.

This method is considered as more reliable, precise and safest procedure. But however the Risk associated with this surgical procedure is haemorrhage and infection.

2.13.2 STEREOTACTIC RADIO SURGERY:

In this technique ionizing radiation is used to target the deep-seated lesions, without causing damage to the surrounding tissues. The ionizing radiation will break the chemical bond resulting in the production of free radicals. The ionizing radiations are produced by photon and proton beam accelerator. Photon accelerators such as cyber knife and gamma knife are the most widely used source of ionizing radiation. The anticonvulsive effect of Stereotactic radio surgery was first observed in the treatment of tumors and vascular lesions

The advantage of this method is deep-seated and multiple lesions are treated without any surgical approach, by avoiding the brain injury.

The disadvantage of the method includes injury to collateral tissue secondary to radiation, latent period of efficacy and late onset of secondary malignancies.

Uses: It is mainly used in the treatment of Hypothalamic hamartoma and Hippocampal sclerosis and also used in the treatment of generalized epilepsy by corpus callosotomy.

2.13.3 NEUROMODULATION:

Functional neurosurgery is a process of surgical manipulation of brain behaviour by either stimulating or removing the population of neuron. The successful application of functional neurosurgery is in the treatment of movement disorders such as idiopathic Parkinson's disease, essential tremor, chronic pain disorders, psychiatric disorders, and epilepsy. The Functional neurosurgery in epilepsy refers to the stimulation of cell populations, either by cranial nerve or directly by implanted electrode.

2.13.4 VAGUS NERVE STIMULATION: [49]

In vagus nerve stimulation, a device is used to prevent or reduce seizure, this device will send regular, small pulses of electrical energy to brain via the vagus nerve in the neck. The vagus stimulator device consists of implantable, powered generator and a lead. The VNS therapy lead is placed surgically round the left vagus within the carotid sheath and connected to a subcutaneous programmable pacemaker device that's placed over the left chest wall. Electrical signals are produced from the pulse generator, and they are transmitted to the vagus nerve via the VNS therapy lead VNS has caused sudden interruption of an ongoing seizure and decreases the frequency of chronic seizures.

The high synchronization of the cortical and thalamocortical regions are the basis of the complex partial seizures in, VNS intervention will break these synchronized networks and thus reduce a seizure activity. Left cervical VNS is an accepted therapy for refractory epilepsy.

Disadvantages of this method includes-Voice alteration, Hoarseness, Cough, Tingling, Dyspnea, Vocal cord paralysis Implant site infection, Left facial nerve paralysis, Horner syndrome.

2.13.5 TRIGEMINAL NERVE STIMULATION:

Similar to vagus nerve stimulation, this device would stimulate specific nerves to reduce frequency of seizures. But unlike vagus nerve stimulation, this device would be worn externally so that no surgery to implant the device is needed. In studies, external trigeminal nerve stimulation provided improvements in both seizure control and mood.

2.13.6 DEEP BRAIN STIMULATION.

In deep brain stimulation, electrodes are implanted into a specific part of brain, typically in thalamus. The electrodes are connected to a generator implanted in the chest. The generator regularly sends electrical pulses to the brain at timed intervals and may reduce the seizures. Deep brain stimulation is often used for people whose seizures don't get better with medication.

2.13.7 RESPONSIVE NEUROSTIMULATION.

In this type of treatment an implantable, pacemaker-like devices will help significantly to reduce the seizure. These responsive stimulation devices analyse brain activity patterns to detect when the seizures start, and they deliver an electrical charge or drug to stop the seizure before it causes impairment.

2.13.8 TRANSCRANIAL MAGNETIC STIMULATION.

TMS applies focused magnetic fields on areas of the brain where seizures occur, this is a method to treat seizures without the need for surgery. It may be used for patients whose seizures occur close to the surface of the brain.

2.14 ANIMAL MODELS IN EPILEPSY: [55,56]

Animal models of epilepsy provide information about the pathogenesis of epileptic disorder and for studying the efficacy of potential therapies and their mechanism of action.

2.14.1 KAINIC ACID MODEL:

Kainic acid was one of the first compounds used to model Temporal Lobe Epilepsy in rodents. It is an L glutamate analogue, the systemic or intra-cerebral administration of which causes neuronal depolarization and seizures, preferentially targeting the hippocampus.

2.14.2 PILOCARPINE MODEL:

Pilocarpine is a muscarinic acetylcholine receptor agonist. Systemic or intracerebral injection of pilocarpine causes seizures that build up into a limbic Status epilepticus. Structural damages and subsequent development of spontaneous recurrent seizures resemble those of human complex partial seizures.

2.14.3 HYPERTHERMIC SEIZURE:

Febrile seizures are frequent in early life, with a prevalence of 2%–5% in children younger than 5 years (defined as seizures longer than 15 minutes with focal onset and possible recurrence within 24 hours). Animal models of febrile seizure were developed to investigate whether febrile seizures induce neuronal damage leading to epileptogenesis, and which mechanisms generate febrile seizures.

2.14.4 AUDIOGENIC MODEL:

Audiogenic seizures (AS) are generalized seizures provoked by high-intensity acoustic stimulation. Activation of auditory pathways is crucial for AS development, and the inferior colliculus in the auditory midbrain plays a key role in audiogenic seizure initiation, although other structures participate in AS progression.

2.14.5 STRYCHNINE (STR) INDUCED CONVULSIONS:

The convulsing action of strychnine is due to interference with postsynaptic inhibition mediated by glycine. Glycine is an important inhibitory transmitter to motoneurons and interneurons in the spinal cord, and strychnine acts as a selective, competitive antagonist to block the inhibitory effects of glycine at all glycine receptors. Strychnine-sensitive postsynaptic inhibition in higher centers of the CNS is also mediated by glycine. Compounds which reverse the action of strychnine have been shown to have anxiolytic properties.

The rodents are treated either orally with the test compound or the standard (e.g., diazepam 5 mg/kg). One hour later the rodents are injected with 2 mg/kg strychnine nitrate i.p. The time until occurrence of tonic extensor convulsions and death is noted for a period of one hour.

2.14.6 PICROTOXIN (PTX) INDUCED CONVULSIONS:

Picrotoxin induced convulsions are used to further evaluate CNS-active compounds. Picrotoxin is regarded as a $GABA_{A-}$ antagonist modifying the function of the chloride ion channel of the $GABA_A$ receptor complex. The rodents are treated either orally or i.p. with the test compound or the standard (e.g., 10 mg/kg diazepam i.p.). Thirty min after i.p. treatment or 60 min after oral administration the animals are injected with 3.5 mg/kg s.c. picrotoxin and are observed for the following symptoms during the next 30 min.

1. Onset of convulsion, duration of clonic convulsion, duration of tonic convulsion
2. Incidence (number of mice showing convulsions); mortality

2.14.7 PENTYLENETETRAZOL (PTZ) INDUCED CONVULSIONS:

This assay has been used primarily to evaluate antiepileptic drugs. The rodents are treated either with test compound or the reference drug injected sc. or i.p. or given orally. Fifteen min after sc.-injection, 30 min after i.p. injection, or 60 min after oral administration 60 mg/kg MTZ (Metrazol) are injected subcutaneously, and Each animal is placed into an individual plastic cage for 1 hour and they are observed for the following symptoms.

1. Onset of convulsion, duration of clonic convulsion, duration of tonic convulsion
2. Incidence (number of mice showing convulsions); mortality.

2.14.8 YOHIMBINE-INDUCED CONVULSIONS:

Antagonism against yohimbine-induced seizures in rodents is considered to be a model predictive of potential anxiolytic and GABA-mimetic agents. Rodents are individually placed in clear plastic cylinders and test compounds are administered i.p. 30 min prior to 45 mg/kg s.c. of yohimbine HCl. The animals are observed for the onset and number of clonic seizures for 60 min.

2.14.9 BICUCULLINE TEST IN RATS:

Seizures can be induced by the $GAGA_A$-antagonist bicuculline and are antagonized by known anti-epileptics. Female Sprague-Dawley rats are injected i.v. with 1 mg/kg bicuculline.
At this dose, a tonic convulsion appears in all treated rats within 30 sec after injection. Test compounds are administered orally 1 or 2 hours before bicuculline injection.

And the following parameters are evaluated
1.Dose-response curve.
2.Percentage of protected animals is evaluated.
*3.ED*50-values and 95% confidence limits are calculated by probit analysis.

2.14.10 KINDLED RAT SEIZURE MODEL:

Kindling, results from repetitive sub convulsive electrical stimulation of certain areas of the brain. Initially, local after discharge is associated with mild behavioral signs; however, with continued stimulation electrical activity presumably spreads, and generalized convulsions occur. Although the pathogenesis of kindled seizures is not fully understood, it serves as a useful tool for investigating the efficacy of experimental anticonvulsant agents.

Adult female Sprague-Dawley rats (270–400 g) are used. The rats are implanted with an electrode in the right amygdala region. At least 1 week has to elapse before electrical stimulation of the brain is started. After discharge threshold is determined for each rat. Duration and amplitude, behavioral seizure duration and seizure stage are recorded with increased stimuli after discharges. Seizure severity is classified into 5 stages. Rats are kindled on the first stimulation causing a stage 5 seizure which is followed by at least 2 consecutive stage 5 seizures. The animals are tested on the day before and after treatment with the test compound (i.p. or orally). Amygdala stimulation is applied at various time intervals and the following results are calculated.

The occurrence and the degree of seizures are compared between test group and control

2.14.11 GENETIC ANIMAL MODELS OF EPILEPSY:

Several animal species exhibit epilepsy with spontaneous recurrent seizures such as dogs, rats, and mice It was described spontaneous epileptic rats which are double mutants and exhibit both tonic and absence-like seizures.

Spontaneous epileptic rats are obtained by mating the tremor heterozygous rat (tm/+) with the zitter homozygous rat (zi/zi) found in a Sprague-Dawley colony. The behavior of the spontaneous epileptic rats is recorded weekly for 2 h on videotapes. The frequency of tonic convulsions and wild jumping occurring in the absence of external stimuli are recorded. Under anesthesia silver ball-tipped and monopolar stainless-steel electrodes are chronically implanted in the left frontal cortex and hippocampus. An indifferent electrode is placed on the frontal cranium. The frequency of absence-like seizures and tonic convulsions, as well as the duration of each seizure, are measured on the EEG. A mild tactile stimulus is given on the back of the animal every 2.5 min to induce consistent tonic convulsions.

Compounds are given i.p. or orally and the following parameters are observed

1. The number of seizures and the duration of each seizure are obtained, and the total duration of the seizures is calculated every 5 min before and after injection of the drug.
2. Percent changes between values before and after drug administration are calculated.

TABLE:2 COMMON METHODS USED TO INDUCE CONVULSION IN ANIMAL MODELS [57]

Animal models	**Methods to induce convulsion**	**Types of seizures**
In vivo model **Electrical stimulation:**	Maximal electroshock (MES)	Generalized tonic-clonic seizures
	Kindling	Chronic partial seizures
In vivo model **Chemoconvulsants:**	Pentylenetetrazol (PTZ)	Myoclonic and absence seizures
	Strychnine	Acute simple partial seizures
	Picrotoxin	Acute simple partial seizures
	Isoniazid	Clonic-tonic seizures
	Lithium pilocarpine	Status epilepticus
	Yohimbine	Clonic seizures
	Bicuculline	Acute simple partial seizures
	4-aminopyridine	Clonic-tonic seizures
	N-methyl d- aspartate	Status epilepticus
	N-methyl d- aspartate Penicillin	Generalized tonic-clonic and Absence Seizures
***Invitro* model**	• Hippocampal slices • $GABA_A$ receptor binding Assay	Complex partial seizures
Genetic model	• Photosensitive baboons • Audiogenic seizures mice • Totterer mice and seizures -prone Mouse Strains • Genetically epilepsy- prone rats	Generalized tonic- clonic seizures

Plant.... Profile.....

3. PLANT PROFILE

DESCRIPTION

- Plant name: *Ipomoea batatas* Lam
- Family: Convolvulaceae

SCIENTIFIC CLASSIFICATION: [58,59,60]

- Kingdom: Plantae
- Phylum: Magnoliophyta
- Class: Eudicotyledones
- Order: Solanales
- family: Convolvulaceae
- Genus: Ipomoea
- Species: batatas
- Common name: sweet potato

VERNACULAR NAMES:

- Tamil: Sarkaraivalli kizhangu, Seeni kizhangu, Vellikkilangu.
- English: Mithaalu
- Telugu- Chilakada dumpa
- Malayalam- Madhurakizhangu

Sweet potato, *Ipomoea batatas* (L.) Lam, is a perennial crop which belongs to the morning glory family or Convolvulaceae. It is a popular staple food of the tropical and subtropical areas with a nutritional benefit evidenced by increase in its cultivation and consumption. Sweet potato is mostly harvested for its tubers. Sweet potato contains several phytochemicals, which are important for human health. Several reports have indicated that the phytochemicals in sweet potato possess multifaceted actions, including antioxidant, antimutagenic, anti-inflammatory, antimicrobial and anti-carcinogenesis and thus are important for several health-promoting functions in humans.

Figure: 5 Whole plant of *Ipomoea batatas* Lam.

Figure: 6 Tuberous roots of *Ipomoea batatas* Lam

Tuberous-rooted perennial, usually grown as an annual; top herbaceous, stems forming a running vine up to 4 m long, usually prostrate and slender, with milky juice, lateral stem-branches arising from the short stem and usually not branched; leaves ovate-cordate, borne on long petioles, palmately veined, angular or lobed, depending on variety, green or purplish; flowers rare, especially in United States, like common morning glory, white or pale violet, axillary, funnel-shaped, borne singly or in cymes on short peduncles; pods round; seeds 1–4 per pod, flattened, hard-coated, angular. [58,59,60]

The leaf decoction of *Ipomoea batatas* Lam is used in folk remedies for tumors of the mouth and throat. Reported to be alterative, aphrodisiac, astringent, bactericide, demulcent, fungicide, laxative, and tonic, sweet potato is a folk remedy for asthma, bugbites, burns, catarrh, ciguatera, convalescence, diarrhea, dyslactea, fever, nausea, renosis, splenosis, stomach distress, tumors.

LITERATURE....

REVIEW.....

4. LITERATURE REVIEW:

1) Anti-inflammatory activity:

- Marcelia Sugata et al (2015) reported that, the extracts of Purple-fleshed *Ipomoea batatas* had potential anti-inflammatory activities. The Anthocyanin-rich extracts could suppress the production of nitric oxide (NO) and some proinflammatory cytokines, such as NFκ-β, TNFα, and IL-6, in LPS-induced macrophage cell there by producing the anti-inflammatory effect. [61]

2) Anti-Cancer effect:

- Marcelia Sugata et al (2015) reported that, the tuberous extracts of *Ipomoea batatas* possess anticancer effect. And it could inhibit the growth of some cancer cell lines, such as human breast cancer (MCF, gastric cancer SNU1, and colon adenocarcinoma (WiDr), in concentration-and time-dependent manner. It also has the ability to induce apoptosis in MFC-7 cancer cell line through extrinsic and intrinsic pathways. [61]

3) Anti-Arthritis activity:

- Muhammad Majid et al. (2018) reported that, Carrageenan-induced paw edema, croton oil-induced ear and anal edema inhibition and Complete Freund's Adjuvant (CFA)-induced antiarthritic assays were carried out using the ethyl acetate and methanol extracts of *Ipomoea batatas* tuber and roots at a dose of 300 mg/kg body weight on Sprague-Dawley rats. Serum levels of interleukins IL-1β and IL-6 and nitric oxide (NO) were assessed to measure the inhibition of inflammation. The High percentage of inflammation inhibition by the roots of I. batatas clearly suggests that *Ipomoea batatas* is a potential agent for curing acute and chronic inflammatory arthritis. [62]

4) Antioxidant activity: -

- Marcelia Sugata et al (2015) reported that Purple-fleshed *Ipomoea batatas* possesses high amount of antioxidative compounds, such as phenolics, flavonoid, and anthocyanin. The major anthocyanin is cyanidin and peonidin and their acylated derivatives. [61]

- Hanju Sun et al (2018) reported that purple *Ipomoea batatas* contains a high amount of peonidin-based anthocyanins. These peonidin-based components showed good properties regarding scavenging 1,1-diphenyl-2-picrylhydrazyl (DPPH) radicals and superoxide anions and had good potential in reducing the total power activity and Fe2+ chelating ability, hence the Five peonidin-based anthocyanin monomers exerted stronger in vitro antioxidant activities. [63]

- Pritha, Chakraborty et al (2018) reported that the total antioxidant capacity was evaluated by the DPPH assay, using methanol and hexane extract of *Ipomoea batatas*. It was noted that the extract showed good antioxidant activity. [64]

- Chengcheng Zhang et al (2019) reported that, the ethyl acetate fractions of *Ipomoea batatas* leaves displayed the highest phenolic and flavonoid contents showing highest scavenging activities towards 2,2-diphenyl-1-picrylhydrazyl (DPPH) and higher ferric ion reducing antioxidant power (FRAP)- possessing best antioxidant activity. [65]

5) Prebiotic activity:

- Hanju Sun et al (2018) reported that, the five peonidin-based anthocyanins extracted from purple *Ipomoea batatas* induce the proliferation of bacteria such as *Bifidobacterium bifidum, Bifidobacterium adolescentis, Bifidobacterium infantis and Lactobacillus acidophilus*, and at the same time they inhibited the growth of *Staphylococcus aureus and Salmonella typhimurium*, suggesting the anthocyanins might have prebiotic-like activity through the modulation of the intestinal microbiota, hence the peonidin-based anthocyanin monomers might be considered as a potential natural probiotic sources. [63]

- Xin Zhang et al (2016) reported, the modulatory effect of purple *Ipomoea batatas* anthocyanins on human intestinal microbiota, it induced the proliferation of *Bifidobacterium and Lactobacillus/Enterococcus spp* and inhibited the growth of *Bacteroides-Prevotella and Clostridium histolyticum*, which exert a better effect on intestinal microecology, suggesting that purple *Ipomoea batatas* anthocyanins may have prebiotic-like activity by generating short chain fatty acid and modulating the intestinal microbiota, contributing to improvements in human health. [66]

6) Antidiabetic effect:

- Shagufta Kamal et al 2018 reported, the effects of aqueous extract of *Ipomoea batatas* on alloxan induced diabetic Wistar rats, which showed a gradual decrease in blood glucose level, and it also decreased protein glycation level total cholesterol, triglycerides, and LDL-cholesterol. Increase in HDL-cholesterol was also observed after treating the rats with aqueous extract of Ipomoea batatas. Additionally, it had also shown positive results on total protein concentration, albumin, globulin, and plasma enzymes (SGOT and SGPT). It might be concluded that antidiabetic potential of sweet potato extract is due to the presence of bioactive compounds like glycoprotein, anthocyanins, alkaloids, and flavonoids, which act as insulin-like molecules or insulin secretagogues constituents.[67]

- Fenglin Li et al (2009) reported that, flavonoids present in *Ipomoea batatas* leaves possess potential antidiabetic effect. when the *Ipomoea batatas* leaf extract was treated against diabetes mellitus mice at a dose of (50, 100, and 150 mg/ kg body weight) for 28 days it resulted in a significant decrease in the concentration of fasting blood glucose, total cholesterol and triglyceride. [68]

7) Sickle cell anemia:

Mpiana et al (2014) reported, the anti-sickling activity of *Ipomoea batatas* leaves. It was evaluated through an in vitro bioassay using the emmel test. The results showed a significant ant sickling activity, thus justifying the use of this plant by traditional healers in the management of sickle cell disease. The biological activity of the leaves of *Ipomoea batatas* would be due to anthocyanins which are particularly abundant in this aliment. [69]

8) Anti-microbial activity:

- Pritha, Chakraborty et al (2018) reported that, antimicrobial activities were carried out by agar well diffusion method against nine clinical pathogens using methanol and hexane extract of *Ipomoea batatas* and the result of the study declares that the methanol and hexane extracts of *Ipomoea batatas* leaves possess good antimicrobial activity. [48]

- Shahidul Islam et al (2008) that, the lyophilized leaf powder of *Ipomoea batatas* strongly suppressed the growth of gram positive and gram-negative bacteria, hence possessing anti-microbial effect. [70]

9) Wound healing activity:

- Vandana Panda et al (2011) reported that wound healing property of *Ipomoea batatas* tubers, Usually The wound healing process consists of different phases such as granulation, collagenation, collagen maturation and scar maturation. Hence, in this study two different models (Excision wound model and Incision wound model) were used to assess the effect of peels of *Ipomoea batatas* tubers (sweet potato) on various phases. The result of the study demonstrates that the peels of *Ipomoea batatas* tubers possess a potent wound healing effect, which appears to be related to the free radical scavenging activity of the phytoconstituents, and their ability to inhibit lipid peroxidative processes. [71]

- Daniel Hermes 2013 et al reported that the potential of tuber flour of *Ipomoea batatas* as wound healing effect. In this study Wistar rats were used to induce wounds that were topically treated with Beeler's base containing tuber flour of white sweet potato at 2.5%. Number of cells undergoing metaphase and the degree of tissue re-epithelialization were investigated 4-, 7- and 10-days post-treatment. The results of the study declared that *Ipomoea batatas* possess wound healing activity. [72]

10) Neuroprotective activity:

- Made Oka Adnyana et al (2018) reported the neuroprotective effect of *Ipomoea batatas*, in this study Anthocyanin was extracted from purple sweet potato and subsequently administered to Wistar rat models of induced ischemic stroke and the results of this study indicated a significant neuroprotective effect of anthocyanin derived from sweet potato. [73]

11) Antihyperlipidemic effect:

- Marceline Joelle Mbouche Fanmoe et al. reported the Antihyperlipidemic Effect of *Ipomea batatas* Leaf Powder on rats receiving a high-fat diet. The effect of *Ipomoea batatas* leaf powder on lipid metabolism was assessed in vivo by feeding different groups of rats with a high-fat diet supplemented with 5 and 10% of *Ipomoea batatas* leaf powder for 30 days. At the end of the experiment the test group that received *Ipomea batatas* extract showed a significant reduction in body weight when compared to the control group. The consumption of I. batatas leaf powder for 30 days significantly reduced serum total cholesterol, LDL-cholesterol, triglycerides, these results suggest the use of *Ipomea batatas* leaves as a phytomedicine in the treatment of cardiovascular diseases. [74]

12) Hepatoprotective effect:

- Vianney Jovilyn et al (2010) reported the Hepatoprotective activity of crude leaf extract of *Ipomoea batatas*. This study investigated the protective effect of the crude leaf extract of *Ipomoea batatas* against acetaminophen and alcohol induced liver toxicity in rats. At The end of the study there was a significant decrease in ALT, AST and bilirubin in the test group at a dose of 400 mg/kg body weight. The leaf extract of *Ipomoea batatas* is said to have the potency and therapeutic efficacy in protecting the liver of Sprague-Dawley rats. It is therefore concluded that the crude leaf extract of *Ipomea batatas* has the potential hepatoprotective properties. [75]

13) Effect on Haematological Parameters:

- Osime E.O et al (2007) reported the plant *Ipomoea batatas* possess hematinic effects and has been used in the treatment of anemia and other related ailments. Sweet potato leaves were used to feed rabbits. Their blood samples were collected and analysed for PCV, WBC, platelet count and white cell differential count. There was a significant increase in PCV, WBC and platelet count respectively. While the differential white cell count remained the same. Increase in haematological parameters after feeding with the sweet potato leave extract may be a direct effect on haemopoietic tissues. [76]

14) Antiulcer activities:

- Daniel Hermes (2013) et al reported the **antiulcer properties** of *Ipomoea batatas*. The aqueous suspension of tuber flour of *Ipomoea batatas* on gastric mucosa of Wistar rats was studied by using the ethanol-induced ulceration model. Ointment based on white sweet potato at 2.5% effectively triggered the healing of cutaneous wound as attested by the increased number of cells undergoing metaphase and tissue re-epithelialization regardless the time of wound treatment. Tuber flour of sweet potato potentially prevented ethanol-induced gastric ulceration by suppressing edema formation and partly protecting gastric mucosa wrinkles. The results from animal model experiments indicate the potential of tuber flour of *Ipomoea batatas* as the ability to heal ulcer wounds. [72]

15) Anti- Lithiatic Effect:

- R. Sathish et al (2018) reported the reported the Anti- Lithiatic Effect of *Ipomoea batatas*. The leaves and tuberous roots of *Ipomoea batatas* at 200 and 400mg/kg doses in curative and preventive regimens were evaluated on ethylene glycol induced lithiasis in male wistar rats. Lithiasis was induced in rats by 0.75% ethylene glycolated water ad libitum for 28 days. On 28th day urinary excretion of calcium, oxalate, phosphate, uric acid and protein were significantly decreased and magnesium excretion was significantly increased in both curative and preventive regimens of I.batatas leaves and tuberous roots when compared with lithiatic control animals. The significant reduction of serum creatinine, uric acid, blood urea nitrogen levels and significant increase in creatinine clearance were also produced by I.batatas leaves and roots in both curative and preventive regimens.
- The I. batatas leaves and roots supplementation also caused significant diuresis in rats accompanied by increased diuretic index. The maximum responses were produced by ethanolic extract of I.batatas tuberous roots and the effects were significantly more than that of ethanolic extract of I.batatas leaves in both preventive and curative regimens. These observations concluded that the I.batatas roots (sweet potato) can be used as a herbal remedy in the treatment of lithiasis. [77]

16) Aphrodisiac and Gonadoprotective effect:

- Muhammad Majid et al (2018) reported the Aphrodisiac and Gonadoprotective effect of *Ipomoea batatas*. The study was conducted to evaluate the aphrodisiac potential of ethyl acetate and methanol extracts of *Ipomoea batatas* from tuber and aerial part, respectively, via behavioural and biochemical tests and their possible protective role in Bisphenol A-induced gonadotoxicity at the dose 300 mg/kg in male Sprague Dawley rats.

  Inorder to calculate the sexual excitement - mount latency, intromission latency, mount frequency, intromission frequency, ejaculatory latency, and postejaculatory interval were examined while for biochemical ratification semen characteristics, levels of testosterone, follicle stimulating hormone (FSH), luteinizing hormone (LH), and estradiol were measured. Gonadoprotective ability was assessed through comet assay and histomorphological examination of testes.

  Extracts enhanced sexual excitement, improved semen quality, levels of testosterone, FSH, LH, and estradiol, and successfully attenuated toxic effects of Bisphenol A. Levels of endogenous antioxidant enzymes (CAT, SOD, POD, and GSH) were restored and NO abundance was minimized. Significant stimulation in sexual behaviour, amelioration of toxicity symptoms, elevated spermatic production, raised viability, vitalized levels of gonadal hormones, maintained endogenous enzymes, Geno protection, and reformed testicular histology endorsed *Ipomoea batatas* as a better aphrodisiac alternative and gonadoprotective agent. [78]

Scope .....

&

Plan of work .....

5.SCOPE:

According to the WHO, there are over 70 million suffers in the world today of which 80% live in the developing countries. An estimated 3.2 million new cases occur each year globally, with at least 55% of the cases begin in childhood. Epilepsy responds to treatment about 75% of the time, some cases show poor treatment due to inadequate medical supply and proper treatment. Epilepsy increases a person's risk of premature death by about two to three times. It is the most common serious brain disorder worldwide with no boundaries.

Management of epilepsy is a global problem and successful treatment is very essential for preventing or at least delaying the onset of long-term complications. Remedies to treat such different types of seizure are available in nature in the form of herbal medicines or drugs with very minimal adverse effects when compared to the available synthetic drugs. Such herbal drugs as therapeutic agents are a boon when compared to the severe adverse effects of the allopathic medical practice for epileptic seizure, though the quest for a complete and permanent cure for the disease is being pursued by eluding physicians and researchers.

Therefore, herbal medicines have been used for the treatment of various disease because of their fewer adverse effects that conventional medicine. It is believed that the traditional medicines used for the treatment of epilepsy and also in progression of complications of the disease.

Main objective of the proposed work is to evaluate the beneficial effects of *Ipomoea batatas* Lam. for its anti-epileptic activity by using MES and INH model.

6. PLAN OF WORK

- **LITERATURE REVIEW**
- **PLANT SELECTION**

  Collection and Authentication of *Ipomoea batatas* Lam.

- **EXTRACTION**
- Preparation of Ethanolic Extract of *Ipomoea batatas* Lam. (EEIB)
- **EXPERIMENTAL ANIMALS**
- **PRELIMINARY PHYTOCHEMICAL SCREENING OF EEIB.**
- **IN VIVO SCREENING**

  MES Induced Epilepsy in Wistar Rats.

  INH Induced Epilepsy in Wistar Rats.

- **IN VITRO SCREENING**

  Estimation Of GABA Levels on MES Induced Epilepsy Model in Wistar Rats.

- **HISTOPATHOLOGY**

  Histopathological analysis of Brain in MES Induced Epilepsy in wistar rats

- **STATISTICAL ANALYSIS BY ONE WAY ANOVA FOLLOWED BY DUNNET'S TEST**
- **RESULT AND DISCUSSION**

MATERIALS AND METHOD:

6.1 COLLECTION AND AUTHENTICATION:

The tuberous roots of *Ipomoea batatas* Lam. were collected from local market, Tamil Nadu. The plant material was identified and authenticated by P. Jayaraman, M.Sc., Ph.D., Professor, Director of Plant anatomy research Centre (PARC), Chennai–600045, Tamilnadu. Certificate number PARC/2021/4522. A voucher specimen was submitted at C.L. Baid Metha College of Pharmacy, Chennai- 600097

6.2 PREPARATION OF ETHANOLIC EXTRACT OF *Ipomoea batatas* LAM. (EEIB)

The tuberous root of *Ipomoea batatas* was collected from local market and they were sliced into thin pieces and dried in shade and made to a coarse dry powder. And they were subjected to extraction.

6.2.1 Method of Extraction:

A weighed Quantity of the powder were extracted with 70 % ethanol at room temperature for 5 days using Soxhlet's apparatus. The filtrates were collected and then evaporated under reduced pressure to give a viscous mass, which gave a brownish golden colour residue. The extract was stored at 0-4°C

6.2.2 Percentage Yield:

The percentage yield of hydro alcoholic extract was 5.22 % w/w, and it was preserved in refrigeration for further use.

6.3 EXPERIMENTAL ANIMALS:

Wistar rats of weighing 100 -150 gm were used for this study. The inbred animals were procured from the animal house of C.L. Baid Metha College of Pharmacy, Thoraipakkam, Chennai- 97. They were housed three per cage under standard laboratory conditions at a room temperature at $22\pm2_0$ C with 12 hr light/dark cycle. The animals were acclimatized to laboratory conditions for one week provided with standard pellet chow and water *ad libitum*. Ethical committee approval was obtained from IAEC of CPCSEA. (07/321/PO/Re/S/01) dated: 17/11/2021)

6.4 PRELIMINARY PHYTOCHEMICAL ANALYSIS OF EEIB: [79, 80]

The *Ipomoea batatas* Lam. was subjected to preliminary phytochemical screening for the presence or absence of phytoconstituents by the following methods.

I. Test for alkaloid:

The EEIB was treated with dilute hydrochloric acid and filtered. The filtrate was used in the following tests.

a) Mayer's reagent (Potassium Mercuric Iodine Solution)
0.5ml of the EEIB was treated with Mayer's reagent and the appearance of cream colour indicates the presence of alkaloid

b) Dragendroff' s test (Potassium Bismuth Iodide)

0.5ml of the EEIB was treated with Dragendroff' s reagent and the appearance of reddish-brown colour precipitate indicates the presence of alkaloid.

c) Hager's test (Saturated solution of Picric acid)

0.5ml of the EEIB was treated with Hager's test and the appearance of yellow colour precipitate indicates the presence of alkaloid.

d) Wagner's test (Iodine-Potassium Iodide Solution)

0.5ml of the EEIB was treated with Wagner's test and the appearance of brown colour precipitate indicates the presence of alkaloid.

II. Test for Carbohydrates:

a) Molisch's test:

The EEIB was treated with 3ml of alpha-naphthol in alcohol and concentrated sulphuric acid was added along the sides of the test tube carefully. Formation of violet colour ring at the junction of two liquids indicates the presence of carbohydrates.

b) Fehling's test ($CuSO_4.7H_2O$+KOH+Potassium Tartartes):

The EEIB was treated with Fehling's solution A and B heated in boiling water for few minutes. The appearance of reddish-brown colour precipitate indicates the presence of reducing sugars.

c) Benedict's test (Sodium citrate + sodium carbonate + $CuSO_4.7H_2O$)

The EEIB was treated with Benedict's test and heated in boiling water for few minutes. The appearance of reddish orange colour precipitate indicates the presence of reducing sugars.

d) Barfoed's test (Copper Acetate+ Glacial acetic acid)

The EEIB was treated with Barfoed's test and heated in boiling water for few minutes. The appearance of reddish orange colour precipitate indicates the presence of non- reducing sugars.

III. Test for steroids

a) Liberamannburchard test:

The EEIB was treated with small quantity of concentrated sulphuric acid, glacial acetic acid and acetic anhydride. The appearance of green colour indicates the presence of steroids.

IV. Test for proteins

a) Biuret's test:

The EEIB was treated with copper sulphate and sodium hydroxide solution. The appearance of violet colour indicates the presence of proteins.

b) Millon's test:

The EEIB was treated with Millon's reagent. The appearance of pink colour indicates the presence of proteins.

V. Test for Tannin's:

a) The EEIB was treated with 10% lead acetate solution. The appearance of white precipitate indicates the presence of tannins.

b) The EEIB was treated with aqueous bromine solution. The appearance of white precipitate indicates the presence of tannins.

VI. Test for Phenols:

a) The EEIB was treated with neutral ferric chloride solution. The appearance of violet indicates the presence of phenols.

b) The EEIB was treated with 10% sodium chloride solution. The appearance of cream colour indicates the presence of phenols.

VII. Test for Flavonoid:

a) 5ml of EEIB solution was hydrolysed with 10%v/v sulphuric acid and cooled. Then, it is extracted with diethyl ether and divided into three portions in three separate test tubes. 1ml ofdiluted sodium carbonate, 1ml of 0.1N sodium hydroxide, and 1ml of strong ammonia solution were added to the first, second and third test tubes respectively. In each test tube, development of yellow colour demonstrated the presence of flavonoids.

b) Shinoda's test:

The EEIB were dissolved in alcohol, to that one piece of magnesium is added followed by concentrated hydrochloric acid along the sides of the test tube drop wise. It is heated in a boiling water bath for few minutes. The appearance of magenta colour indicates the presence of flavonoids.

VIII. Test for Gums and Mucilage:

The EEIB was treated with 25ml of absolute alcohol and then solution was filtered. The filtrate was examined for its swelling properties.

IX. Test for Glycosides:

The EEIB was dissolved in the glacial acetic acid and few drops of ferric chloride solution was added, followed by the addition of concentrated sulphuric acid, formation of red ring at the junction of two liquids indicates the presence of glycosides.

X. Test for Saponins:

1ml of the EEIB was diluted to 20ml with distilled water and shaken well in a test tube. The formation of foam in the upper part of the test tube indicates the presence of saponins.

XI. Test for Terpenes:

The EEIB was treated with tin and thionyl chloride, appearance of pink colour indicates the presence of terpenes.

XII. Test for sterols:

The EEIB was treated with 5% potassium hydroxide solution: appearance of pink colour indicates the presence of sterols.

6.5 ACUTE TOXICITY STUDIES: [82]

Acute toxicity studies for tuberous roots of *Ipomoeas batatas* Lam was performed and it was found to be safe. p. o. Hence the dose selected for the study was 200 mg/kg p.o (Low dose) and 400 mg/kg p.o (High Dose)

IN VIVO METHODS:

- Method:1 - Maximal electroshock (MES) induced epilepsy in Wistar rats
- Method:2- Isoniazid (INH) induced epilepsy in Wistar rats

EXPERIMENTAL METHOD- I [56,57,86]

6.6 MAXIMAL ELECTROSHOCK (MES) INDUCED EPILEPSY IN WISTAR RATS :

MES model is one of the physical methods to evaluate the anti-epileptic activity of drug.

This model is used to screen drugs which are effective for generalized tonic-clonic (grandmal) and focal seizures whereas anti- absence seizure drugs cannot be tested.

Rats or mice are commonly used for this method. A stimulating apparatus with corneal or ear electrodes supplying a constant current 50 mA for mice and 150 mA for rats at a frequency of 50-60 Hz is applied for a duration of 0.2 seconds. The animals are observed for a period of 2 minutes after application of electrical stimulus. The seizure which occurs passes through various phases: phase of tonic limb flexion, phase of tonic limb extension and a variable short clonic interval. Efficacy of new antiepileptic drugs is measured by the suppression of tonic hind limb extension.

- **Inducing Agent**-Electrical stimulus by Electro convulsiometer.
- **Animals:** Male Wistar rats.

Table:3 Group category for MES induced epilepsy in wistar rats.

GROUPS	TREATMENT
Group I	Normal control
Group II	Negative control- Convulsion induced by MES 60 Hz alternating current of 150 mA intensity for 0.2 sec.
Group III	Convulsion induced by MES 60 Hz alternating current of 150 mA intensity for 0.2 sec treated with standard drug - Phenytoin (25mg/kg p.o.)
Group IV	Convulsion induced by MES 60 Hz alternating current of 150 mA intensity for 0.2 sec treated with Lower dose of EEIB (200 mg/kg p.o).
Group V	Convulsion induced by MES 60 Hz alternating current of 150 mA intensity for 0.2 sec treated with Higher dose of EEIB (400 mg/kg p.o).

Procedure:
The animals were divided into 5 groups consisting of 6 each.

Group I was normal control.

Group II Seizure was induced by MES 60 Hz alternating current of 150 mA intensity for 0.2 sec on 21 st day.

Group III Seizure was induced by MES 60 Hz alternating current of 150 mA intensity for 0.2 sec after the last dose of standard drug (Phenytoin 25mg/kg p.o) on 21 st day

Group IV Lower dose of (EEIB 200mg/kg p. o) administered for 21 days, on 21 st day seizure was induced by MES 60 Hz alternating current of 150 mA intensity for 0.2 sec (after the last dose)

Group V Higher dose of (EEIB 400mg/kg p. o) administered for 21 days, on 21 st day seizure was induced by MES 60 Hz alternating current of 150 mA intensity for 0.2 sec (after the last dose)

Observational parameters:

The various stages of epilepsy which was listed below were observed:

- Flexion
- Extensor
- Clonus
- Stupor
- Recovery.
- The percentage protection of animals was estimated.

EXPERIMENTAL METHOD- II

6.7 ISONIAZID (INH) INDUCED EPILEPSY IN WISTAR RATS: [56,57,83]

Isoniazid model is one of the chemically induced methods to evaluate anti-epileptic activity of the drug. Isoniazid can precipitate convulsions in patients with seizure disorders.

Isoniazid is regarded as a GABA-synthesis inhibitor, it is an anti-tuberculosis drug, induces epilepsy by depleting brain level of Gamma-Aminobutyric Acid (GABA), a major inhibitory transmitter substance in the mammalian brain, through inhibition of pyridoxal-5-phosphate-dependent Glutamic Acid Decarboxylase (GAD). Pyridoxal-5-phosphate is the active form of

pyridoxine, a cofactor for GAD, and an enzyme required for GABA synthesis, The decrease in GABA levels results in recurrent seizures that characterized epilepsy.

- **Inducing Agent-** Isoniazid
- **Animals:** Male Wistar rats.

Table:4 Group category for INH induced epilepsy in wistar rats.

GROUPS	**CATEGORY**
Group I	Normal control – Vehicle Treated
Group II	Negative control - Convulsion induced by Isoniazid (300mg/kg i.p.)
Group III	Convulsion induced by Isoniazid (300mg/kg i.p) treated with standard drug -Diazepam (5 mg/kg i.p)
Group IV	Convulsion induced by Isoniazid (300mg/kg i.p) treated with Lower dose of EEIB (200 mg/kg p.o).
Group V	Convulsion induced by Isoniazid (300mg/kg i.p) treated with Higher dose of EEIB (400 mg/kg p.o).

Procedure:

Group I was normal control.

Group II Seizure was induced by Isoniazid (300mg/kg i.p.) on 21 st day

Group III Seizure was induced by Isoniazid (300mg/kg i.p.) after the last dose of standard drug (Diazepam 5mg/kg p.o) on 21 st day

Group IV Lower dose of (EEIB 200mg/kg p. o) administered for 21 days, on 21 st day seizure was induced by Isoniazid (300mg/kg i.p.) after the last dose.

Group V Higher dose of (EEIB 400mg/kg p. o) administered for 21 days, on 21 st day seizure was induced by Isoniazid (300mg/kg i.p.) after the last dose.

Observational Parameter:

Morbidity and Mortality status of the animals after 30min, 24 hrs. were observed.

6.8 *IN -VITRO* METHOD: [84,85]

Determination of the effect of EEIB and standard on neurotransmitter concentration in wistar rat brain after induction of epilepsy:

The Wistar rats from all the Groups (I, II, III, IV &V) were anaesthetized and sacrificed. The brains were removed carefully by opening the skull. The collected brain samples were placed in buffer solution, and they were homogenised and centrifuged. The supernant fluid was collected and subjected to GABA estimation.

Estimation of GABA levels on MES induced epilepsy in wistar Rats.

Preparation of standard solutions

1 N HCl was prepared in 80% ethanol which was used to dissolve GABA (γ-amino butyric acid) and glutamate.

Preparation of stock solution:

Stock solutions of GABA and glutamate were prepared by dissolving 10 mg of the respective amino acid in 10 ml of 0.1 N HCl in 80% ethanol. From this stock solution, working standard solutions of concentration 10ng, 20ng, 40ng, 80ng, 120ng, 160ng, 200ng in 5µl for GABA were prepared in 10 ml volumetric flasks and adjusting the volume with 0.1 N HCl in 80% ethanol.

Preparation of 0.2% ninhydrin solution:

200 mg of ninhydrin was dissolved in a small amount of acetone in a 100 ml standard flask. To this, 1 ml of pyridine was added and the volume was made up to 100 ml with acetone.

Chromatographic condition

- Stationary phase : Silica gel GF254;
- Mobile phase : n-butanol: glacial acetic acid: water (65:15:25 v/v/v)
- Saturation time : 3 hr
- Instrument : HPTLC
- Applicator : Linomat V
- Scanner : Camag TLC scanner III
- Developing chamber : Twin trough glass chamber (20×10)
- Developing mode : Ascending mode (multiple development
- Detection reagent : 0.2% ninhydrin in acetone;
- Scanning wavelength : 486 nm;
- Experimental condition : 25^{o} C; Temp/RH: 55–65%.

Calibration curve

Ten µl of different concentration of standard 5µl of GABA and glutamate standard solution were applied in triplicate on a pre-coated HPTLC plate. Spots were dried in a hot air oven at 60–650C for 1–2 min and the plate was developed in the mobile phase n-butanol: glacial acetic acid: water (65:15:25 v/v/v). When the solvent front reached about 8.0 cm (marked previously), the plates were removed and dried at 60–650C for 3–4 min in a hot air oven. A second run was performed in a similar way. The plates were then dipped in 0.2% ninhydrin reagent for 1 sec and dried in a hot air oven at 60–650C for 3–4 min scanned at 486 nm and the peak areas were recorded. Calibration curves of GABA and glutamate were prepared by plotting areas v/s concentration.

Calculation

- Brain samples of all the groups (I, II, III, IV & V) were homogenized each 10mg in 200µl of solvent. Hence 1 mg tissue needs 20µl volume. Final results were expressed of ng of protein per mg of tissue.
- Total 10µl of sample volume were taken to measure neurotransmitter quantity. These samples gave peak area as a measure of concentration that was interpolated from standard plot with the help linear regression statistics of graph pad prism 4.01.

To express the neurotransmitter quantity in ng/mg tissue, final interpolated concentrations from standard plot were multiplied by 2.

6.9 HISTOPATHOLOGICAL ANALYSIS OF BRAIN IN MES INDUCED EPILEPSY IN WISTAR RATS: [84,85]

The Wistar rats from all the Groups (I, II, III, IV &V) were anaesthetized and sacrificed. The brains were carefully removed by opening the skull. The collected brains were washed with ice cold normal saline and fixed in 10% formalin saline.

Paraffin embedded sections were taken 100µm thickness and processed in alcohol-xylene series and stained with Haematoxylin-Eosin dye. The sections were examined microscopically for histopathological changes in the cortex zone.

6.10 STATISTICAL ANALYSIS: [84,85,87]

The statistical analysis was carried by one way ANOVA followed by Dunnet's ―t test. P values <0.05 (95% confidence limit) was considered statistically significant, using Software Graph pad Prism 9.3.1

Results .....

&

Discussion....

7. RESULTS:

7.1 Preliminary Phytochemical analysis of Ethanolic extract of *Ipomoea batatas* Lam. (EEIB)

The result of preliminary phytochemical analysis of Ethanolic extract of ***Ipomoea batatas*** Lam. showed presence of various phytochemical constituents such as Carbohydrates, phenols, Flavonoids, steroids, alkaloids, glycoside protein, tannins, terpenes and saponins with absence of sterol, gums and mucilage.

Table: 5 -Preliminary Phytochemical analysis of Ethanolic extract of Tuberous roots of

Ipomoea batatas Lam

S.NO	PHYTOCHEMICALCONSTITUENTS	PRESENCE/ABSENCE
1	Alkaloids	*Present*
2	Carbohydrates	*Present*
3	Steroids	*Present*
4	Proteins	*Present*
5	Tannins	*Present*
6	Phenol	*Present*
7	Flavonoids	*Present*
8	Gums and mucilage	*Absent*
9	Glycoside	*Present*
10	Saponins	*Present*
11	Terpene	*Present*
12	Sterols	*Absent*

7.2 EFFECT OF EEIB ON MES INDUCED EPILEPSY IN WISTAR RATS

Table: 6 Effect of EEIB on Flexion in MES induced epilepsy in wistar rats.

GROUPS	FLEXION(SEC)
Group I	0
Group II	25.83 ± 2.37 a****
Group III	2.33 ± 0.42 a ^{ns} b****
Group IV	9.50 ± 1.28 a**** b****C**
Group V	4.83 ± 0.31 a*b****C ^{ns}

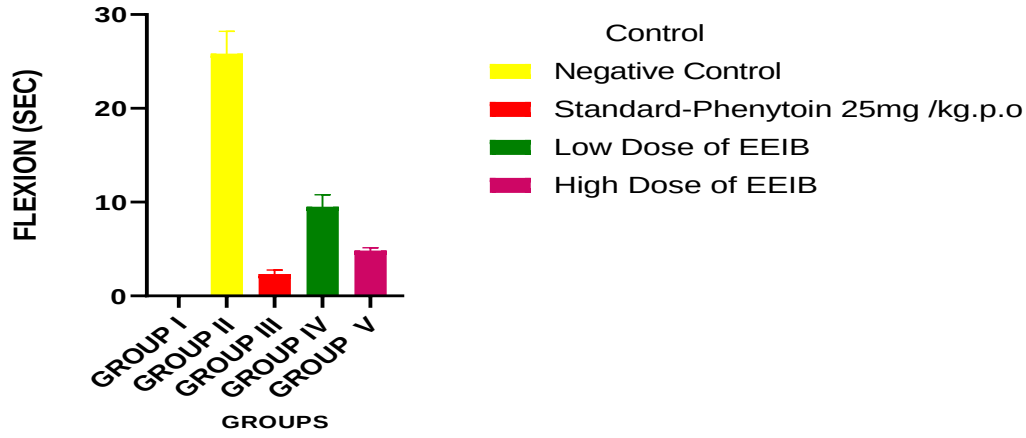
Values are expressed as mean ± SEM of 6 animals.

Comparisons were made between the following:

- Group I compared with Group II, III, IV and V was considered as a
- Group II compared with Group III, IV and V was considered as b
- Group III compared with Group IV and V was considered as c

Statistical Significance test for comparison was done by one way ANOVA followed by Dunnets't' test. Where * ($p< 0.05$), **($p< 0.01$), *** ($p<0.001$), ****($p<0.0001$) and ns- nonsignificant.

Figure:7 Effect of EEIB on Flexion in MES induced epilepsy in wistar rats.



Flexion in MES induced epilepsy in wistar rats

- The Flexion phase in Group II, IV ($p<0.0001$), V ($p< 0.05$) was significantly increased when compared with Group I (vehicle treated) and Group III was nonsignificant when compared with Group I
- The Flexion phase in Group II was significantly increased when compared with group III, IV and V ($p<0.001$).
- The Flexion phase in Group III was significantly decreased when compared with Group IV ($p< 0.01$), and nonsignificant with Group V.

Table: 7 Effect of EEIB on Extensor in MES induced epilepsy in wistar rats.

GROUPS	EXTENSOR (SEC)
Group I	0
Group II	10.17 ± 0.65 a****
Group III	2.00 ± 0.89 a ^{ns} b****
Group IV	5.67 ± 1.03 a****b***C**
Group V	2.50 ± 0.55 a^{ns} b **** C^{ns}

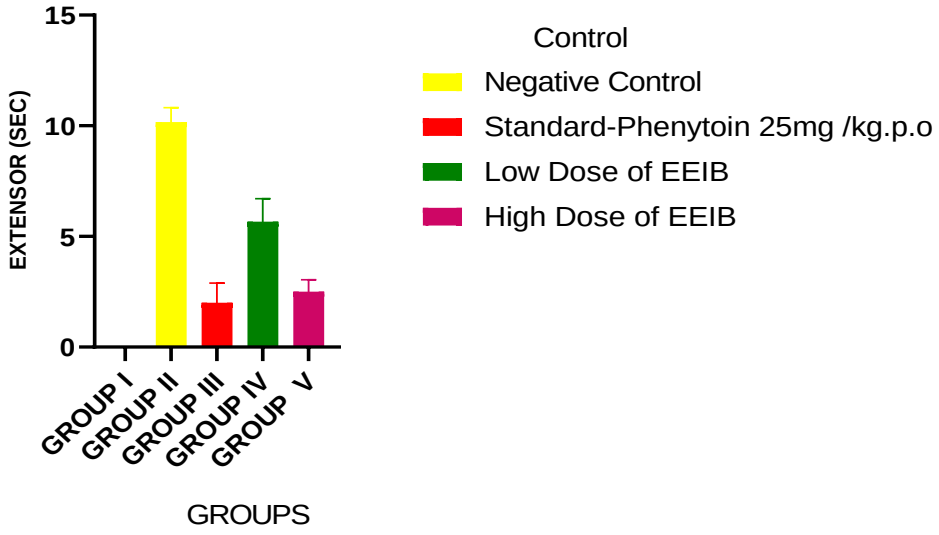
Values are expressed as mean ± SEM of 6 animals.

Comparisons were made between the following:

- Group I compared with Group II, III, IV and V was considered as a
- Group II compared with Group III, IV and V was considered as b
- Group III compared with Group IV and V was considered as c

Statistical Significance test for comparison was done by one way ANOVA followed by Dunnets't' test. Where * (p< 0.05), **(p< 0.01), *** (p<0.001), ****(p<0.0001)
ns- nonsignificant.

Figure:8 Effect of EEIB on Extensor in MES induced epilepsy in wistar rats.



Extensor in MES induced epilepsy in wistar rats.

- The Extensor phase in Group II and IV (p<0.0001) was significantly increased when compared with Group I (vehicle treated) and Group III and V was nonsignificant when compared with Group I
- The Extensor phase in Group II was significantly increased when compared with group III, V (p<0.0001) and IV (p<0.001).
- The Extensor phase in Group III was significantly decreased when compared with group IV (p< 0.01) and non-significant with group V

Table: 8 Effect of EEIB on Clonus in MES induced epilepsy in wistar rats.

GROUPS	CLONUS (SEC)
Group I	0
Group II	12.50 ± 0.62 a****
Group III	2.50 ± 0.56 a*b****
Group IV	7.83 ± 0.87 a****b****C****
Group V	6.50 ± 0.34 a****b****C***

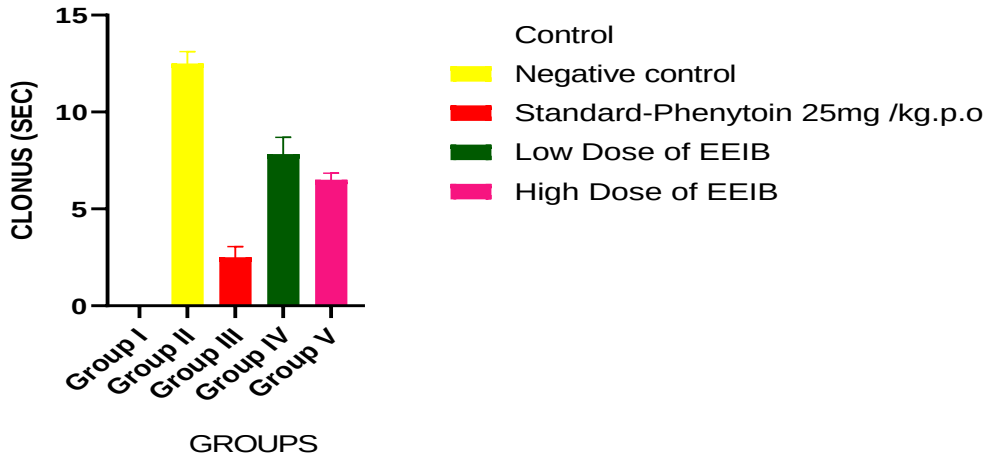
Values are expressed as mean ± SEM of 6 animals.

Comparisons were made between the following:

- Group I compared with Group II, III, IV and V was considered as a
- Group II compared with Group III, IV and V was considered as b
- Group III compared with Group IV and V was considered as c

Statistical Significance test for comparison was done by one way ANOVA followed by Dunnets't' test. Where * (p< 0.05), **(p< 0.01), *** (p<0.001), ****(p<0.0001) ns- nonsignificant.

Figure: 9 Effect of EEIB on Clonus in MES induced epilepsy in wistar rats.



Clonus in MES induced epilepsy in wistar rats.

- The Clonus phase in Group II, IV, V (p<0.0001) and III (P<0.05) was significantly increased when compared with Group I (vehicle treated)
- The Clonus phase in Group II was significantly increased when compared with group III, IV and V (p<0.0001).
- The Clonus phase in Group III was significantly decreased when compared with group IV and V (p<0.0001).

Table: 9 Effect of EEIB on Stupor in MES induced epilepsy in wistar rats.

GROUPS	STUPOR(SEC)
Group I	0
Group II	6.67 ± 0.49 a ****
Group III	0.83 ± 0.31 a^{ns} b****
Group IV	3.50 ± 0.76 a***b***C**
Group V	1.33± 0.33 a ^{ns} b**** c ^{ns}

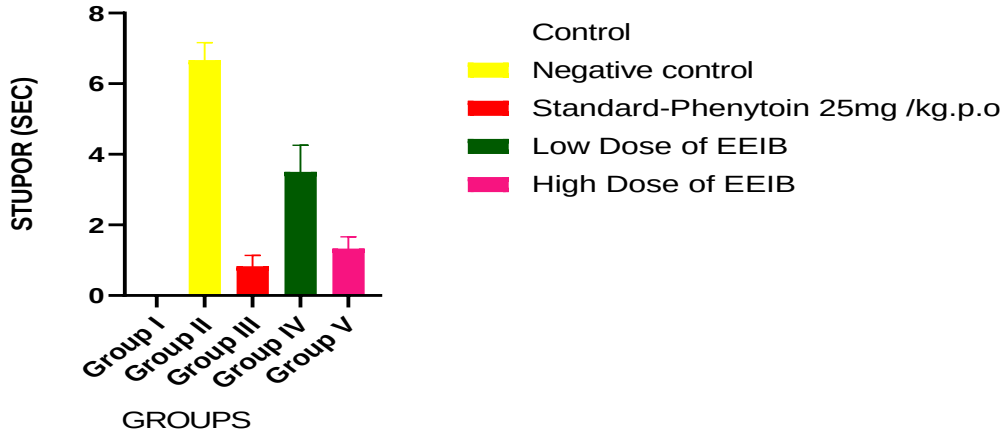
Values are expressed as mean ± SEM of 6 animals.

Comparisons were made between the following:

- Group I compared with Group II, III, IV and V was considered as a
- Group II compared with Group III, IV and V was considered as b
- Group III compared with Group IV and V was considered as c

Statistical Significance test for comparison was done by one way ANOVA followed by Dunnets't' test. Where * (p< 0.05), **(p< 0.01), *** (p<0.001), ****(p<0.0001)
ns- nonsignificant.

Figure: 10 Effect of EEIB on Stupor in MES induced epilepsy in wistar rats



Stupor in MES induced epilepsy in wistar rats.

- The Stupor phase in Group II (p<0.0001) and IV (p<0.001) was significantly increased when compared with Group I (vehicle treated).
  Group III and V was nonsignificant when compared with Group I
- The Stupor phase in Group II was significantly increased when compared with Group III, V (p<0.0001) and IV (p<0.001)
- The Stupor phase in Group III was significantly decreased when compared with group IV (p< 0.01) and non-significant with group V.

Table: 10 Effect of EEIB on Recovery in MES induced epilepsy in wistar rats.:

GROUPS	RECOVERY(SEC)
Group I	0
Group II	105.83 ± 5.54 a****
Group III	10.00 ± 0.00 a ^{ns} b****
Group IV	65.83 ± 4.17 a****b****C***
Group V	29.17 ±2.71 a****b****C**

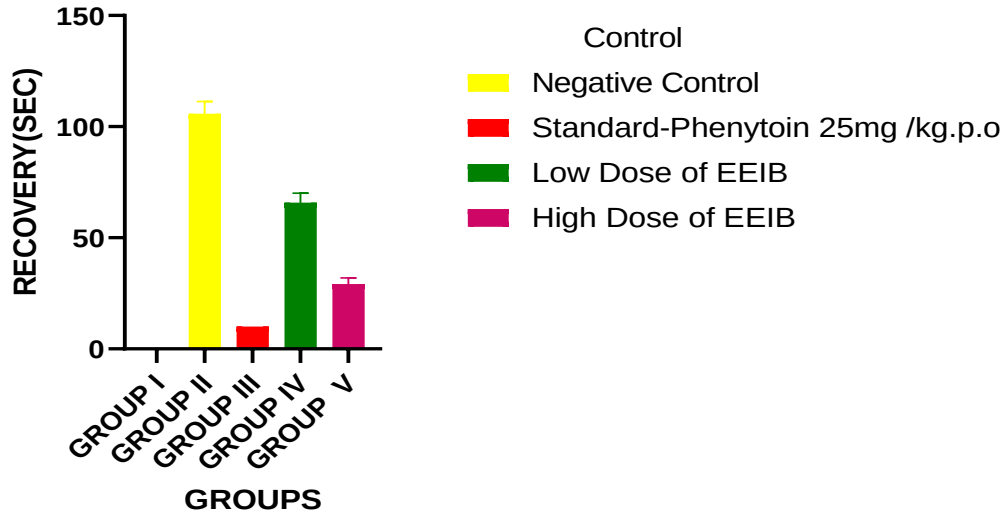
Values are expressed as mean ± SEM of 6 animals.

Comparisons were made between the following:

- Group I compared with Group II, III, IV and V was considered as a
- Group II compared with Group III, IV and V was considered as b
- Group III compared with Group IV and V was considered as c

Statistical Significance test for comparison was done by one way ANOVA followed by Dunnets't' test. Where * ($p< 0.05$), **($p< 0.01$), *** ($p<0.001$), ****($p<0.0001$)
ns- nonsignificant.

Figure: 11 Effect of EEIB on Recovery in MES induced epilepsy in wistar rats.



Recovery time in MES induced epilepsy in wistar rats.

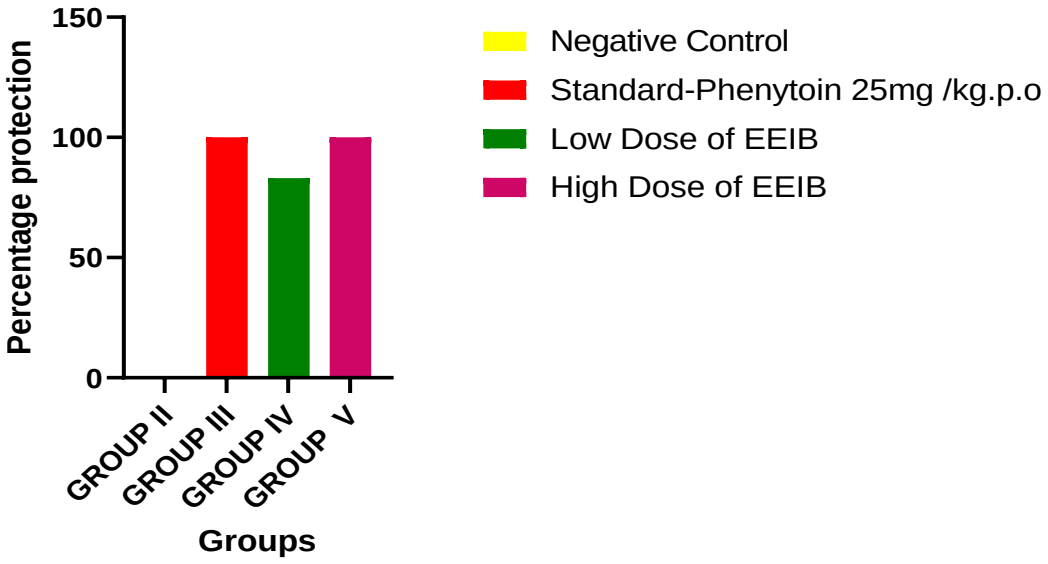
- The Recovery time in Group II, IV &V ($p<0.0001$) was significantly increased when compared with Group I (vehicle treated)
  Group III was nonsignificant when compared with Group I
- The Recovery time in Group II was significantly increased when compared with Group III, IV and V ($p<0.0001$).
- The Recovery time in Group III was significantly decreased when compared with Group IV ($p<0.001$) and V ($p< 0.01$).

Table: 11 Effect of EEIB on Percentage protection in MES induced epilepsy in wistar rats.

GROUPS	PERCENTAGE PROTECTION
Group I	NIL
Group II	0%
Group III	100%
Group IV	83%
Group V	100%

Values are expressed as Percentage

Figure: 12 Effect of EEIB on Percentage protection in MES induced epilepsy in wistar rats.



Percentage protection in MES induced epilepsy in wistar rats.,

- The percentage protection in Group II was significantly abolished when compared with group III, IV and V.
- The percentage protection in Group III was significantly increased when compared with group IV and V.

7.4 EFFECT OF EEIB ON ISONIAZID (INH) INDUCED EPILEPSY IN WISTAR RATS.

Table: 12 Effect of EEIB on Latency in INH induced epilepsy in wistar rats.

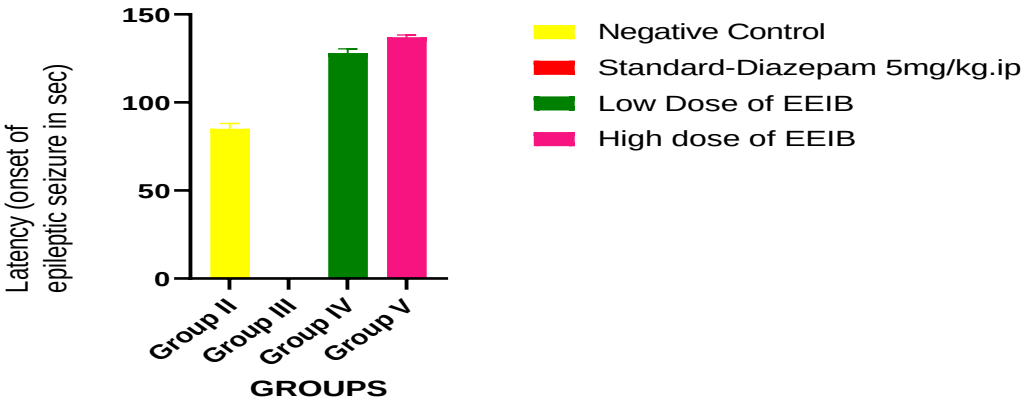
GROUPS	Latency (onset of epileptic seizure in SEC)
Group I	NIL
Group II	85 ± 3.12
Group III	NIL
Group IV	128 ± 2.43 a****b****
Group V	137 ± 1.28 a****b****

Values are expressed as mean ± SEM of 6 animals.
Comparisons were made between the following:

- Group II compared with Group III, IV and V was considered as a
- Group III compared with Group IV and V was considered as b

Statistical Significance test for comparison was done by one way ANOVA followed by Dunnets't' test. Where * ($p< 0.05$), **($p< 0.01$), *** ($p<0.001$), ****($p<0.0001$)
ns- nonsignificant.

Figure: 13 Effect of EEIB on Latency in INH induced epilepsy in wistar rats.



Latency in INH induced epilepsy in wistar rats.

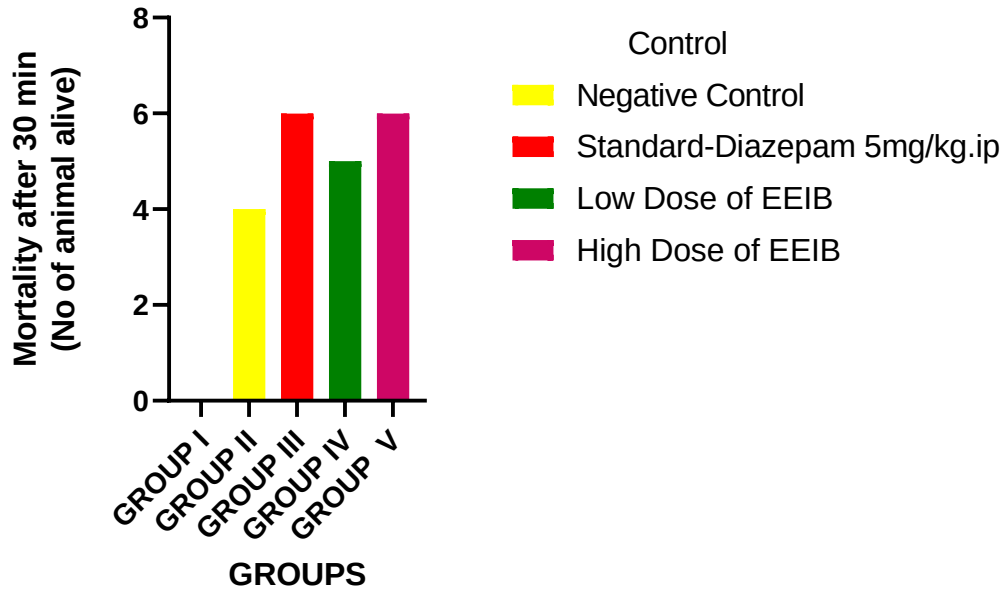
- The Latency in Group II was significantly decreased compared with group III, IV and V ($p<0.0001$).
- The Latency in Group III was significantly abolished when compared with group IV and V ($p<0.0001$).

Table: 13 Effect of EEIB on Mortality after 30 minutes in INH induced epilepsy in wistar rats.

GROUPS	Mortality after 30 min (No of animal alive)
Group I	NIL
Group II	4
Group III	6
Group IV	5
Group V	6

Values are expressed in Numbers

Figure: 14 Effect of EEIB on Mortality after 30 minutes in INH induced epilepsy in wistar rats.



Mortality in INH induced epilepsy in wistar rats at 30 min interval.

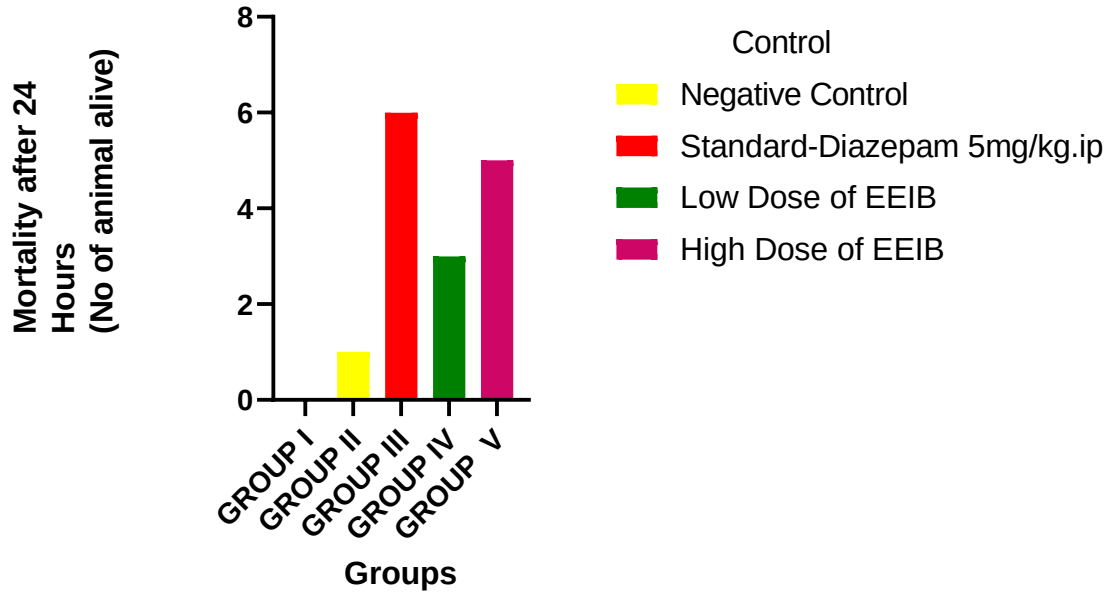
- No mortality in Group I (vehicle treated)
- The Number of animals in Group II was significantly decreased when compared with group III, IV and V.
- The Number of animals in INH treated Group III was significantly increased when compared with Group IV and V.

Table: 14 Effect of EEIB on Mortality after 24 Hours in INH induced epilepsy in wistar rats:

GROUPS	Mortality after 24 Hours (No of animal alive)
Group I	NIL
Group II	1
Group III	6
Group IV	3
Group V	5

Values are expressed in Numbers

Figure: 15 Effect of EEIB on Mortality after 24 Hours in INH induced epilepsy in wistar rats.



Mortality in INH induced epilepsy in wistar rats after 24 hours.

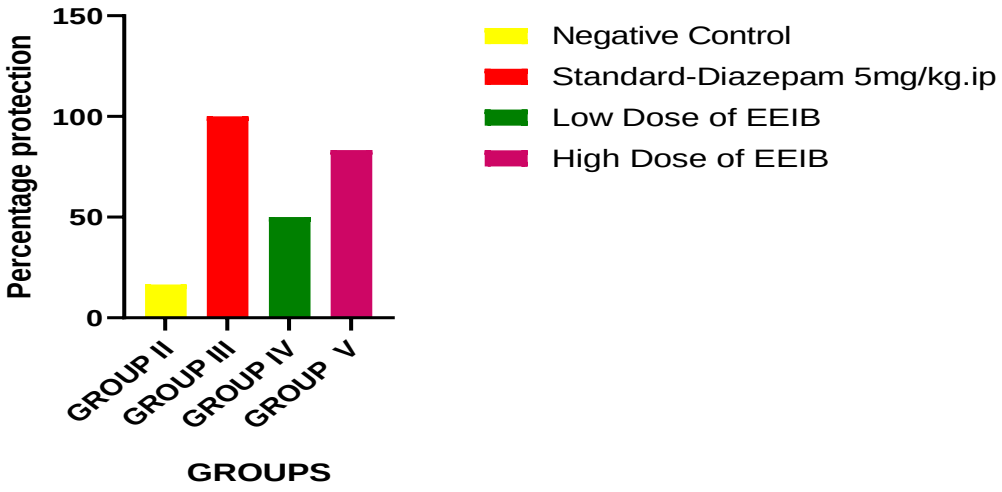
- No mortality in Group I (vehicle treated).
- The Number of animals in Group II was significantly decreased when compared with group III, IV and V.
- The Number of animals in Group III was significantly increased when compared with Group IV and V.

Table: 15 Effect of EEIB on Percentage protection in INH induced epilepsy in wistar rats.

Groups	Percentage protection
Group I	NIL
Group II	16.6 %
Group III	100%
Group IV	50%
Group V	83.3%

Values are expressed in Percentage.

Table: 16 Effect of EEIB on Percentage protection in INH induced epilepsy in wistar rats.



The percentage protection in INH induced epilepsy in wistar rats

- The percentage protection in Group II was significantly decreased when compared with group III, IV and V.
- The percentage protection in Group III was significantly increased when compared with group IV and V.

7.5 IN VITRO-EFFECT OF EEIB ON ESTIMATION OF GABA IN MES INDUCED EPILEPSY IN WISTAR RATS

Table: 16 Effect of EEIB on estimation of GABA in MES induced epilepsy in wistar rats

Groups	GABA (ng/mg tissue)
Group I	333.67 ± 0.71
Group II	215.5 ±0.58a****
Group III	309.83 ± 0.54 a****b****
Group IV	238.67 ± 1.99 a****b****c****
Group V	292.17 ±0.91 a****b****c****

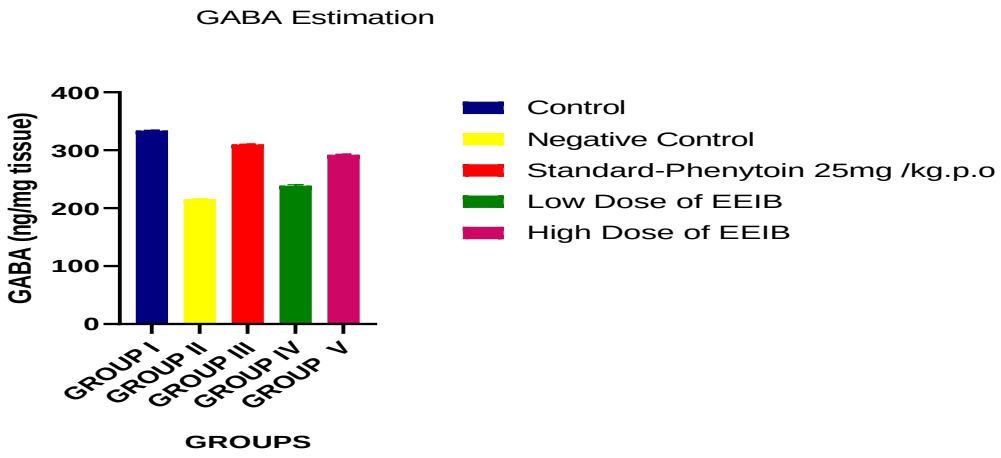
Values are expressed as mean ± SEM of 6 animals.

Comparisons were made between the following:

- Group I compared with Group II, III, IV and V was considered as a
- Group II compared with Group III, IV and V was considered as b
- Group III compared with Group IV and V was considered as c

Statistical Significance test for comparison was done by one way ANOVA followed by Dunnets't' test. Where * ($p< 0.05$), **($p< 0.01$), *** ($p<0.001$), ****($p<0.0001$)
ns- nonsignificant.

Figure: 17 Effect of EEIB on estimation of GABA in MES induced epilepsy in wistar rats



Estimation of GABA in MES induced epilepsy in wistar rats

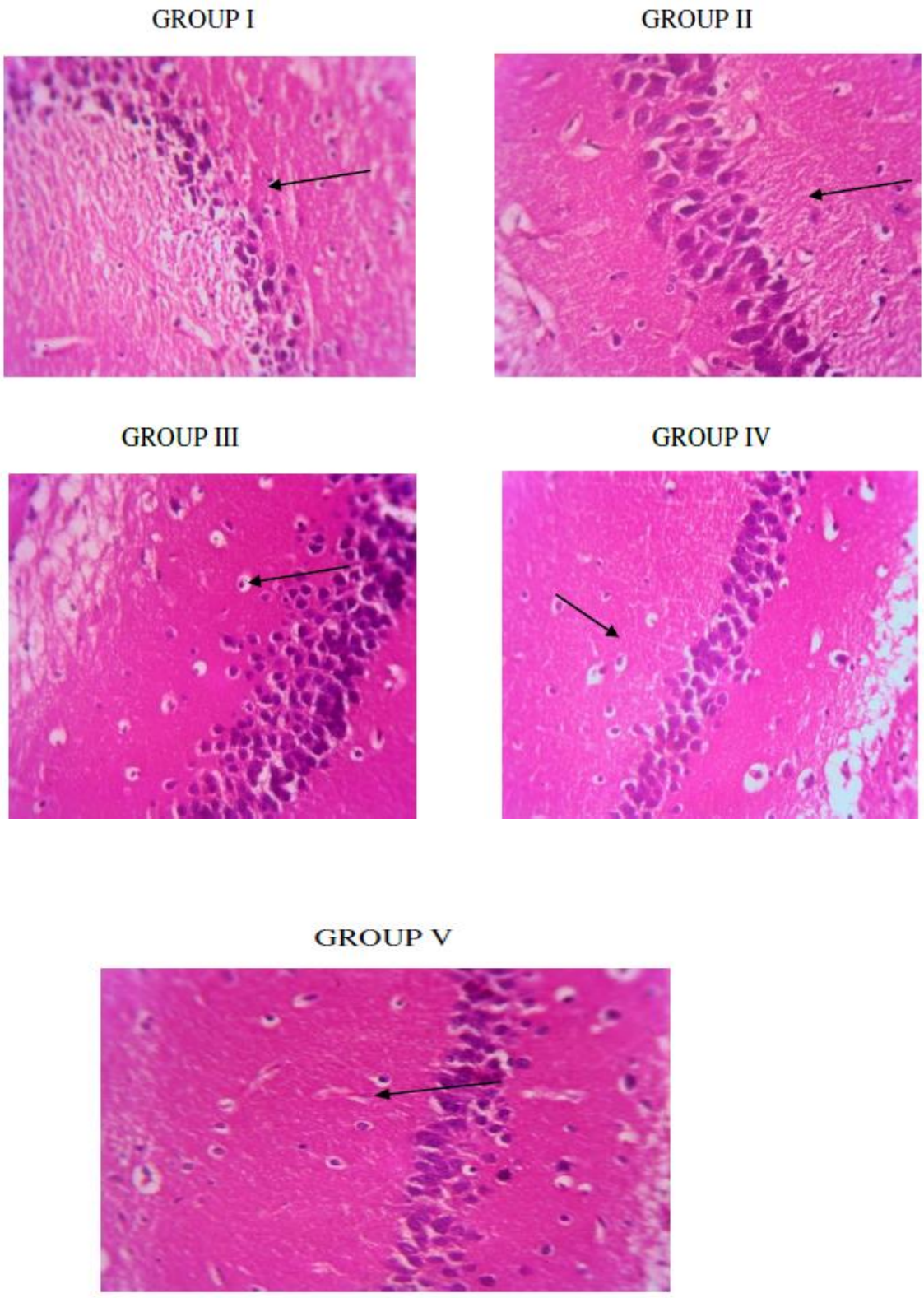
- The Concentration of GABA in Group I (Vehicle Control) was significantly increased when compared with Group II, III, IV and V ($p<0.0001$).
- The Concentration of GABA in Group II was significantly decreased when compared with Group III, IV and V ($p<0.0001$).
- The Concentration of GABA in Group III was significantly increased when compared with Group IV and V ($p<0.0001$).

7.6 HISTOPATHOLOGICAL ANALYSIS OF BRAIN IN MES INDUCED EPILEPSY IN WISTAR RATS:

Table: 16 Histopathological analysis of brain in MES induced epilepsy in wistar rats

GROUP I	Normal control	Haematoxylin and Eosin-stained section shows the normal brain tissue depicted intact cell architecture with normal amount of neurotransmitters
GROUP II	Negative control- Convulsion induced by MES 60 Hz alternating current of 150 mA intensity for 0.2 sec.	Haematoxylin and eosin-stained section show there is less neuron density.
GROUP III	Convulsion induced by MES 60 Hz alternating current of 150 mA intensity for 0.2 sec treated with standard drug - Phenytoin (25mg/kg p.o.)	Haematoxylin and eosin-stained section of the brain tissue showed no significant alterations observed in this group and tissues showed a normal picture or brain cells, less proliferation and more neuronal density at hippocampal region
GROUP IV	Convulsion induced by MES 60 Hz alternating current of 150 mA intensity for 0.2 sec treated with Lower dose of EEIB (200 mg/kg p.o).	Haematoxylin and Eosin-stained section of the brain tissue showed no pathological damages and cellular architecture are intact with more neuronal density compared to the MES alone treated group.
GROUP V	Convulsion induced wistar rats by MES 60 Hz alternating current of 150 mA intensity for 0.2 sec treated with Higher dose of EEIB (400 mg/kg p.o).	Haematoxylin and Eosin stained section of the brain tissue showed increased neuron density when compared to the EEIB (200mg/kg/p.o)

Figure: 18 Histopathology of Brain in MES induced epilepsy in wistar rats



8.DISCUSSION:

According to WHO, Epilepsy is a chronic non communicable disease of the brain that affects around 50 million people worldwide. It is characterized by recurrent seizures, which are brief episodes of involuntary movement that may involve a part of the body (partial) or the entire body (generalized) and are sometimes accompanied by loss of consciousness and control of bowel or bladder function. [1]

Seizure episodes are a result of excessive electrical discharges in a group of brain cells. Different parts of the brain can be the site of such discharges. Seizures can vary from the briefest lapses of attention or muscle jerks to severe and prolonged convulsions. Seizures can also vary in frequency, from less than 1 per year to several per day.

A seizure has a clear beginning, middle, and end. Epilepsy was one of the first brain disorders to be Described. Epileptic seizures are manifested by an abnormal, excessive, and hyper synchronous electrical discharge of neurons in the brain. Each distinct form of epilepsy has its own natural history and response to treatment [89]. This diversity probably reflects the many different underlying causes of epilepsy and the variety of epilepsy syndromes in which the clinical and pathological characteristics are distinctive and suggest a specific under lying etiologic mechanism. [90]

The International League against Epilepsy (ILAE) published a modified version of the International Classification of Epileptic Seizures (ICES), which has continued to be a very useful system. This system is based on the clinical features of seizures and associated EEG findings. The etiology or cellular substrate is not considered. There are three main types of seizures: partial, generalized, and unclassified.

There are many kinds of seizures, each with characteristic behavioral changes and electrophysiological disturbances that can usually be detected in scalp electroencephalographic recordings. A seizure is a transient epileptic event, indicating a disturbance in brain function. Having a single seizure does not necessarily mean that a person has epilepsy. Ten percent of adults experience a seizure sometime during their lifetime. [91]

Globally, an estimated 2.4 million people are diagnosed with epilepsy each year. In high income countries, annual new cases are between 30 and 50 per 100000 people in the general population. In low and middle-income countries, this figure can be up to two times higher. In many parts of the world, people with epilepsy and their families suffer from stigma and discrimination.

Epileptic seizures arise from an excessively synchronous and sustained discharge of a group of neurons. The single feature of all epileptic syndromes is a persistent increase of neuronal excitability. Abnormal cellular discharges may be associated with a variety of causative factors such as trauma, oxygen deprivation, tumours, infection, and metabolic derangements.

However, no specific causative factors are found in about half of the patients suffering from epilepsy. Underlying causes and pathophysiological mechanisms are (partially) understood for some forms of epilepsy, e.g., epilepsies caused by disorders of neuronal migration and

monogenic epilepsies. For several other types of epilepsy, current knowledge is only fragmentary.

Both neurotransmitter systems and ion channels play a crucial role in neuronal Excitability [28]. The major developmental disorders giving rise to epilepsy are disorders of neuronal migration that may have genetic or intrauterine causes. Abnormal patterns of neuronal migration lead to various forms of agyria or pachygyria whereas lesser degrees of failure of neuronal migration induce neuronal heterotopia in the subcortical white matter.

Recent experimental data suggest that cortical malformations can both form epileptogenic foci and alter brain development in a manner that diffuse hyperexcitability of the cortical network occurs. Other studies revealed increases in postsynaptic glutamate receptors and decreases in gamma aminobutyric acid receptors in microgyric cortex which could promote epileptogenesis.[92]

The GABA hypothesis of epilepsy implies that a reduction of GABA-ergic inhibition results in epilepsy whereas an enhancement of GABA-ergic inhibition results in an anti-epileptic effect. Inhibitory postsynaptic potentials (IPSPs) gradually decrease in amplitude during repetitive activation of cortical circuits. This phenomenon might be caused by decreases in GABA release from terminals, desensitization of GABA receptors that are coupled to increases in Cl^- conductance or alterations in the ionic gradient because of intracellular accumulation of Cl^- In case of intracellular accumulation of Cl^- passive redistribution is ineffective.[93]

Moreover, $Cl^- K^+$ co-transport becomes less effective during seizures as it depends on the K^+ gradient. As $Cl^- K^+$ co-transport depends on metabolic processes, its effectiveness may be affected by hypoxia or ischemia as well. These mechanisms may play a critical role in ictogenesis and interictal- ictal transition. Several studies have shown that GABA is involved in pathophysiology of epilepsy in both animal models and patients suffering from epilepsy.

GABA levels and glutamic acid decarboxylase (GAD) activity were shown to be reduced in epileptic foci surgically excised from patients with intractable epilepsy and in CSF of patients with certain types of epilepsy. In stiff-man syndrome, a disease associated with epilepsy and diabetes mellitus, auto-antibodies to GAD were demonstrated. A reduction of 3H-GABA binding has been reported in human brain tissue from epileptic patients whereas PET studies demonstrated reduced benzodiazepine receptor binding in human epileptic foci. The degree of benzodiazepine receptor reduction showed a positive correlation with seizure frequency. [94,95]

The GABA receptor complex is involved in various animal models of epilepsy as well.Low CSF levels of GABA were revealed in dogs with epilepsy. Reduced GAD levels were revealed in the substantia nigra of amygdala-kindled rats. Significant alterations in GABA and benzodiazepine binding have been shown in the substantia nigra of genetically seizure-prone gerbils. Rats with a genetic susceptibility to audiogenic seizures have a lower number of GABA receptors than animals of the same strain that are not seizure prone [118]. Several endogenous (guanidino compounds) and exogenous (e.g., bicuculline, picrotoxin, penicillin, pilocarpine, pentylenetetrazol) convulsant inhibit GABAergic transmission through inhibition of GABA synthesis or through interaction with distinct sites at the postsynaptic $GABA_A$ receptor.[96,97]

Convulsant agents that block synaptic GABA-mediated inhibition, amplify the dendritic spike generating mechanism that involves Ca^{2+}. Synaptic inputs are thought to trigger and synchronize this process throughout a population of cells which then might result in an epileptic fit. Several AEDs are GABA analogues, block GABA metabolism (e.g., vigabatrin, tiagabine, and valproate) or facilitate postsynaptic effects of GABA. However, a study evaluating dose-dependent behavioral effects of single doses of vigabatrin in audiogenic sensitive rats, suggests that the antiepileptic properties of vigabatrin not only depend on GABAergic neurotransmission but might also be explained by decreased central nervous system levels of excitatory amino acids or increased glycine concentrations. [98, 99,100]

Glutamatergic synapses play a critical role in all epileptic phenomena. Activation of both ionotropic and metabotropic postsynaptic glutamate receptors is proconvulsant. Antagonists of N-methyl-D aspartate (NMDA) receptors are powerful anti-convulsant in many animal models of epilepsy.

Abnormalities of CNS catecholamines have been reported in several genetic models of epilepsy. In spontaneous epileptic rat, dopamine was decreased in the nucleus caudatus whereas noradrenaline was increased in midbrain and brainstem. Decreased levels of dopamine have been found in epileptic foci of epilepsy patients [125]. In animal models of absence epilepsy, seizures are exacerbated by dopamine antagonists while fits are alleviated by dopamine agonists. These results suggest that decreased dopamine facilitates appearance of seizures by lowering the threshold triggering such seizures. [101, 102]

Affected females present with epilepsy whereas affected males die embryonically. However Recently, a male patient with bilateral periventricular and subcortical heterotopia was described which raises the possibility of a novel gene involved in brain formation. X-linked lissencephaly and double cortex syndrome is another disorder of neuronal migration. Double cortex or subcortical band heterotopias often occurs in females whereas more severe lissencephaly is found in affected males. A causal mutation in a gene called double cortin was recently identified. It was suggested that doublecortin acts as an intracellular signalling molecule critical for the migration of developing neurons. Although these disorders are relatively rare, studying the underlying pathophysiological mechanisms may shed light on the pathophysiology of more common epileptic syndromes.[103,104,105]

About 40% of patients suffering from epilepsy have a genetic background that contributes to the etiology of epilepsy. Most familial epilepsies like juvenile myoclonic epilepsy, childhood absence epilepsy, and benign childhood epilepsy with centrotemporal spikes have a complex mode of inheritance resulting from the interaction of several loci together with environmental factors. In patients with absence seizures (and their first-degree relatives), biochemical changes (e.g., increased plasma glutamate levels) have been identified which can be related to a generalized increase in cortical excitability.

Probably, the genetic predisposition of absence epilepsy is based on a gene-dependent biochemical derangement leading to increased cortical excitability. Genetic data generated by studies on animal models of absence epilepsy show a relatively simple inheritance factor of one gene that determines being epileptic or not while other genes determine number and duration of epileptic fits [136].

Monogenic epileptic disorders are rare, accounting for no more than 1% of patients. Recent advances in the genetics and molecular biology of these diseases unravelled the underlying Pathophysiology of some of these epileptic syndromes.

Although various epileptic syndromes were shown to differ pathophysiologically, they apparently share common ictogenesis-related characteristics such as increased neuronal excitability and synchronicity. Emerging insights point to alterations of synaptic functions and intrinsic properties of neurons as common mechanisms underlying hyper excitability. Progress in the field of molecular genetics revealed arguments in favor of this hypothesis as mutations of genes encoding ion channels were recently discovered in some forms of human epilepsy.

Antiepileptic drugs that are presently in clinical use include phenytoin, carbamazepine, ethosuximide, phenobarbitone, tiagabine, vigabatrin, gabapentin and clonazepam are the major drugs used for the treatment of epilepsy. The drug anti-epileptic drug phenytoin acts by blockade of voltage dependent sodium channels and stabilizes the neuronal membrane. It inhibits the generation of repetitive action potentials. Voltage dependent Na^+ channels enter an inactivated state and delay the recovery of these channels from inactivation.

AEDs have prominent side effects and fail to alter the course of epileptic complications. Dyskinesia, gingival hypertrophy, macrocytic anaemia, dermatitis, thyroiditis, taste disturbance, loss of appetite, dizziness, headache, flushing, increased urine output, gastrointestinal disturbance, skin rashes, drowsiness, overgrowth of hair, acne, hair loss, constipation, diarrhoea, double vision, insomnia, attention difficulties, visual disturbance, cough, weight changes, abdominal pain are the adverse effect produced, which make more disturbance in medication periods of patients.

Hence herbal drugs as therapeutic agents are preferred to reduce severe adverse effects of the allopathy therapies. Therefore, scientists are on the hunt for newer alternatives, with lesser side effects, self-administrable, less expensive and with complete reversibility. Much of these properties are observed in drugs of natural plant origin. Globally traditional system of medicine has been used to treat various diseases throughout the human history. Many plants are reported to have anti-epileptic activity. Moringa oleifa *(Moringaceae)*[107], *Acorus calamus* (Araceae)[108], *American ginseng* (Araliaceae)[109, 110], *Delphinium denudatum* (Ranunculaceae)[111] *Nardostachys jatamansi* (Valerianaceae)[112], *Herpestis monniera* (Scrophulariaceae)[113], *Ambrosia paniculata* (Asteraceae)[114] are the some of the plants having anti-epileptic activity.

In the present study the EEIB was evaluated for its anti-epileptic activity in experimental Rats. The root is commonly known as sweet potato and has been used extensively in traditional medicines for various ailments. The roots and skin of *Ipomoea batatas* contain high levels of polyphenols such as anthocyanins and phenolic acids and are a good source of vitamins A, B and C, iron, calcium and phosphorus. *Ipomoea batatas* has been reported to possess antioxidant, anti-diabetic, wound healing, anti-ulcer, anti-bacterial, and anti-mutagenic activities. It is also used as an immune booster and for relief of gastrointestinal and upper respiratory symptoms. The boiled roots of *Ipomoea batatas* are believed to relieve diarrhoea, and crushed leaves are used to treat acne and boils. [61]

Maximal electroshock (MES) induced epilepsy in wistar rats:

Flexion is the first stage in convulsive epilepsy, where the bending of joints, limbs occur. At this stage the rapid onset of a rigid posture with head flexed forwards, elevation of both arms, and flexion of the trunk forwards at the thigh. Convulsion induced by MES treated with EEIB for 21 days shows significant reduction in flexion phase, which elicits antiepileptic effect.

Extensor is the next stage followed by flexion, where limb extension occurs. Both flexion and extensor occur at very short duration. Convulsion induced by MES treated with EEIB for 21 days shows significant reduction in **Extensor** phase, which elicits antiepileptic effect.

Clonus stage in seizures consist of bilaterally synchronous involuntary muscle jerks that results in singly or in a brief salvo of repeated jerks. **Stupor** is characterized by impaired reaction to external stimuli, stuporous state is rigid, mute and only appear to be conscious, as the eyes are open. Convulsion induced by MES treated with EEIB for 21 days shows significant reduction in Clonus and Stupor phase

Recovery- Convulsion induced by MES treated with EEIB for 21 days shows significant reduction in **Recovery** period which elicits antiepileptic effect.

The Maximal electroshock induced seizures produce repetitive stimulation of high frequency action potentials thus opening of Na^{+} channels and increasing Ca^{2+} intracellularly leading depolarisation of cell. It has been found out that treatment of Rats with *Ipomoea batatas* Lam. showed significant decrease in the hind limb extensor period. Animal models of seizures induced by electrical stimulation convey the advantage of reproducing epileptogenic features in the intact brain with low mortality and high reproducibility. Moreover, unlike chemical-induced seizures, postictal alterations from electrical stimulation can be investigated when the epileptogenic cause is no longer present. However, seizure modelling by electrical stimulation does not provide cell-type specificity in the brain. In addition, stimulation protocols can be costly and laborious when used for chronic studies [115]

GABA is an inhibitory neurotransmitter and glutamate is an excitatory neurotransmitter which is responsible for the production of excitation of neurons thus plays an important role in the generation of seizures. The Maximal Electroshock (MES) induced seizure showed significant decreased levels of GABA in brain, thus showing that GABA plays an important role in the inhibition of seizures i.e., The percentage protection in MES induced seizure, treated with EEIB is significantly increased when compared to MES alone induced seizure groups. GABA level in MES induced seizure, treated with EEIB is significantly increased when compared to MES alone induced seizure group.

Isoniazid (INH) induced Epilepsy in wistar rats:

In order to study the Temporal Lobe Epilepsy and Status Epilepticus the INH induced epilepsy models are chosen. Isoniazid is regarded as a GABA-synthesis inhibitor. Clonic tonic seizures are elicited in Rats which is due decreasing in the pyridoxine metabolism. Due to decrease in the pyridoxine level, it produces the convulsion in Rats.

The EEIB and INH treated animals showed significant decrease in the onset and decreased duration of the seizure when compared with INH alone treated group animals. With that increased percentage protection from epilepsy in INH model shows that plant having anti-epileptic activity which can be used in TLE.

The presence of Flavonoids may help in the anti-epileptic property of *Ipomoea batatas* Lam.

The Histopathological study of brain shows that there is increased neuronal density produced by the EEIB with MES induced seizure groups compared to the MES alone induced seizure group.

The increased activity of GABA in EEIB treated group may be due Inhibition of GABA transaminase enzyme or by increased synthesis of GABA.

The antioxidant activity of *Ipomoea batatas*, helps to protect the brain from toxicity, which can help from seizures and other epilepsy conditions.

9. CONCLUSION:

The Tuberous roots of *Ipomoea batatas* Lam. showed reduction in the flexion, extensor, clonus and stupor duration in MES induced epilepsy model. Which shows the antiepileptic activity of EEIB. Hence the Ethanolic extract of *Ipomoea batatas* Lam can be used in Grandmal epilepsy.

The Tuberous roots of *Ipomoea batatas* Lam. showed reduction in morbidity and mortality of animals in INH induced epilepsy model, which shows the antiepileptic activity of EEIB. Hence the Ethanolic extract of *Ipomoea batatas* Lam can be used in TLE (Temporal Lobe Epilepsy)

The Histopathology of brain showed normal architecture and there is increased neuronal density which is comparable with phenytoin.

GABA level is increased in EEIB treated group, so the drug may probably act by GABA mechanism by Inhibiting the GABA transaminase enzyme or by increasing the synthesis of GABA

The Standard drug Diazepam acts by GABA mediated mechanism. Hence it is used in the treatment of Epilepsy. Aslike Diazepam, the EEIB also shows increase in GABA level as it contain the active constituent GABA in it. Hence it is used in treatment of epilepsy

Thus, it may be concluded that ***Ipomoea batatas* Lam.** produces significant Anti-Epileptic activity in both MES and INH induced epilepsy in Wistar Rats, which is comparable with that of Phenytoin and Diazepam.

Further work is necessary to elucidate the mechanism of action involved in the antiepileptic activity of *Ipomoea batatas* Lam. with special reference to Phytochemical constituents.

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Enclosure…

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