Syeda Nishat Fathima et al /J. Pharm. Sci. & Res. Vol. 7(11), 2015, 994-1003

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

A Review on Phytoextracts with Antiepileptic Property

Syeda Nishat Fathima*[1], Dr. S. Vasudevamurthy[1], N. Rajkumar[2]

[1.] *Department of Pharmacology, Jayamukhi College of Pharmacy, Narsampet, Warangal, TS, India*

[2.] *Department of Pharmaceutical Chemistry, Jayamukhi College of Pharmacy, Narsampet, Warangal, TS, India*

Abstract:

Epilepsy is a serious neurological disorder that affects around 50 million people worldwide. A large number of agents called antiepileptic drugs are available to treat various types of seizures with the objective to reduce seizure frequency and severity with in a framework of acceptable level of side effects. The ideal antiseizure drug would suppress all seizures without causing any unwanted effect. Unfortunately drugs used currently not only fail to control seizures activity in some patients but they frequently cause side effects and deleterious drug interactions. In addition safety, tolerability, efficiency, expenses especially in long term therapy, serum drug monitoring etc. are other limitations with synthetic antiepileptic drugs. Traditional systems of medicine are popular in developing countries and up to 80% of the population relies on traditional medicines or folk remedies for their primary health care need. Medicinal plants are believed to be an important source of new chemical substances with potential therapeutic effects. The present review highlights study of different plant extracts that are used in traditional system and that have demonstrated a potentiality for the treatment of epilepsy.

Keywords: Traditional medicine, Antiepileptic drugs, plant extracts.

DEFINITION:

Epilepsy was defined by Hughlings Jackson as an "an episodic disorder of the nervous system arising from the excessive synchronous and sustained discharge of a group of neurons" [1]. It is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure.

Epilepsy is a common chronic neurological disorder characterized by recurrent unprovoked seizures. These seizures are transient signs and/or symptoms of abnormal, excessive or synchronous neuronal activity in the brain. It is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure [2].

EPIDEMIOLOGY:

It is the most common serious brain disorder worldwide with no age, racial, social class, neither national nor geographic boundaries. Approximately 50 million people currently live with epilepsy 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. However, some studies in low- and middle-income countries suggest that the proportion is much higher, between 7 and 14 per 1000 people [3].

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 100 000 people in the general population. In low- and middle-income countries, this figure can be up to two times higher. Close to 80% of people with epilepsy live in low- and middle-income countries.

CLASSIFICATION:

The numerous epileptic seizure types are most commonly defined and grouped according to a scheme proposed by the International League Against Epilepsy. This classification is based on observation (clinical and EEG) rather than the underlying pathophysiology or anatomy [4].

I. PARTIAL SEIZURES (OLDER TERM: FOCAL SEIZURES)
A. Simple partial seizures - consciousness is not impaired
1 With motor signs
2 With sensory symptoms
3 With autonomic symptoms or signs
4 With psychic symptoms

B. Complex partial seizures - consciousness is impaired (Older terms: temporal lobe)
1 Simple partial onset, followed by impairment of consciousness
2 With impairment of consciousness at onset

C Partial seizures evolving to secondarily generalized seizures
1 Simple partial seizures evolving to generalized seizures
2 Complex partial seizures evolving to generalized seizures
3 Simple partial seizures evolving to complex partial seizures evolving to generalized seizures

II. GENERALIZED SEIZURES
A. Absence seizures (Older term: petitmal)
1 Typical absence seizures
2 Atypical absence seizures

B. Myoclonic seizures
C. Clonic seizures
D. Tonic seizures
E. Tonic-clonic seizures (Older term: grand mal)
F. Atonic seizures

III. UNCLASSIFIED EPILEPTIC SEIZURES

This classification was widely accepted but has also been criticized mainly because the underlying causes of epilepsy (which are a major determinant of clinical course and prognosis) were not covered in detail. In 2011 International League Against Epilepsy classified epilepsy into four categories and a number of subcategories reflecting recent technologic and scientific advances [5].

I. Unknown cause (mostly genetic or presumed genetic origin)
- **A.** Pure epilepsies due to single gene disorders
- **B.** Pure epilepsies with complex inheritance

II. Symptomatic (associated with gross anatomic or pathologic abnormalities)
- **A.** Mostly genetic or developmental causation
1. Childhood epilepsy syndromes
2. Progressive myoclonic epilepsies
3. Neurocutaneous syndromes
4. Other neurologic single gene disorders
5. Disorders of chromosome function
6. Developmental anomalies of cerebral structure
- **B.** Mostly acquired causes
1. Hippocampal sclerosis
2. Perinatal and infantile causes
3. Cerebral trauma, tumor or infection
4. Cerebrovascular disorders
5. Cerebral immunologic disorders
6. Degenerative and other neurologic conditions

III. Provoked (a specific systemic or environmental factor is the predominant cause of the seizures)
- **A.** Provoking factors
- **B.** Reflex epilepsies

IV. Crytogenic (presumed symptomatic nature in which the cause has not been identified

PATHOPHYSIOLOGY OF EPILEPSY:

Seizures are paroxysmal manifestations of the cerebral cortex. A seizure results when a sudden imbalance occurs between the excitatory and inhibitory forces with in the network of cortical neurons. The basic physiology of a seizure episode is detected to in an unstable cell membrane or its surrounding/adjacent supportive cells. The seizure originates from the gray matter of any cortical or subcortical area. Many different mechanisms can cause neuronal hyperexcitability and lead to the development of seizures. These factors include changes in ion channel conduction, membrane receptor response, messenger systems, and gene transcription. Imbalances between excitatory (glutamate) and inhibitory (gamma-aminobutyricacid, or GABA) neurotransmitters, as well as excessive acetylcholine, norepinephrine, and serotonin levels, may also precipitate seizures.

Excitatory and inhibitory currents are primarily mediated by different channels including voltage- and ligand-gated channels. Voltage-gated channels include sodium and calcium channels. Ligand-gated channels include GABA and glutamate channels. Most of the pharmacologic agents used in treating epilepsy target these different channels [6].

SYMPTOMS:

Seizures involve abnormal electrical activity that can produce changes in consciousness, motor and sensory activity, and behavior. The symptoms that occur can vary significantly from patient to patient and generally depend on the type of seizure or epilepsy. Generally, partial seizures originate in one hemisphere and can involve disturbances in motor function, sensory perception, autonomic function, and behavior. Sensory symptoms include paresthesias, abnormal tastes or smells, flashing lights, and hearing changes. Patients can report different autonomic symptoms, like sweating, epigastric sensation, or piloerection. Some patients can experience psychic symptoms including dysphasia, fear, and hallucinations. Automatisms, or repetitive movements, can be described in some patients and often present as chewing, swallowing, or sucking. A number of patients can experience an aura or warning symptoms minutes to hours before a seizure. Aura symptoms can differ significantly; examples include irritability, nausea, headache, and fear. Loss of consciousness and memory loss may also occur with partial seizures. Partial seizures may not terminate and can evolve into secondary generalized seizures. Generalized seizures involve both hemispheres and typically include bilateral motor symptoms and loss of consciousness [7].

PRESENTLY AVAILABLE ANTIEPILEPTIC DRUGS ALONG WITH THEIR MECHANISM OF ACTION, CLINICAL APPLICATIONS AND LIMITATIONS [8] [9]:

Drug	Mechanism of Action	Clinical Applications	Adverse Effects
Phenytoin	Blocks high frequency firing of neurons through action on voltage gated Sodium ion channels	Partial seizures and generalized tonic clonic seizures	Ataxia, diplopia, nystagmus, coarsening of facial features gingival hyperplasia, hirsutism, skin rashes, Stevens–Johnson syndrome, agranulocytosis, aplastic anemia, teratogenicity
Phenobarbital	Enhances phasic $GABA_A$ receptor responses	Generalized tonic clonic seizures and Partial seizures	Sedation, lethargy, dysarthria, coarsening of facial features, skin rashes, Dupuytrens' contracture, reduced libido, osteomalacia
Ethosuximide	Reduces low-threshold Calcium currents (T-type)	Absence seizures	Gastrointestinal changes, drowsiness, lethargy, mood changes, headache, visual changes, aplastic anemia

Drug	Mechanism of Action	Clinical Applications	Adverse Effects
Carbamazepine	Blocks high-frequency firing of neurons through action voltage gated Sodium ion channels and decreases synaptic release of glutamate	Generalized tonic-clonic seizures and partial seizures	Diplopia, dizziness, headache, ataxia, nystagmus, skin rashes, hyponatremia, aplastic anemia, agranulocytosis, weight gain, Stevens–Johnson syndrome, osteomalacia, hepatoxicity, teratogenicity
Diazepam	Potentiates $GABA_A$ responses	Status epilepticus and seizure clusters	Sedation, lethargy, drowsiness, dizziness, behavioral disturbances in children, hypersalivation
Gabapentin	Decreases excitatory transmission by acting on voltage gated Calcium ion channels.	Generalized seizures and partial seizures	Drowsiness, dizziness, ataxia, fatigue, hyperactivity (in children), weight gain
Pregabalin	Decreases excitatory transmission by acting on voltage gated Calcium ion channels.	Partial seizures	Weight gain, peripheral edema, dizziness, somnolence, asthenia, headache, ataxia
Vigabatrin	Irreversibly inhibits GABA transaminase	Partial seizures and infantile spasms	Drowsiness, dizziness, ataxia, tremor, lethargy, insomnia, psychosis, weight gain, visual field defects and blindness
Valproate	Blocks high frequency firing of neurons and modifies amino acid metabolism	Generalized seizures, partial seizures ,absence seizures and myoclonic seizures	Tremor, weight gain, dyspepsia, peripheral edema, pancreatitis, hair loss, thrombocytopenia, polycystic ovaries, Stevens–Johnson syndrome, hepatoxicity,
Lamotrigine	Prolongs inactivation of voltage gated Sodium ion channels, acts presynaptically on voltage gated Calcium ion channels and decreases glutamate release	Generalized tonic-clonic seizures, partial seizures and absence seizures	Dizziness, sedation, headache, diplopia, ataxia, skin rash, Stevens-Johnson syndrome
Levetiracetam	Action on synaptic protein SV_2A	Generalized tonic-clonic seizures and partial seizures	Sedation, fatigue, dizziness, headache, anorexia, psychiatric disturbances, leucopenia
Retigabine	Enhances K+ channel opening	Adjunctive treatment of partial seizures	Dizziness, somnolence, confusion, blurred vision
Rufinamide	Prolongs inactivation of voltage gated Sodium ion channels	Adjunctive treatment Lennox-Gastaut syndrome	Somnolence, vomiting, pyrexia, diarrhea
Tiagabine	Blocks GABA reuptake in forebrain by selective blockade of GAT-1	Partial seizures	Dizziness, lethargy, tremor, nervousness, emotional changes
Topiramate	Multiple actions on synaptic function, probably via actions on phosphorylation	Generalized tonic-clonic seizures, partial seizures, absence seizures and migraine	Cognitive problems, word finding difficulty, kidney stones, paresthesias, anorexia, weight loss, acute angle closure glaucoma
Zonisamide	Blocks high-frequency firing via action on voltage gated Sodium ion channels	Generalized tonic-clonic seizures, partial seizures and myoclonic seizures	Sedation, dizziness, headache, GI distress, skin rash, aplastic anemia, agranulocytosis, kidney stones, weight loss
Lacosamide	Enhances slow inactivation of voltage gated Sodium ion channels and effect of neurotrophins	Generalized tonic-clonic Seizures and partial seizures	Dizziness, nausea, diplopia, blurred vision, vomiting, headache, tremor and somnolence
Felbamate	Inhibits N-methyl-D-aspartate responses and potentiated GABA responses.	Severe and/or refractory epilepsies	Anorexia, weight loss, insomnia, dizziness, headache, ataxia, skin rashes, aplastic anemia, hepatoxicity
Stiripentol	Enhancement of inhibitory, GABAergic neurotransmission	Dravet's syndrome	Loss of appetite, drowsiness, cognitive impairment, ataxia, diplopia, nausea, abdominal pain

EXTRACTS WITH ANTICONVULSANT ACTIVITY:

- The methanol extract of the seed of *Adenanthera parvonina* protected mice against picrotoxin, Pentylenetetrazole, strychnine induced convulsions. It produces its anticonvulsant activity by enhancing GABAergic neurotransmission or facilitating GABAergic action and/or prevention of cell membrane destabilization in the brain [10].
- The aqueous extract isolated from the fruit of *Aegle marmelos* Corr. protected mice against tonic convulsions induced by Maximal Electroshock Seizures and especially by Pentylenetetrazole in mice [11].
- The ethanolic extract of leaves of *Albizzia lebbeck* has been shown to protect the mice from Maximal Electroshock Seizures, electrical kindling and Pentylenetetrazole induced convulsions. The bioassay-guided fractionation further indicated that the activity lies in the methanolic fraction of chloroform soluble part of ethanolic extract of leaves [12].
- The hydroalcoholic extract of *Argyreia speciosa* significantly delayed the latency and the onset of first clonus as well as onset of death in Pentylenetetrazole treated mice. Whereas in case of Maximal Electroshock Seizures it significantly reduced the duration of hind limb extension [13].
- The alcoholic extract of *Bacopa monnieri* may function in a similar manner to benzodiazepine, given its benzodiazepine-like action. It has been prevent to be a potent anticonvulsant [14].
- The methanolic extract of *Benincasa hispida* significantly increased the latency of convulsion and death induced by Pentylenetetrazole and Strychnine and inhibited the hind limb extension induced by maximal electroshock seizures [15].
- The methanolic extract of *Boerhavia diffusa* roots has anti-convulsant activity against Pentylenetetrazole induced convulsions. Its activity is due to liriodendrin which is calcium channel antagonistic properties [16].
- The various functions of petroleum ether extract of *Butea Monosperma* were studied for its anticonvulsant activity and active constituent was found to be triterpene in the n-hexane ethyl acetate (1:1) fraction. This triterpene significantly inhibited seizure induced by Maximal Electroshock Seizures, Pentylenetetrazole, electrical kindling and combination of lithium sulphate with pilocarpine nitrate while was not effective against strychnine and picrotoxin induced convulsions [17].
- The chloroform extract and aqueous extract of *Calotropis procera* roots provided protection against seizures induced by Maximal Electroshock Seizures, Pentylenetetrazole, lithium-pilocarpine and electrical kindling seizures [18].
- An alcoholic extract of aerial parts of *Capparis decidua* including flowers and fruits decreased the duration of tonic hind leg extension in Maximal Electroshock Seizures and dose-dependently decreased the number of animals with convulsions and increased convulsion latency in Pentylenetetrazole induced seizures test [19].
- The ethanolic root extract of *Carissa carandas* produce its anticonvulsant effects via non-specific mechanisms since it reduced the duration of seizures produced by Maximal Electroshock Seizures as well as delayed the latency of seizures produced by Pentylenetetrazole and picrotoxin [20].
- The alcoholic extract of heart wood of *Cedrus deodara* significantly increased the onset of clonus and tonic seizures in Pentylenetetrazole induced convulsions and decreased duration of tonic extensor phase in MES induced convulsions. It also showed significant modulation of GABA levels of cerebellum and whole brain other than cerebellum [21].
- The methanolic extract of *Chrysanthellum indicum* possessed anticonvulsant properties on MES, Pentylenetetrazole and strychnine induced seizures model [22].
- The aqueous extract of the stems of *Cissus quadrangularis* possesses anticonvulsant activity in Maximal Electroshock Seizures, N methyl -d-aspartate, Pentylenetetrazole, isonicotinic hydrazid acid and strychnine induced convulsions or turning behavior [23].
- The hydroalcoholic extract obtained from the aerial parts of *Cissus sicyoides* significantly increased protection against Pentylenetetrazole induced convulsions. [24]
- The ethanolic and aqueous extract of seeds of *Cleome viscose* Linn possesses the anticonvulsant activity against Maximal Electroshock Seizures and Pentylenetetrazole induced seizures [25].
- The saponins isolated from leaves of *Clerodendrum infortunatum* decreased the duration of seizures and gave protection in a dose dependent manner against Pentylenetetrazole induced convulsions [26].
- The aqueous and ethanolic seed extracts of *Coriander sativum* have anticonvulsant activity in the Pentylenetetrazole and Maximal Electroshock Seizures models. They increased the latency of convulsion induced by Pentylenetetrazole and showed activity against Maximal Electroshock Seizures [27].
- The aqueous and methanol extracts of the plant *Cotyledon orbiculata* was studied for seizures induced by Pentylenetetrazole, bicuculline, picrotoxin and N-methyl-dl-aspartic in mice. Aqueous extract and methanol extract significantly prolonged the onset of tonic seizures induced by Pentylenetetrazole, bicuculline, picrotoxin and NMDA [28].
- The aqueous and ethanolic extracts of stigmas of *Crocus sativum* have anticonvulsant activity in Pentylenetetrazole and Maximal Electroshock induced seizures [29].
- The ethanolic root extract of *Croton zambesicus* delayed the onset and latency of convulsion caused by Pentylenetetrazole and Picrotoxin. The root extract possesses anticonvulsant properties [30].
- The methanolic extract of rhizomes of *Cyperus articulatus* was tested for its anticonvulsant action against Pentylenetetrazole, Maximal Electroshock Seizures, strychnine and picrotoxin induced

convulsions. Further studies suggest that the aqueous extract of Cyperus articulatus showed dose dependent reduction in spontaneous epileptic form discharge and NMDA induced depolarization in rat cortical wedge preparation at concentration at which L-amino-3-hydroxy-5methyl-isoxazole-4-propionic acid (AMPA) induced depolarization are not affected. This indicates that the extract may contain components acting as AMPA antagonist responsible for the possible antiepileptic action [31].

- A study of anticonvulsant screening of ethanolic extract and aqueous fraction of the Dried roots of *Delphinium denudatum* plant against Maximal Electroshock Seizures, Pentylenetetrazole, bicuculline, picrotoxin and strychnine induced convulsions was carried out. Wherein ethanolic extract showed dose dependent anticonvulsant action on seizures induced by Pentylenetetrazole and bicuculline while aqueous extract showed activity against Pentylenetetrazole and Maximal Electroshock Seizures induced convulsions especially inhibition of hind limb extension [32].
- Dichloromethane, ethyl acetate, and ethanol extracts of the roots of *Diospyros fischeri* inhibited convulsions induced by Pentylenetetrazole [33].
- In Pentylenetetrazole induced seizures, the administration of *Drosera burmannii* alcoholic extract showed significant antiepileptic activity [34].
- The methanolic extract of *Echium amoenum* Fisch and C.A. Mey increased the latency of seizure, delayed the death time and decreased the percentage of mortality significantly against Picrotoxin induced seizure in mice [35].
- The seed acetone extracts of *Ferula gummosa* protected mice against tonic convulsions induced by maximal electroshock and Pentylenetetrazole [36].
- The saponins rich fraction (SFG) obtained *Ficus platyphylla* stem bark were studied on Pentylenetetrazole, strychnine and MES induced seizures in mice. SFG protected mice against Pentylenetetrazole and strychnine induced seizures; and significantly delayed the onset of myoclonic jerks and tonic seizures. SFG failed to protect mice against maximal electroshock seizures. SFG neither abolished the spontaneous discharges induced by 4-aminopyridine in a neonatal rat brain slice model of tonic–clonic epilepsy nor could it modulate chloride currents through $GABA_A$ receptor channel complex in cultured cortical cells. However, it was able to non-selectively suppress excitatory and inhibitory synaptic traffic, blocked sustained repetitive firing and spontaneous action potential firing in these cultured cells. It probably acts by blocking voltage-gated sodium channel [37].
- The extract obtained from the leaves of *Ficus Religiosa* has anticonvulsant activity against Pentylenetetrazole induced convulsion in albino rats [38].
- The aqueous extract of the stem bark of *Ficus sycomorus* conferred 100% protection to rats treated with a convulsive dose of Pentylenetetrazole indicating its anticonvulsive effect [39].
- The ethanolic extract of roots and rhizomes of *Glychrizza glabra* did not reduced the Hind limb tonic extension in Maximal Electroshock Seizures induced seizures. However it significantly and dose dependently delayed the onset of clonic seizures produced by Pentylenetetrazole and protected all the rats against picrotoxin induced seizures [40].
- Gossypin significantly reduced the tonic extensor convulsion induced by strychnine and Maximal Electroshock Seizures induced convulsions. It has anticonvulsant property and may probably be affecting both GABA aminergic and glycine inhibitory mechanism [41].
- The ethanol extract of inner bark *of Guettarda speciosa* increased the monoamines such as noradrenaline, dopamine, serotonin and Gamma amino butyric acid in forebrain of rats which may be decrease the susceptibility to MES and Pentylenetetrazole induced seizure in rats [42].
- The secondary aqueous root extracts of *Harpagophytum procumbens* possesses anticonvulsant activity against Pentylenetetrazole, picrotoxin and bicuculline induced seizures in mice. Its anticonvulsant activity is by enhancing GABAergic neurotransmission and/or facilitating GABAergic action in the brain [43].
- The antiepileptic efficacy of the root extract of *Hemidesmus indicus* on Maximal electroshock and Isoniazide induced convulsion was investigated. In MES induced convulsion method, the extract of *Hemidesmus indicus* at the different concentration significantly reduced the time spent in hind limb extensor phase. The *Hemidesmus indicus* extract significantly reduced the onset of convulsions in isoniazide induced seizures. This indicates that *Hemidesmus indicus* possess antiepileptic property similar to standard drug diazepam. Thus *Hemidesmus indicus* was regarded as a favorable anticonvulsant agent [44].
- In Pentylenetetrazole induced seizures, the aqueous and ethanol extract of aerial parts of *Hypericium perforatum* delayed the onset of tonic convulsion and protected the mice against mortality while in MES model the result was not significant. Furthermore, the study also reported that, a nitric oxide synthase inhibitor, reduced anticonvulsant effect of extract, indicating possible role of nitric oxide pathways [45].
- The aqueous extract of *Hypoxis hemerocallidea* Fisch. & C. A. Mey. (Hypoxidaceae) corm possesses the anticonvulsant activity against Pentylenetetrazole, picrotoxin and bicuculline induced seizures in mice. They produce its antiseizure effect by enhancing GABAergic neurotransmission and/or action in the brain [46].
- Results based on the lithium-pliocarpine induced *status epilepticus* rat model demonstrated that the ethanol extract of *Indigofera tinctoria*is effective in reducing the severity of *status epilepticus*. This, therefore,

supports traditional use of the plant in treatment of epilepsy [47].

- The aqueous, ethanol and chloroform extracts of *Ipomoea stans* root possessed antiepileptic activity against MES inducing test and subcutaneously injected Pentylenetetrazole [48].
- The aqueous-methanolic extract of *Lavandula stoechas* significantly reduced the severity and increased the latency of convulsions induced by Pentylenetetrazole and reduced Pentylenetetrazole's lethality [49].
- Water extract of *Leonotis leonurus* has anticonvulsant activity against Pentylenetetrazole, picrotoxin, bicuculline and N-methyl-DL-aspartic acid and may probably be acting through non-specific mechanisms, since it affects both GABAergic and glutaminergic systems [50].
- The crude methanol extract of *Leonotis nepetifolia* Linn (Lamiaceae) capitulum showed anticonvulsant activity in maximal electroshock test `in chicks; Pentylenetetrazole, strychnine and 4-aminopyridine induced seizure tests in mice [51].
- The decoction of *Mimosa pudica* leaves protected mice against Pentylenetetrazole and strychnine-induced seizures. *M. pudica* had no effect against picrotoxin-induced seizures. It also antagonized N-methyl-D-aspartate- induced turning behavior [52].
- The anticonvulsant effect of *Mitragyna africanus* stem bark against strychnine induced convulsions in rats have been reported causing protection by increasing the period of onset of convulsions along with decrease in the number of episodes of spasms [53].
- The ethanolic extracts of fruits of *Momordica cymbalaria* showed significant dose-dependent activity against the seizures by inhibiting the onset and incidence of convulsion [54].
- Fruit extract of *Morinda citrifolia* significantly reduced the time taken for righting reflex. There was a significant level of restoration of levels of biogenic amines such as dopamine, serotonin and nor-adrenaline in the forebrain region [55].
- Methanolic extract of *Moringa oleifera* root showed antiepileptic property to the extent of 70 percent whereas petroleum ether extract of *Mucuna pruriens* and *Vitex negundo* showed 50 percent protection [56].
- The n-hexane fraction of acetone insoluble part of petroleum ether extract of *Myristica fragrans* in MES model showed significant reduction in the duration of hind limb extension and in Pentylenetetrazole model it significantly delayed the myoclonic spasm. The delayed onset of clonic convulsions were recorded in picrotoxin model while in case of lithium pilocarpine induced status epilepticus, the gradual decrease in the progression as well as severity of status epilepticus was reported[57].
- Different extracts (Petroleum ether, methanolic, aqueous) of *Nerium oderum* were screened for the anticonvulsant activity using MES & Pentylenetetrazole Induced Seizures test models. Petroleum ether extract of *N. oderum* showed better anticonvulsant activity as compared to other extracts. Anticonvulsant activity of *N. oderum* in inhibiting seizures may be by regulating GABA mediated synaptic inhibition through action at distinct sites of the synapse [58].
- Thymoquinone is major constituent of *Nigella sativa* seeds, a traditional medicine claimed to be useful in convulsions. A study conducted for anticonvulsant effect of Thymoquinone using Pentylenetetrazole and Maximal Electroshock induced seizures found that it prolonged the onset of seizures and reduce the duration of myoclonic seizures induced by Pentylenetetrazole treatment but not by Maximal Electroshock Seizures. The complete protective effect against mortality was reported in both the tests. In addition, flumazenil, an antagonist of benzodiazepine inhibited the prolongation of seizure latency without affecting the duration of myoclonic seizures while pretreatment with different doses of naloxone inhibited the prolongation of myoclonic seizures as well as reduced the duration of myoclonic seizures induced by thymoquinone which indicate that the effect of thymoquinone in Pentylenetetrazole model probably through an opioid receptor mediated increase in GABAergic tone [59].
- Aqueous and methanol leaf extracts of *Nylandtia spinosa* possessed anticonvulsant activity against tonic seizures produced in mice by Pentylenetetrazole, bicuculline, picrotoxin, and NMDA [60].
- The leaf extracts and fraction of *Ocimum gratissimum* increased the latency of tonic and tonic-clonic seizures and death and elicited 50% protection against mortality in Pentylenetetrazole induced seizures [61].
- The saponins isolated from the stems of *Opuntia vulgaris* possess the anticonvulsant effects in Pentylenetetrazole induced convulsion in a dose dependent manner [62].
- The extract of *Passiflora edulis* showed anticonvulsant activity in mice. It protected mice against strychnine induced seizures and antagonized NMDA induced turning behavior in mice [63].
- The hydro- alcoholic extract of *Passiflora incarnata* prolonged the onset time of seizure and decreased the duration of seizures produced by Pentylenetetrazole. Flumazenil and naloxone suppressed anticonvulsant effects of *Passiflora incarnata* suggesting that the related to effect may be due to GABAergic and opioid systems [64].
- The aqueous extract of leafs of *Persea americana* significantly delayed the onset of, and antagonized, Pentylenetetrazole induced seizures, profoundly antagonized picrotoxin induced seizures, but only weakly antagonized bicuculline induced seizures. It produces its anticonvulsant effect by enhancing GABAergic neurotransmission and/or action in the brain [65].
- An aqueous leaf extract of *Pyrenacanthia staundii* showed protection against strychnine induced convulsions probably acting on glycinergic transmission [66].
- The aqueous leaf extract of *Rauvolfia vomitoria* possess anticonvulsant activity against strychnine,

picrotoxin and Pentylenetetrazole induced seizures in mice [67].

- The aqueous extract of *Rhus chirindensis* stem bark significantly delayed the onset of, and antagonized Pentylenetetrazole induced seizures. The plant's stem bark aqueous extract also profoundly antagonized picrotoxin induced seizures, but only weakly antagonized bicuculline-induced seizures [68].
- The flavonoids of *Rosa damascena* can attenuate the latent periods of the beginning of convulsions as well as the severity of seizures in a dose dependent manner against the Pentylenetetrazole induced seizures in rats and it may act via $GABA_A$ receptors [69].
- Hexanoic fraction of *Rubus brasiliensis* prevented the Pentylenetetrazole induced seizures. The fraction was found to contain a benzodiazepine like principle and hence indicated possible involvement of $GABA_A$ receptors. This involvement is further supported by reversal of anxiolysis in rodents induced by lumozenil, a specific GABA–A– benzodiazepine receptor antagonist [70].
- The ethanolic root extract of *Schumanniophyton magnifum* provided anticonvulsant activity against picrotoxin and strychnine induced convulsions [71].
- *Sclerocarya birrea* possesses anticonvulsant activity against Pentylenetetrazole, picrotoxin, and bicuculline induced seizures in mice. The plant extract also depressed the central nervous system. [72]
- The ethanolic extract of *Senna spectabilis* completely antagonized NMDA-induced turning behaviors well as protected mice against picrotoxin, Pentylenetetrazole and strychnine-induced seizures in mice. The extract of *S. spectabilis* completely antagonized Maximal Electroshock induced seizures by probably prolonging the inactivation of sodium channels they are assumed to identify anticonvulsant drugs effective against generalized tonic-clonic/partial seizures and generalized clonic seizures [73].
- The ethanolic roots extract of *Sphaeranthus indicus* significantly reduced the duration of seizures induced by Maximal Electroshock Seizures and protected animals from Pentylenetetrazole induced tonic seizures and significantly delayed the onset of tonic seizures produced by picrotoxin and N-methyl-dl-aspartic acid. It may produce its anticonvulsant effects via non-specific mechanisms [74].
- The air-dried *Spondias mombin* leaves extracted with aqueous, methanol and ethanol solvents provided protection against picrotoxin induced seizures probably by GABAergic mechanism [75].
- The alcohol extract of roots of Tagara (*Valeriana jatamansi*. Jones) or *Nymphoides macrospermum*. Vasudevan significantly reduced the severity and increased the latency of convulsions induced by Pentylenetetrazole and also reduced the time taken for recovery [76].
- Methanol extract of *Viscum sapense* was tested for activity against seizures in albino mice induced by Pentylenetetrazole, bicuculline and NMDA. Methanol extract protected the mice against Pentylenetetrazole and bicuculline-induced tonic seizures but did not significantly alter NMDLA-induced tonic seizures which indicate that the extract has anticonvulsant activity [77].
- The ethanolic leaf extra*ct of Vitex negundo* possessed anticonvulsant activity against MES seizures and Pentylenetetrazole induced seizures [78].
- *Withania somnifera* root extract increased the Pentylenetetrazole seizure threshold for the onset of tonic extension phase. Co-administration of sub effective dose with sub protective dose of exogenous GABA, a GABA receptor agonist or diazepam, a GABA receptor modulator increases the seizure threshold. The anticonvulsant activity of *Withania somnifera* root extract against Pentylenetetrazole seizure threshold paradigm involved the $GABA_A$ergic modulation [79].

FORMULATIONS WITH ANTIEPILEPTIC ACTIVITY:

- Ayurveda Bramhi Ghrita containing *Bacopa monnieri* (48g), *Acorus calamus* (4 g), *Evolvus alsinoids* (4g), *Sausserea lappa* and cow's ghee (80 gm.) showed the anticonvulsant effect of various doses when tested against Pentylenetetrazole and Maximum Electroshock induced seizures in mice. The study predicted possible mechanism of the formulation mediated through chloride channel of the GABA or benzodiazepine receptor complex [80].
- A poly herbal extract comprising of *Withania somnifera* Dunal, *Bacopa monnieri*, *Chlorophytum borivillianum, Curcuma longa, Glycyrrhiza glabra* and *Terminalia arjuna* was evaluated for its protective effect against seizures induced by Maximal Electroshock Seizures method in rats. A significant reduction in the time taken for righting reflex recovery was noted in the experimental animals. The levels of biogenic amines such as dopamine, serotonin and nor-adrenaline in the forebrain region were also estimated and a significant level of restoration was observed in the extract treated animals. Its possible mechanisms may be due to the inhibition of prostaglandin synthesis and monoamine oxidase enzyme or may be by the decreased influx of calcium ions [81].
- Panchagavya Ghrutham, a polyherbal ayurvedic formulation containing *Glycerrhiza glabra*, *Acorus calamus* and panchagavyam - the five products from cow, viz., milk, ghee (clarified butter fat), curd, urine and dung protected mice against tonic convulsions induced by maximal electroshock seizures and slightly prolonged the phases of seizure activity induced by Pentylenetetrazole [82].
- Unmadgajakesari Minerals - mercury, sulfur, realgar (manashila) and Herbs Dhatura.inoxia, Acorus.calamus, Sesbania.grandiflora and Bacopa.monierri have significant antiepileptic activity after prolonged administration against Pentylenetetrazole and maximum electroshock induced seizures in mice [83].

.**MARKETED HERBAL FORMULATIONS WITH ANTIEPILEPTIC ACTIVITY:** [84]

S.no	Brand name	Mfg.Company	Ingredients
1	APSA	IMIS	Withania somnifera, Hemamakshika Blasma, Rajatha Blasma, Extract of Rasona Vacha, Atimadhura, Mandukaparni, Kushta, Jatamansi, ParasikaYavani, Brahmi, Shatavari, Kushmanda, Sarpagandha, Triphal, Jeeraka, Krishana Beeja, Shirisha Beeja, Guduchi And Apapajitha
2	Ned forte	Charak	Akika Bhasma, Mass Extracts Of Yashthimadhu, Brahmi, and Vacha.
3	Zandopa	Zandu	Mucuna Pruriens.
4	Raswatarishta	Baidyanath	Brahmi, Shatavar, Vidara, Haritaki, Ushri, Sontha, Saunf, Nishoth, Laung Papal, Vacha, Kust, Ela, Ashvagandha, Bahera, Giloe, Vidanga, Dachini, Dhataki, Jaggery (Gud).
5	Chaturbhuj Ras	Baidyanath	Ras Sindoor, Kasturi, Swarna Blasma, Manashila and Hartal, Ghrit Kumari
6	Chaturmukha Ras.(with gold)	Baidyanath	Parad, Gandhak, Lauha, Bhasma, Abhrak, Bhasma, Swarna Bhasma

CONCLUSION:

Epilepsy is one of the most common neurological disorders with an incidence of 3% in the general population. Currently available Anti-epileptic drugs do not provide cure nor prevent relapse and they are often associated with serious side effects, including teratogenicity, chronic toxicity and adverse effects on cognition and behavior. This review clearly demonstrates the potency of different plant extracts in successful treatment of epilepsy in different animal models. The phytoconstituents present in different extracts has the promising effect in the management of epilepsy. This review gives a glance on the clinical effectiveness, minimal side effect profile and relatively low costs of herbal drugs in treatment and management of epilepsy. Further research should be done to isolate the bioactive components responsible for the antiepileptic activity in different types of seizures.

REFERENCES:

1. R. A. Webster. Neurotransmitters, drugs, and brain function. Chichester: John Wiley and Sons Ltd; 2001. Chapter 16, The epilepsies; 325-350.
2. Fisher RS, van Emde Boas W, Blume W, Elger C, Genton P, Lee P, Engel J Jr. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia. 2005 Apr;46(4):470-2.
3. World Health Organization. Epilepsy- Fact Sheet May 2015[Internet]. 2015 [cited on 15 July 2015]. Available from: http://www.who.int/mediacentre/factsheets/fs999/en/
4. Bancaud J, Henriksen O, Rubio-Donnadieu F, Seino M, Dreifuss FE, Penry JK . Proposal for revised clinical and electroencephalographic classification of epileptic seizures. From the Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia. 1981; 22(4):489–501.
5. Shorvon SD (2011). "The etiologic classification of epilepsy". *Epilepsia* 52 (6): 1052–1057.
6. Hien Ha, Renee Bellanger; Epilepsy: Treatment and Management. US Pharmacist. 2013;38(1):35-39.
7. Epilepsy Foundation. What Happens During A Seizure? [Internet]. 2015 [cited on 15 July 2015]. Available from: http://www.epilepsy.com/learn/epilepsy-101/what-happens-during-seizure
8. Brunton LL, Goodman LS, Blumenthal D, Buxton I. Goodman and Gilman's manual of pharmacology and therapeutics. United States: McGraw-Hill Professional; 2007. Chapter 19 Pharmacotherapy of the Epilepsies; 321-337.
9. Katzung BG, Masters SB, & Trevor AJ. Basic & clinical pharmacology. New York: McGraw-Hill Medical; 2012. Chapter 24 Antiseizure drugs; 403-426
10. Olukayode OJ, Emmanuel AO, Olajide AO, Makinde MJ. Anticonvulsant and depressant activities of the seed extracts of *Adnanthera parvonina*. Journal of Natural Products. 2009; 2: 74-80.
11. Ramdas BP, Popat BM, Shantaram GK, Sangameswaran B. In vivo anticonvulsant activity of *Aegle marmelos* Corr. Against pentylenetetrazole and electroconvulsive seizure in mice. Journal of Pharmacy Research. 2009; 2(12):1852-1854.
12. Kasture VS, Kasture SB, Pal SC. Anticonvulsant activity of *Albizzia lebbeck* leaves. Indian Journal of Experimental Biology. 1996; 34(1):78-80.
13. Vyawahare NS, Bodhankar SL. Anticonvulsant activity of *Argyreia speciosa* in mice. *Indian Journal of* Pharmaceutical Sciences. 2009; 71(2):131-134.
14. Kaushik D, Tripathi A, Tripathi R, Ganachari M, Khan SA. Anticonvulsant activity of *Bacopa monniera* in rodents. Brazilian Journal of Pharmaceutical Sciences. 2009; 45(4): 643-649.
15. Kumar A, P. Ramu P. Anti-convulsant activity of *Benincasa hispida* fruit, methanol extract. Journal of Natural Remedies. 2004; 4(2):195-198.
16. Adesina SK. Anticonvulsant Properties of the Roots of *Boerhaavia diffusa* Linnaeus. Pharmaceutical Biology. 1979; 17 (2): 84-86.
17. Silambujanaki P, Chitra V, Kumari S, Sankari M, Raju D, Chandra CHBT. Anti-convulsant activity of methanolic extract of *Butea monosperma* leaves. Research Journal of Pharmaceutical, Biological and Chemical Sciences. 2010; 1(2):431-435.
18. Jalalpure SS, Salahuddin M, Imtiyaz Shaikh MI, Manvi FV. Anticonvulsant effects of *Calotropis procera* root in rats. Journal Pharmaceutical Biology. 2009; 47(2):162-167.
19. Goyal M, Nagori BP, Sasmal D. Sedative and anticonvulsant effects of an alcoholic extract of *Capparis deciduas*. Journal of Natural Medicines. 2009; 63(4):375-379.
20. Hegde K, Thakker SP, Joshi AB, Shastry CS, Chandrashekhar KS. Anticonvulsant Activity of *Carissa carandas* Linn.Root Extract in Experimental Mice. Tropical Journal of Pharmaceutical Research. 2009; 8 (2):117-125.
21. Viswanatha GL, Nandakumar K, Shylaja H, Ramesh C, Rajesh S, Srinath R. Anxiolytic and anticonvulsant activity of alcoholic extract of heart wood of *Cedrus deodara* Roxb in rodents. *Journal of Pharmaceutical Research and Health Care. 2009; 1(2)*:217-239.
22. Yaro AH, Anuka JA, Salawu OA, Magaji MG. Anticonvulsant activities of methanol extract of *Chrysanthellum indicum* linn. vatke

in mice and chicks. Nigerian Journal of Pharmaceutical Sciences. 2007; 6(2): 22-27.
23. Vijay P, Vijayvergia R. Analgesic, anti-inflammatory and antipyretic activity of *Cissus quadrangularis*. Journal of Pharmaceutical Science and Technology. 2010; 2 (1):111-118.
24. Almeida ER, Rafael KRO, Couto GBL, Ishigami ABM. Anxiolytic and Anticonvulsant Effects on Mice of Flavonoids, Linalool, and α-Tocopherol Presents in the Extract of Leaves of *Cissus sicyoides* L. (Vitaceae). Journal of Biomedicine and Biotechnology. 2009, Article ID 274740. doi: 10.1155/2009/274740.
25. Mishra A, Mishra1 AK, Jain SK. Anticonvulsant activity of *Cleome viscosa* seed extracts in Swiss albino mice. International Journal of Pharmacy and Pharmaceutical Sciences. 2010; 2(1): 177-181.
26. Pal DK, Sannigrahi S, Mazumder UK. Analgesic and anticonvulsant effect of saponins isolated from the leaves of *Clerodendrum infortunatum* Linn. in mice.. Indian Journal of Experimental Biology. 2009; 47:743-747.
27. Hosseinzadeh H, Madanifare M. Anticonvulsant effects of *Coriandrum sativum* L. seeds extracts in mice. Archives of Iranian Medicine. 2000; 3:182-184.
28. Amabeoku GJ, Green I, Kabatende J. Anticonvulsant activity of *Cotyledon orbiculata* L. (Crassulaceae) leaf extract in mice. Journal of *Ethnopharmacology*. 2007; 112(1):101-107.
29. Hosseinzadeh H, Khosravan V "Anticonvulsant effects of aqueous and ethanolic extracts of *crocus sativus* l. Stigmas in mice. Archives of Iranian Medicine. 2002; 5(1): 44-4.
30. Ayanniyi AO, Wannang NN. Anticonvulsant activity of the aqueous leaf extract of *Croton zambesicus* (Euphorbiaceae) in Mice and rats. Iranian Journal of Pharmacology & Therapeutics. 2008; 7 (1):79-82.
31. Bum EN, Schmutz M, Meyer C, Rakotonirina A, Bopelet M, Portet C, Jeker A, Rakotonirina SV, Olpe HR, Herrling P. Anticonvulsant properties of the methanolic extract of *Cyperus articulatus* (Cyperaceae). Journal of *Ethnopharmacology*. 2001; 76(2):145-150.
32. Raza M, Shaheen F, Choudhary MI, Sombati S, Rafiq A, Suria A, Rahman A, DeLorenzo RJ. Anticonvulsant activities of ethanolic extract and aqueous fraction isolated from *Delphinium denudatum*. Journal of *Ethnopharmacology*. 2001; 78(1):73-78.
33. Moshi MJ, Masimba PJ, Nondo RSO, Mbwambo ZH, Kapingu MC, Mohamed M, Kimbokota F. Anticonvulsant activity of extracts of *Diospyros fischeri* stem bark. African Journal of Traditional, Complimentary and Alternative Medicines. 2007; 4(1):94-98.
34. Hema B, Bhupendra S, Saleem TSM, Gauthaman K. Anticonvulsant Effect of *Drosera burmannii* Vahl", International Journal of Applied Research in Natural Products. 2009; 2(3):1-4.
35. Heidari MR, Mandegary A, Hosseini A, Vahedian M. Anticonvulsant effect of methanolic extract of *Echium amoenum* Fisch & C.A.Mey against seizure induced by picrotoxin in mice. Pakistan Journal of Biological Sciences. 2006; 9:772-776.
36. Sayyah M, Kamalinejad M, Rajab BH, Rustaiyan A. Antiepileptic potiential and composition of the fruit essential oil of Ferula gummosa boiss. *Indian Journal of* Medical Research. 1975; 63(3):462-468.
37. Wakeel OK, Aziba PI, Ashorobi RB, Umukoro S, Aderibigbe AO, Awe EO. Neuropharmacological activities of *Ficus platyphylla* stembark in mice. African Journal of Biomedical Research. 2004; 7:75-78.
38. Singh D, Goel RK. Anticonvulsant effect of *Ficus religiosa*: role of serotonergic pathways. Journal of Ethnopharmacology. 2009; 123(2):330-334.
39. Ibrahim G, Abdulmumin S, Musa KY, Yaro AH. Anticonvulsant Activities of Crude Flavonoid Fraction of the Stem Bark of *Ficus sycomorus* (Moraceae). Journal of Pharmacology and Toxicology. 2008; 3:351-356.
40. Ambawade SD, Kasture VS, Kasture SB. Anticonvulsant activity of roots and rhizomes of Glycyrrhiza glabra. Indian Journal of Pharmacology. 2002; 34:251-255
41. Rasilingam D, Duraisamy S, Subramanian R. Anticonvulsant activity of bioflavonoid gossypin. A Journal of the Bangladesh Pharmacological Society. 2009; 4:51-54.
42. Kumar AS, Gandhimathi R. Effect of *Guettarda speciosa* extracts on biogenic amines concentrations in rat brain after induction of seizure. International Journal of Pharmacy and Pharmaceutical Sciences. 2009; 1(1):237-243.
43. Mahomed IM, Ojewole JAO. Anticonvulsant activity of *Harpagophytum procumb*ens DC [Pedaliaceae] secondary root aqueous extract in mice. Brain Research Bulletin. 2006; 69(1):57-62.
44. Madhu M, Prashanth HVK, Singh J, Gowda KPS. To evaluate the anti-epileptic activity of aqueous root extract of *Hemidesmus indicus* in rats. Archives of Pharmaceutical Sciences and Research. 2009; 1(1): 43-47.
45. Hosseinzadeh H, Karimi GR, Rakhshanizadeh M. Anticonvulsant effect of *Hypericum perforatum*: role of nitric oxide. Journal of Ethnopharmacology. 2005; 98(1-2):207-208
46. Ojewole, JAO. Anticonvulsant activity of *Hypoxis hemerocallidea* Fisch. & C. A. Mey. (Hypoxidaceae) corm (African potato) aqueous extract in mice. Phytotherapy Research. 2007; 22(1):91-96.
47. Asuntha G, Prasannaraju Y, Prasad KVSRG. Effect of Ethanol Extract of *Indigofera tinctoria* Linn (Fabaceae) on Lithium/Pilocarpine-Induced Status Epilepticus and Oxidative Stress in Wistar Rats. Tropical Journal of Pharmaceutical Research. 2010; 9(2):2010:149-156.
48. Ruiz AN, Mora GP, Michel MTV, Rodriguez JRD, Ramirez BEB, Arellano JDQ, Madrigal BR. Anticonvulsant Effect of Aqueous, Hydroalcohol and Chloroform Extracts from *Ipomoea stans* Root in the Rat. Phytotherapy Research. 1998; 10(3):242-244.
49. Gilani AH, Aziz N, Khan MA, Shaheen F, Jabeen Q, Siddiqui BS, Herzig JW. Ethnopharmacological evaluation of the anticonvulsant, sedative and antispasmodic activities of *Lavandula stoechas* L. Journal of Ethnopharmacology. 2000; 71(1-2):161-167.
50. Bienvenu E, Amabeoku GJ, Eagles P, Scott G, Springfield EP. Anticonvulsant activity of aqueous extract of *Leonotis leonurus* (Lamiaceae). Phytomedicine. 2002; 217(2):217-223.
51. Ayanwuyi LO, Yaro AH, Adamu YS. Studies on anticonvulsant activity of methanol capitulum extract of *Leonotis nepetifolia* linn. Nigerian Journal of Pharmaceutical Sciences. 2009; 8(1)73-79.
52. Bum EN, Dawack DL, Schmutz M, Rakotonirina A, Rakotonirina SV, Portet C, Jeker A, Olpe HR. *Anticonvulsant activity of Mimosa pudica* decoction. Fitoterapia. 2004; 75(3-4):309-314.
53. Aji BM, Onyeyili PA, Osunkwo UA. The central nervous effects of Mitragyna africanus (Willd) stembark extract in rats. Journal of *Ethnopharmacology*. 2001; 77(2-3):143-149.
54. Murthy NS, Snehalatha N, Anuradha N, Seetharam YN. Anticonvulsant activity of ethanolic extract of Momordica cymbalaria Fenzl. ex Naud. *Focus* on *Alternative* and Complementary Therapies. 2007; 12(1):45-47.
55. Muralidharan P, Srikanth J. Anti Epileptic Activity of *Morinda Citrifolia* Linn Fruit Extract. E-Journal of Chemistry. 2010; 7(2):612-616.
56. Gupta M, Mazumder UK, Chakrabarti S. CNS activities of methanolic extract of *Moringa oleifera* root in mice. *Fitoterapia. 199; 70*(3)*:244-250.*
57. Sonavane GS, Palekar RC, Kasture VS, Kasture SB. Anticonvulsant and behavioural actions of *Myristica fragrans* seeds. Indian Journal of Pharmacology. 2002; .34:332-338.
58. Saini P, Kannapan N, Diwan A, Kumar P, Antil V, Sharma S, Singh S. Anticonvulsant activity of flower part of *N. Oderum*. International Journal of Pharma and Bio Sciences. 2010; 1(2):1-4.
59. Hosseinzadeh H, Parvardeh S. Anticonvulsant effects of thymoquinone, the major constituent of Nigella sativa seeds, in mice. Phytomedicine. 2004; 11 (1):56-64.
60. Amabeoku GJ. Anticonvulsant activity of *Nylandtia spinosa* L. Dumont (Polygalaceae) aqueous and methanol leaf extracts in mice. Human and Experimental Toxicology. 2008; 27(11): 811-818.
61. Okoli CO, Ezike AC, Agwagah OC, Akah PA. Anticonvulsant and anxiolytic evaluation of leaf extracts of *Ocimum gratissimum*, a culinary herb. Pharmacognosy Research, 2010; 2(1):36-40.
62. Pal DK, Sahoo M, Mishra AK. Analgesic and anticonvulsant effects of saponin isolated from the stems of O*puntia vulgaris* mill. In mice. European Bulletin of Drug Research. 2005; 13:91-97.
63. Bum EN, Ngah E, Ekoundic BC, Dong C, Mbomo REA, Rakotonirina SV, Rakotonirina A. Sedative and anticonvulsant properties of *Passiflora edulis* dried leaves decoction in mice. African Journal. Traditional, Complementary and Alternative Medicines. 2004:1(1):63-71.
64. Nassiri-As M, Shariati-Rad S, Zamansoltani F. Anticonvulsant effects of aerial parts of *Passiflora incarnata* extract in mice: involvement of benzodiazepine and opioid receptors. *BMC Complementary and Alternative Medicine. 2007; 7:26.*

65. Ojewole JAO, Amabeoku GJ. Anticonvulsant effect of *Persea americana* Mill (Lauraceae) (Avocado) leaf aqueous extract in mice. Phytotherapy Research. 2006; 20(8):696-700.
66. Awe EO, Makinde JM, Olajide OA, Wahkeel OK, Adeloye AO. Evaluation of analgesic, anticonvulsant and hypnotic activities of P*yrenacanthia staundtii***.** African Journal. Traditional, Complementary and Alternative Medicines. 2005; 2(2):122-128.
67. Olatokunboh AO, Kayode YO, Adeola OK. Anticonvulsant activity of *Rauvolfia Vomitoria* (Afzel). African Journal of Pharmacy and Pharmacology. 2009; 3(6):319-322.
68. Ojewole JAO. Anticonvulsant effect of *Rhus chirindensis* (Baker F.) (Anacardiaceae) stem-bark aqueous extract in mice. Journal of *Ethnopharmacology.* 2008; 117(1):130-135.
69. Kheirabadi M, Moghimi A, Rakhshande H, Rassouli MB. Evaluation of the Anticonvulsant Activities of *Rosa damascena* on the PTZ Induced Seizures in Wistar Rats. Journal of Biological Sciences. 2008; 8(2): 426-430.
70. Nogueira E, Vassilieff VS. Hypnotic, anticonvulsant and muscle relaxant effects of *Rubus brasiliensis*. Involvement of $GABA_A$-system. Journal of Ethnopharmacology. 2000; 70(3):275-280.
71. Ogbonnia SO, Jäger AK, J Staden JV, Coker HAB. Anticonvulsant Activity of *Schumanniophyton magnificum* Roots Extracts in Mice. West African Journal of Pharmacology and Drug Research. 2003; 19(1&2):33-36.
72. Ojewole JAO. Anticonvulsant effect of *Sclerocarya birrea* (A. Rich.) Hochst. subsp. caffra (Sond.) Kokwaro (Anacardiaceae) stem-bark aqueous extract in mice. Journal of Natural Medicines. 2007; 61(1):67-72.
73. Rakotonirina A, Pelanken MM, Njikam N, Taiwe GS, Ngoupaye GT, Bum EN, Nkantchoua GN, Maidawa F, Rakotonirina SV. Anticonvulsant and Sedative Activity of Leaves of *Senna spectabilis* in Mice. International Journal of Pharmacology. 2010; 6(2):123-128.
74. Nanda BK, Jena J, Rath B, Behera BR. Anticonvulsant activity of whole parts of *Sphaeranthus indicus Linn.* extract in experimental mice. Drug Invention Today. 2010; 2(3):202-206.
75. Ayoka AO, Akomolafe RO, Iwalewa EO, Akanmu MA, Ukponmwan OE. Sedative, antiepileptic and antipsychotic effects of *Spondias mombin* L. (Anacardiaceae) in mice and rats. Journal of Ethnopharmacology. 2006; 103(3):166-175.
76. Murali A, Sudha C, Madhavan V, Yoganarasimhan SN. Anticonvulsant and Sedative Activity of Tagara (*Nymphoides macrospermum*.). Pharmaceutical Biology. 2007; 45(5):407-410.
77. Amabeoku GJ, Leng MJ, Syce JA. Antimicrobial and anticonvulsant activities of *Viscum capense*. Journal of Ethnopharmacology. 1998; 61(3):237-41.
78. Tandon VR, Gupta RK. An experimental evaluation of anticonvulsant activity of *Vitex negundo*. Indian Journal of Physiology and Pharmacology. 2005; 49(2):199–205.
79. Kulkarni SK, Akula, Dhir A. Effect of *Withania somnifera* Dunal root extract against pentylenetetrazole seizure threshold in mice: Possible involvement of GABAergic system. Indian Journal of Experimental Biology. 2008; 47:465-469.
80. Achliya GS, Wadodkar SG, Dorle AK. Evaluation of CNS activity of *Bramhi Ghrita.* Indian Journal of Pharmacology. 2005; 37:33-36.
81. Balamurugan G, Muralidharan P, Selvarajan S. Anti-epileptic activity of poly herbal extract from indian medicinal plants. Journal of Scientific Reasearch. 2009; 1(1): 153-59.
82. Anupama K, Satyanarayana S, Mukkanti K, Khan KA, Kumar KP. Anticonvulsant activity of Panchagavya Ghrutham: A polyherbal Ayurvedic formulation. Journal of Pharmacy Research 2009 Vol. 2 No. 5 pp. 795-797
83. Rajeeta J, Vijaya P, Asmita W, Gouraav D. Antiepileptic activity of Unmadgajakesari- A herbomineral formulation: An experimental evaluation. International Journal of Phytommedicine 7 (2015) 106-111
84. Vyawahare NS, Khandelwal AR, Batra VR, Nikam AP. Herbal anticonvulsants. Journal of Herbal Medicine and Toxicology.2007; 1(1):9-14.