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Herbal Therapies for Epilepsy: Chemistry, Biology and Potential Applications of Selected Plants and Compounds

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Abstract: Epilepsy is traditionally treated with antiseizure drugs. These medications may not work for every individual, and they come with a risk of side effects. Alternative remedies, such as herbal treatment, although not a replacement for normal treatment, can help to relieve convulsions without the typical side effects that are connected with an anti-epileptic drug. These herbal treatments are supported by a modest amount of research, especially during last three decades. Present review reports on 28 herbal remedies including medicinal plants and natural products [with their chief phyto-constituent(s)] evaluated for the treatment of epilepsy experimentally induced by various methods including Pentylenetetrazole (PTZ), Maximal Electroshock (MES), N-Methyl-D-Aspartate (NMDA), Isonicotinic acid (INH), Picrotoxin (PIC), Strychnine (STR), Lithium-Pilocarpine Hypoxic Episode (LPHE), Kainic Acid (KA), Bicuculine (BIC) and Nikethamide (NKTM) as found in 71 references compiled from the major databases, viz., Chemical Abstracts, Science Direct, SciFinder, PubMed and Google Scholar.

Keywords: Epilepsy; Antiepileptic; Anticonvulsant; Herbal Antiepileptic treatment; Chemical structure; Bio-active constituents.

Abbreviations: PTZ, Pentylenetetrazole: MES, Maximal Electroshock: NMDA, N-Methyl-D-Aspartate: INH, Isonicotinic acid: PIC, Picrotoxin: STR, Strychnine: LPHE, Lithium-Pilocarpine Hypoxic Episode: KA, Kainic Acid: BIC, Bicuculine: NKTM, Nikethamide: TLE, Temporal Lobe Epilepsy: SE, Status Epilepticus: IPI, initial precipitating injury: AEDs, antiepileptic drugs: HLTE, hind limb tonic extension: PHT, Phenytoin: PB, Phenobarbitone: GABA, Gamma Amino Butyric Acid.

1. Introduction: Impact and Pathogenesis of Epilepsy

Epilepsies are a group of CNS disorders characterized by paroxysmal cerebral dysrhythmia, manifesting as brief episodes (seizures) of loss or disturbance of consciousness, with or without characteristic

body movements (convulsions), sensory or psychiatric phenomena [1] . Epileptic seizures typically involve excessive firing and synchronization of neurons. This interrupts the normal working of the parts of the brain involved, leading to the clinical symptoms and semiology of the specific type of epilepsy.[2] A seizure is a convulsive episode, which starts of as atypical, excessive hyper-synchronous discharges from a group of neurons in the brain and then recruits surrounding neurons to comprise one area of the brain (partial seizures), or may affect nerve cells throughout the brain (generalized seizures) [3]. The danger that results from seizures reside in the fact these episodes may cause extensive brain damage. The brain damage as a result from seizures is a dynamic process that comprises multiple factors contributing to neuronal cell death, including but not limited to genetic factors, the extent of glutamate-mediated toxicity leading to disturbances in the intracellular electrolyte metabolism, mitochondrial dysfunction, oxidative stress, growth factor depletion and increased concentration of cytokines [4]. Intense seizure activity also initiates massive influx of calcium via voltage gated and N-methyl-D-aspartate (NMDA)-dependent ion channels [5]. Elevated calcium levels within the cell results in activation of biochemical cascades which trigger acute neuronal cell death after the Status Epilepticus (SE) and may induce generation of free radicals [4, 5].

Seizures are primarily organized according to where the seizures origins and area effected within the brain. Partial seizures affect nerve discharge in a localized area of the brain, whereas in generalized seizures nerve discharge is affected through the whole brain. Partial seizures maybe further described in the context of if the state of consciousness was not affected (simple partial) or if consciousness was affected (complex partial). Partial seizures that spread within the brain occur through a process known as secondary generalization. Temporal Lobe Epilepsy (TLE) encompasses partial seizures and is among the most frequent types of epilepsy [4-6]. Generalized seizures are further described according what manner the body is affected, however all involve loss of consciousness. These include but are not limited to absence (petit mal), myoclonic, clonic, tonic, tonic-clonic (grand mal) and atonic seizures (Figure 1).

About 25% of people diagnosed with epilepsy have seizures that cannot be controlled by antiepileptic drugs [6, 7]. However, there are various types of therapeutic approaches that aim to prevent the epileptogenesis after the SE or an IPI. Extensive efforts have been made to achieve neuroprotection through effective seizure suppression with antiepileptic drugs (AEDs). The anticonvulsive mechanisms of conventional and newly introduced drugs vary considerably. The most common actions were shown to effect ion channels, GABA-ergic and glutamatergic metabolism, receptors or secondary messengers [8].Various reports suggest that conventional as well as recently introduced anticonvulsants have some neuroprotective activity in models of ischemia[9, 10].

Herbal remedies have been employed for the treatment and management of various ailments since the beginning of human civilization. Over the last two decades, there has been a rapid expansion in the number and types of available AEDs and it may be easy to overlook and be sceptical about non-pharmacological treatments. Historically, more holistic approaches were taken in epilepsy management, ranging from herbal remedies and dietary manipulation (including fasting) to spiritual rituals [11].

2. Herbal therapies for Epilepsy: A review of anticonvulsant property of selected plants and compounds

Nature is a rich source of biological and chemical diversity and a number of plants in the world have been used in traditional medicinal system, i.e., anticonvulsant, anxiolytic, analgesic, antidepressant etc. Over thousands of years, people with epilepsy are using a variety of botanicals and herbs, hereafter referred to simply as herbal therapies (although no clinical benefit is implied by this term) [12]. Traditional systems of medicine are popular in developing countries and up to 80% of the population relies on traditional medicines for their primary healthcare needs. Several plants used for the treatment of epilepsy in different systems of traditional medicine have shown activity when tested on modern bioassays for the detection of anticonvulsant activity [13]. Herbal medicine is an area of complementary alternative medicine that is readily amenable to empirical research. Numerous herbal medicines have effects in the central nervous system and are found to have antiepileptic potential; some important ones, especially those investigated during last three decades are presented here along with their most important biologically active moiety as reported in the literature (Table 1).

Further, it is imperative to mention here that the current available AEDs that are clinically effective in the management of generalized tonic–clonic and partial seizures such as carbamazepine, phenytoin, primidone, phenobarbital, valproate and lamotrigine all suppress hind limb tonic extension (HLTE) in MES- induced test [14, 15]. Protection against HLTE also indicates the ability of a testing material to inhibit or prevent seizures discharge within the brainstem seizure substrate [14]. The ability of the test drug/ compound to inhibit the HLTE in MES Test as compared to phenytoin (100% protection) in the model suggests anticonvulsant activity for the management of generalized tonic–clonic and partial seizures. AEDs effective in the therapy of generalized seizures of (absence or myoclonic) petit mal type such as phenobarbitone, valproate, ethosuximide and benzodiazepines exhibit dose-dependent suppression of various seizure pattern induced by Pentylenetetrazole (PTZ) [16]. PTZ-induced seizures are similar to the symptoms observed in the absence seizures and drugs such as valproate and ethosuximide which are useful in the management of absence seizures inhibit PTZ-induced seizures [17]. At cellular level, one of the basic mechanisms of actions of AEDs such as ethosuximide and valproate is the suppression of T-type calcium currents in thalamic neurons [15, 18].

2.1 ***Acanthus montanus*:** The leaves of Acanthus montanus (Family Acanthaceae) are used in traditional herbal practices in South Eastern Nigeria and in some other parts of West Africa for the treatment of gonorrhoea, syphilis, wounds and boils. Other uses of A. montanus in herbal medicine include the treatment of hypertension, cardiac dysfunctions, hepatitis and heart diseases. E.N. Bum *et al.* evaluated *A. Montanus* for its anticonvulsant activity. The aqueous extract of *A. montanus* protected 83.3% of mice at a dose of 100 mg/kg against PIC-induced seizures, 83.3% of mice at a dose of 100 mg/kg against STR-induced seizures, 83.3% of mice at a dose of 1000 mg/kg against PTZ-in-duced seizures, and 66.6% of mice at doses of 500 and 1000 mg/kg against MES-induced seizures. A. montanus also delayed the onset of seizures in the INH. In the diazepam-induced sleep test, 1000 mg/kg A. montanus increased by a factor of 4 the sleep time of the control group [19].

2.2 ***Alchornea laxiflora:*** Alchornea laxiflora (Benth.) Pax and Hoffman (Family Euphorbiaceae) is a shrub or forest understorey tree spread throughout tropical Africa. When tested for its anti

convulsant activity, the decoction of A. laxiflora at a dose of 60 mg/kg protected 100% of mice against NMDA-induced turning behavior and at a dose of 120 mg/kg, A. laxiflora also protected 75% of mice against STR-induced seizures [19].

2.3 ***Alpha terpineol:*** α-Terpineol is a volatile monoterpenoid alcohol and component of the essential oils of several species of plants. This compound is widely used in the perfumery, cosmetic, and soap industries. It is also used as a scenting agent in household products (e.g., disinfectant spray). In an investigation carried out to evaluate the anticonvulsant activity of α-terpineol, the compound increased the latency to convulsions induced by pentylenetetrazole at doses of 100 and 200mg/kg and decreased the incidence of hind limb extension produced by MES in a dose-related manner at doses of 200 and 400mg/kg [20].

2.4 ***Bacopa monnieri:*** Bacopa monnieri (L), belonging to the Scrophulariaceae family and commonly known as Brahmi, is well known in India for its CNS activity. The ethanolic extract of Bacopa monniera was tested by D. Kaushik *et al.* for anticonvulsant activity in albino rats, using different convulsive models. The ethanolic extract of leaves produced significant anticonvulsant activity for all the different models studied. The study showed a probable mechanism of action similar to that of benzodiazepines (GABA agonist) [21].

2.5 ***Berberine:*** Isoquinoline alkaloid berberine is one of widespread representatives belonging to the family of protoberberine alkaloids. Berberine is produced by many plant species including the barberry (Berberis), the meadow rue (Thalictrum), the celandine (Chelidonium), the goldenseal (Hydrastis canadensis L.), Phellodendron amurense, etc. [22]. It has been reported that berberine possess multiple pharmacological effects and hold promising properties as a drug for cardiovascular diseases, diabetes, hyperlipidemia, cancer, diarrhoea, alzheimer's, etc. In addition, it also possesses antiplatelet, antiviral, antibacterial, and immunostimulant activity [23]. In order to evaluate the therapeutic value of berberine as anticonvulsant, P. Bhutada *et al.* tested its influence in different animal models viz., PTZ, MES and KA-induced seizures in Swiss albino mice. The overall results revealed that treatment with berberine (10 and 20 mg/kg) protected against MES and KA-induced convulsions and mortality, inhibited NMDA-induced turning behavior, and these effects were comparable with standard anticonvulsant agents [24].

2.6 ***Carissa edulis:*** *Carissa edulis* belongs to the family Apocynaceae. The plant parts are used in ethnomedicine for wide variety of illnesses, such as epilepsy, headache, chest complaints, gonorrhea, syphilis, rheumatism, rabies and as well as a diuretic [25]. The anticonvulsant activity of root bark extract of *Carissa edulis* was evaluated by J. Ya'u *et al.* The results of the study have demonstrated that *Carissa edulis* possessed anticonvulsant activity on the animal models investigated (MES and PTZ). The median lethal dose (LD_{50}) of *Carissa edulis* was 282.8 mg/kg and >5000 mg/kg following intraperitoneal and oral administration, respectively. *Carissa edulis* produced 40% and 20% protection against convulsion at 5 and 20 mg/kg, respectively, compared with 100% protection with benzodiazepine.

Carissa edulis exhibited dose-dependent inhibition of the convulsion induced by MES with 20 mg/kg providing 90% protection while phenytoin (20 mg/kg) produced 100% protection [26].

2.7 ***Casimiroa edulis:*** *Casimiroa edulis* Lave et Lex. (Rutaceae), commonly known as 'zapote blanco', is a tree widely distributed throughout the central and south- eastern States of Mexico. An aqueous extract of *Casimiroa edulis* leaves was tested in adult male Wistar rats for anticonvulsant activity utilizing two models of experimental epilepsy: MES and scPTZ. Single dose of 100 mg/kg *C. edulis* vacuum dried aqueous extracts (VDA) orally administered to experimental animals elicited 50% and 70% abolition of MES and scPTZ-induced seizures, respectively. Two firmly established antiepileptic drugs in human therapy, phenytoin and phenobarbital, abolished 90% of MES-induced seizures, whereas an 80% and 100% absence of clonic seizures was attained in scPTZ test, correspondingly. The seizure abolition observed in C. edulis VDA treated rats was comparable with the anticonvulsive pattern exhibited by PHT and PB. These results suggested that potentially antiepileptic compounds are present in *C. edulis* extracts [27].

2.8 ***Cotyledon orbiculata:*** *Cotyledon orbiculata* L. belongs to the family, Crassulaceae. It is a small shrub with fleshy leaves and widely distributed in Southern Africa. *Cotyledon orbiculata* is used in the treatment of various ailments in different parts of South Africa. The anticonvulsant activity of *Cotyledon orbiculata* was investigated by G.J. Amabeoku *et al.* by studying the effects of both aqueous and methanol extracts of the plant species on seizures induced by PTZ, BIC, PIC and NMDA in mice. Aqueous extract of *Cotyledon orbiculata* (50–400 mg/kg, i.p.) and methanol extract (100–400 mg/kg, i.p.) significantly prolonged the onset of tonic seizures induced by pentylenetetrazole (95 mg/kg, i.p.). Methanol extract (400 mg/kg, i.p.) also significantly reduced the incidence of the seizures. 100-200 mg/kg (i.p.) of aqueous extract of *Cotyledon orbiculata* significantly delayed the onset of the tonic seizures induced by BIC (40 mg/kg, i.p.), PIC (12 mg/kg, i.p.) and NMDA, (400 mg/kg, i.p.). Similarly, methanol extract (100–400 mg/kg, i.p.) significantly delayed the onset of the tonic seizures induced by BIC (40 mg/kg, i.p.) and PIC (12 mg/kg, i.p.) while 100 mg/kg (i.p.) significantly delayed the onset of NMDA (400 mg/kg, i.p.) induced seizures. Methanol extract (200 mg/kg, i.p.) significantly reduced the incidence of the seizures induced by BIC (40 mg/kg, i.p.). Phenobarbitone (12 mg/kg, i.p.) and diazepam (0.5 mg/kg, i.p.) effectively antagonized only seizures induced by PTZ (95 mg/kg, i.p.), BIC (40 mg/kg, i.p.) and PIC (12 mg/kg, i.p.). Phenytoin (30 mg/kg, i.p.) did not affect any of the seizures to any significant extent. It was concluded that both aqueous and methanol extracts of *Cotyledon orbiculata* have anticonvulsant property and may probably be affecting both gabaergic and glutaminergic mechanisms to exert its effect [28].

2.9 ***Cymbopogan winterians***: *Cymbopogon winterianus* Jowitt (Poaceae), popularly known as ''citronella'' and ''java grass'', is an important essential oil yielding aromatic grass cultivated in India and Brazil [29]. *C. winterianus* is used for its analgesic, anxiolytic and anticonvulsant properties in Brazilian folk medicine.

L.J. Quintans Ju´nior *et al.* performed phythochemical screening of *C. winterianus* and to investigate the possible anticonvulsant effects of the essential oil (EO) from fresh leaves of *C. winterianus* in different models of epilepsy viz. PTZ, PIC and STR induced convulsions. The behavioral screening demonstrated that EO (100, 200 and 400 mg/kg; ip) caused depressant activity on CNS. When administered concurrently, EO (200 and 400 mg/kg, ip) significantly reduced the number of animals that exhibited PTZ- and PIC-induced seizures in 50% of the experimental animals ($p<0.05$). Additionally, EO (100, 200 and 400 mg/kg, ip) significantly increased ($p<0.05$) the latencies of clonic seizures induced by STR [30].

2.10 ***Delphinium denudatum:*** Dried roots of *Delphinium denudatum* Wall. ((Ranunculaceae) are a popular folk remedy for the treatment of epilepsy in the traditional Unani system of medicine in the sub-continent. M. Raza *et al.* carried out anticonvulsant screening of the ethanolic extract and aqueous fraction of this plant utilizing the MES and scPTZ, scBIC, scPIC and scSTR tests for anticonvulsant activity. Ethanolic extract was found to have weak dose-dependent anticonvulsant effects on seizures induced by PTZ and BIC. Aqueous fraction exhibited dose-dependent activity against HLTE of MES test and comparatively stronger anticonvulsant activity against seizures induced by PTZ and BIC. The results suggest the presence of potent anticonvulsant compounds in Aqueous fraction of *D. denudatum*.[13]

2.11 ***Erythrina velutina and Erythrina mulungu***: There are many known species of *Erythrina* (Fabaceae) in the tropics and subtropics, including the species *Erythrina mulungu*, a medium-sized well-branched tree native to Southern Brazil and *Erythrina velutina*, a plant endemic to the semi-arid regions in Northeastern Brazil. These and other species are used in some Brazilian communities to treat insomnia and other disorders of the central nervous system [31]. The anticonvulsant effects of hydroalcoholic extracts from the stem bark of *Erythrina velutina* and *Erythrina mulungu* on PTZ- and STR-induced seizure tests and the potentiation of PB-induced sleeping time in mice with the extracts were examined by S.M.M. Vasconcelos *et al.* The extracts of *Erythrina velutina* (intraperitoneally or orally) and *Erythrina mulungu* (intraperitoneally) were administered in mice at single doses (200 or 400 mg/kg). While *Erythrina velutina* and *Erythrina mulungu* did not exhibit any protector effect in PTZ-induced seizures, at any dose, an increase in the latency of convulsion and in the death time was observed with both doses and routes of *Erythrina velutina* and at higher dose of *Erythrina mulungu*, in STR-induced seizure. No alteration was observed with *Erythrina velutina* and *Erythrina mulungu* on sleeping latency at both doses as compared to control However, the sleeping time was increased in both plants as compared to control. The authors concluded that the hydroalcoholic extracts of *Erythrina velutina* and *Erythrina mulungu* have anticonvulsant effects only in the STR-induced seizure model, suggesting their possible action in glycine system and a potentiation of pentobarbital sleeping time, suggesting depressant action in the central nervous system.[31]

2.12 ***Ferula gummosa:*** *Ferula gummosa* Boiss. (Apiaceae) which has been used

as an antiepileptic remedy in Iranian traditional medicine was evaluated by M. Sayyah *et al.* for anticonvulsant activity against experimental seizures. The seed acetone extract of *F. gummosa* protected mice against tonic convulsions induced by MES (the median effective dose [ED_{50}]=198.3 mg/kg) and especially by PTZ (ED_{50}=55 mg/kg). Neurotoxicity (sedation and motor impairment) of the extract was assessed by the rotarod test and the median toxic dose (TD_{50}) value of 375.8 mg/kg was obtained. [32].

2.13 ***Ficus platyphylla***: Preparations of *Ficus platyphylla* (Moraceae) have been used in Nigerian traditional medicine for the management of epilepsy for many years. The anticonvulsant properties of the saponin rich fraction (SFG) obtained from the methanol extract of *F. platyphylla* stem bark were studied by B.A. Chindo *et al.* on PTZ-, STR- and MES-induced seizures in mice. Effects of SFG were also examined in murine models for neurological disease and on relevant in vitro targets for anticonvulsant drugs. SFG protected mice against PTZ- and STR-induced seizures and significantly delayed the onset of myoclonic jerks and tonic seizures. SFG failed to protect mice against MES- seizures at doses tested. 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 (SRF) and spontaneous action potential firing in these cultured cells. The results provided scientific evidence that *F. platyphylla* stem bark may contain psychoactive principles with potential anticonvulsant properties. SFG impaired membrane excitability; a property shared by most anticonvulsants particularly the voltage-gated sodium channel (VGSC) blocking drugs, thus supporting the isolation and development of the saponin components of this plant as anticonvulsant agents [33].

2.14 ***Harpagophytum procumbens:*** *Harpagophytum procumbens* DC (family: Pedaliaceae) is widely used in South African traditional medicine for the treatment, management and/or control of a variety of human ailments. I.M. Mahomed *et al.* examined the anticonvulsant activity of *H. procumbens* secondary root aqueous extract (HPE, 50–800 mg/kg i.p.) against PTZ-, PIC- and BIC-induced seizures in mice. Phenobarbitone and diazepam were used as reference anticonvulsant drugs for comparison. Like the reference anticonvulsant agents used, *H. procumbens* secondary root aqueous extract (HPE, 100–800 mg/kg i.p.) significantly delayed the onset of, and antagonized PTZ-induced seizures. The plant's extract (HPE, 100–800 mg/kg i.p.) also profoundly antagonized PIC-induced seizures, but only partially and weakly antagonized BIC-induced seizures. Although the data obtained in the study did not provide conclusive evidence, it would appear that HPE produced its anticonvulsant activity by enhancing GABAergic neurotransmission and/or facilitating GABAergic action in the brain. In general, the average onset of convulsion was delayed, while the average duration of convulsion was markedly reduced. The plant's extract also depressed the central nervous system [34].

2.15 ***Hyptis spicigera:*** *Hyptis spicigera* belongs to the family Lamiaceae. It is commonly known as Black beniseed, or Black sesame. The plant is found around Senegal to Western Cameroon, possibly native to Brazil, now widely naturalized in tropical Africa and Asia as well as Nigeria.[35] E.N. Bum *et al.* evaluated the decoction of the plant for its anticonvulsant activity. The decoction of *H. spicigera* strongly protected mice against seizures induced by both PTZ (87.5% of protection) and STR (100% of protection) at a dose of 120 mg/kg. However, it did not affect PIC-induced seizures. In the diazepam induced sleep test, 80 mg/kg H. spicigera increased by a factor of 4 the sleep time of the control group [19].

2.16 ***Laurus nobilis:*** The leaf essential oil of *Laurus nobilis* Linn. Lauraceae, which has been used as an antiepileptic remedy in Iranian traditional medicine, was evaluated by M. Sayyah *et al.* for anticonvulsant activity against PTZ- and MES-induced seizures. The essential oil protected mice against tonic convulsions induced by maximal electroshock and especially by pentylenetetrazole. Components responsible for this effect may be methyleugenol, eugenol and pinene present in the essential oil. At anticonvulsant doses, the essential oil produced sedation and motor impairment. This effect seemed to be related in part to cineol, eugenol and methyleugenol [36].

2.17 ***Leonotis leonurus:*** *Leonotis leonurus* (L.) R. Br. is a shrub widely known as wild dagga found in most parts of the world and belongs to the Lamiaceae family. Some of the many traditional applications of *L. Leonurus* include the leaf decoction being a strong purgative and used for wound healing and asthma. The leaves and stem are topically applied to sores and skin infections, or taken for high blood pressure and diabetes. An array of pharmacological studies based on traditional claims reported anticonvulsant, antinociceptive, anti-inflammatory, antidiabetic, anthelmintic activities and hypoglycemic properties of L. leonurus [37]. Water extract of *Leonotis leonurus* was tested for anticonvulsant activity by E. Bienvenu *et al.* against seizures produced in mice by scPTZ, PIC, BIC and NMDA (intraperitoneal injections). *L. leonurus* extract in the doses of 200 and 400 mg/kg respectively protected 37.5% and 50% of animals used and significantly delayed pentylenetetrazole (90 mg/kg)-induced tonic seizures. Similarly, the same doses of *L. leonurus* extract significantly delayed the onset of tonic seizures produced by PIC (8 mg/kg) and NMDA (400 mg/kg). However, all the doses of aqueous extract of *L. leonurus* used did not alter the seizures induced by BIC (20 mg/kg) to any significant extent. The data suggested that the extract of *L. leonurus* has anticonvulsant activity and may probably be acting through non-specific mechanisms, since it affects both gabaergic and glutaminergic systems. HPLC and phytochemical tests carried out respectively showed a spectrum profile, characteristic of *L. leonurus* and the presence of alkaloids, saponins and tannins in the extract [38].

2.18 ***Magnolia grandiflora:*** *Magnolia grandiflora* L. (Magnoliaceae), tree that grows in the south-eastern states of the US and Mexico, is widely used in traditional medicine. This plant has been reported to have beneficial effects on several ailments, such as high blood pressure, heart disturbances, dispnea,

abdominal discomfort, muscle spasm, infertility and epilepsy, among others. The ethyl ether (EE) and hydroalcoholic extract (HE) of *Magnolia grandiflora* L. seeds were studied for anticonvulsant activity by B.E. Bastidas Ramı´rez *et al.* in adult male Wistar rats. EE and HE orally administered in a single dose of 250 mg/kg (calculated on lipidic base) and 200 mg/kg, exhibited abolition of the extensor reflex of maximal electric induced seizure test in 50 and 40% of the experimental animals, respectively. They significantly prolonged the sleeping time induced by Pentobarbital and only the ethanol extract induced hypothermia. No neurological deficit was exhibited by either extract according to the gait, stance and righting test. The results suggested that the chemical constituents of this plant could have utility in the control of epileptic patients presenting convulsive seizures [39].

2.19 ***Microglossa pyrifolia:*** *Microglossa pyrifolia* (Lam.) Kuntze, Asteraceae, is found and used for infection diseases in Rwanda [40]. The decoction of *M. pyrifolia* was tested for anticonvulsant activity by E.N. Bum *et al.* The decoction strongly protected mice against seizures induced by PTZ (75% of protection), MES (87.5% of protection), and PIC (75% of protection) at a dose of 260 mg/kg. At the same dose, *M. pyrifolia* protected 100% of mice in the NMDA test. It also significantly increased the time to onset of seizures in the INH test. However, M. pyrifolia had a moderate effect (50% of protection) on STR-induced seizures. In the diazepam induced sleep test, 260 mg/kg *M. pyrifolia* increased by a factor of 2 the sleep time of the control group [19].

2.20 ***Mimosa pudica:*** *Mimosa Pudica* (Leguminosae) is cultivated throughout India and widely used for its medicinal properties. All parts of the tree are considered to possess medicinal properties and used in the treatment of biliousness, leprosy, dysentery, vaginal and uterine complaints, inflammations, burning sensation, fatigue, asthma, leucoderma, blood diseases etc.[41] The decoction of *Mimosa pudica* leaves was evaluated for anticonvulsant activity by E. Ngo Bum *et al.* Given intra peritoneally at dose of 1000–4000 mg/ kg, it protected mice against PTZ- and STR- induced seizures. *M. pudica* had no effect against PIC-induced seizures It also antagonized NMDA- induced turning behavior [42].

2.21 ***Nardostachys jatamansi:*** The roots and the rhizomes of *Nardostachys jatamansi* DC. (Valerianaceae) mentioned in Ayurveda, have been used to treat epilepsy, hysteria, syncope and mental weakness. It has also been used as herbal combinations with other herbs to evaluate depressant activity [43]. A 50% ethanol extract of Nardostachys jatamansi (whole plant) feeding has been found to increase HDL-cholesterol/total cholesterol ratio and also caused a significant reduction in the ratio of total cholesterol/phospholipids [44]. Ethanol extract of the roots of *N. jatamansi* was studied by V.S. Rao *et al.* for its anticonvulsant activity and neurotoxicity, alone and in combination with phenytoin in rats. The results demonstrated a significant increase in the seizure threshold by *N. jatamansi* root extract against MES model as indicated by a decrease in the extension/flexion (E/F) ratio. However, the extract was ineffective against PTZ-induced seizures. Nardostachys jatamansi root extract also showed minimal neurotoxicity against rotarod test at doses that increased the

seizure threshold. Further, pretreatment of rats with phenytoin at a dose of 12.5, 25, 50 and 75 mg/kg in combination with 50 mg/kg of *Nardostachys jatamansi* root extract resulted in a significant increase in the protective index (PI) of PHT from 3.63 to 13.18. The dose response studies of PHT alone and in combination with *Nardostachys jatamansi* extract on the serum levels of phenytoin clearly demonstrated the synergistic action of both the drugs [45].

2.22 ***Piliostigma reticulatum***: *Piliostigma reticulatum* is a leguminous plant belonging to the family Caesalpiniaceae and is widely distributed in Africa and Asia. Ethnomedically, the bark, root, pod, young stem or leaves have been used for treating leprosy, smallpox, coughs, ulcer, heart pain, gingivitis, snake bite, dysentery, fever, wounds and a variety of closely related disease conditions. [46]. The decoction of *P. reticulatum* at a dose of 50 mg/kg protected 62.5% of mice against PTZ-induced seizures, 75% of mice against STR-induced convulsions, and 100% of mice in the NMDA test. In the diazepam-induced sleep test, 260 mg/kg *P. reticulatum i*ncreased by a factor of 3 the sleep time of the control group [19].

2.23 ***Pimpinella anisum***: *Pimpinella anisum* L., Umbelliferae, is an annual herb indigenous to Iran, India, Turkey and many other warm regions in the world. In Iranian folk medicine, the plant and especially its fruit essential oil have been used for treatment of some disease including seizures and epilepsy. A study carried out by M.H. Pourgholami *et al.* investigated anticonvulsant effects of an essential oil of the fruits of *P. anisum* against seizures induced by PTZ or MES in male mice. The essential oil suppressed tonic convulsions induced by PTZ or MES. It also elevated the threshold of PTZ-induced clonic convulsions in mice [47].

2.24 ***Rhizoma Pinelliae***: *Rhizoma Pinelliae*, the tuber of *Pinelliae ternata* (Thunb.) Breit. (Araceae), has been widely used for antiemetic, anti-tussive, sedative and anti-inflammatory purposes [48]. The sedative, hypnotic and anticonvulsant activities of ethanol fraction from *Rhizoma Pinelliae Praeparatum* (EFRP) were investigated by X.-y. Wu *et al.* with locomotion activity, pentobarbital-induced sleeping and NKTM-induced convulsion tests, respectively. Additionally, the effects of flumazenil (an antagonist of $GABA_A$ receptor) and L-malic acid (blocker of synthetic enzyme for GABA) on the hypnotic activity of EFRP were evaluated. EFRP at dose of 12 g/kg significantly inhibited the locomotion activity of mice. EFRP showed synergic effect on pentobarbital-induced sleeping by increased numbers of mice falling asleep, reduced the sleep latency and prolonged the sleeping time. L-malic acid and flumazenil inhibited the augment effects of EFRP on pentobarbital-induced sleeping. EFRP promoted a significant protection to NKTM-induced convulsion, by prolonged the death latency and decreased mortality. Thus, EFRP possessed sedative, hypnotic and anticonvulsant activities and these activities may be related to the GABAergic system [49].

2.25 ***Sutherlandia frutescens:*** Commomly known as umwele or cancerbush, aerial parts of *Sutherlandia frutescens* R. BR. (family: Fabaceae) are extensively used in South African traditional medicines for the treatment, management and/or control of an array of human ailments, including childhood convulsions and

epilepsy. J.A.O. Ojewole *et al.* examined the anticonvulsant property of the plant's shoot aqueous extract (SFE, 25–400 mg/kg i.p.) against PTZ-, PIC- and BIC-induced seizures in mice. Phenobarbitone and diazepam were used as reference anticonvulsant drugs for comparison. Like the reference antiseizure drugs used, *S. frurescens* shoot aqueous extract (SFE, 50–400 mg/kg i.p.) significantly delayed the onset of, and antagonized, PTZ-induced seizures. The plant's shoot aqueous extract (SFE, 50–400 mg/kg i.p.) also profoundly antagonized PIC-induced seizures, but only weakly antagonized BIC-induced seizures [50].

2.26 ***Taxus wallichiana:*** *Taxus wallichiana* Zucc. (Himalayan Yew) belonging to the family Taxaceae is often used in northern areas of Pakistan for the treatment of pyrexia, acute pains and epilepsy. M. Nisar *et al.* investigated certain pharmacological activities of the methanol leaf extract against convulsion, nociception and pyrexia induced in rodents. The studies were carried out using PTZ-induced convulsions in mice. Plant extract has controlled the PTZ-induced convulsions in mice. 100 and 200 mg/kg i.p doses of the extract significantly inhibited the mioclonus and clonus while inhibition of tonus and HLTE was highly significant [51].

2.27 ***Voacanga africana***: *Voacanga africana* Staph. (Apocynaceae) is used empirically in traditional medicine in Africa to treat many diseases such as leprosy, diarrhea, generalized edema, convulsions in children and madness [52]. These effects are due to the presence of a complex mixture of iboga alkaloids such as voacangine, voacamine, vobtusine, amataine, akuammidine, tabersonine, coronaridine and vobtusine etc [53]. The decoction of *V. africana* at a dose of 140 mg/kg antagonized 75% of PTZ-induced convulsions and 87.5% of NMDA-induced turning behavior in mice. At the same dose, 62.5% of mice were also protected from both MES- and STR-induced convulsions. *V. africana* failed to protect mice against PIC-induced convulsions. The decoction also significantly increased the time to onset of seizures. In the diazepam-induced sleep test, 70 mg/kg *V. africana* increased by a factor of 4 the sleep time of the control group [19].

2.28 ***Withania somnifera:*** *Withania somnifera* (Solanaceae) Dunal (ashwagandha) is widely used in Ayurvedic medicine, the traditional medical system of India. It is an ingredient in many formulations prescribed for a variety of musculoskeletal conditions (e.g., arthritis, rheumatism), and as a general tonic to increase energy, improve overall health and longevity, and prevent disease in athletes, the elderly, and during pregnancy. Ashwagandha possesses anti-inflammatory, antitumor, anti-stress, antioxidant, immunomodulatory, hemopoetic, and rejuvenating properties. It also appears to exert a positive influence on the endocrine, cardiopulmonary, and central nervous systems [54]. To find the efficacy of the alcoholic extract of *W. somnifera* in preventing experimentally-induced seizures, the alcoholic extract of *W. somnifera* was screened for anticonvulsant activity on MES and PTZ-induced seizures models in albino Wistar rats by Raju *et al.* Animals were treated with *W. somnifera* at doses of 100 mg/kg, 200 mg/kg, and 300 mg/kg body weight and compared the results with control and standard. Study results showed that *W. somnifera* extract at the dose of 300 mg/kg body weight when compared to

control group highly significant reduction of hind limb tonic extension and postictal depression in MES. PTZ-induced seizures showed significantly reduced mean duration of hind limb tonic flexion, hind limb tonic extension, clonus, and stupor and there was no postictal depression [55].

3. Conclusion and perspective:

Despite the scientific progress in understanding the pathophysiological processes related to seizure initiation, amplification and propagation in the brain, and despite the large number of first- and second-generation AEDs available on the pharmaceutical market, there are still approximately 30% of epilepsy patients that are inadequately treated with the current frontline antiepileptic drugs [56]. For these patients, the most appropriate therapeutic option is presumably the combined administration of two or more AEDs or the application of novel and potential AEDs [57]. Thus, there is a need for new, more effective anticonvulsant drugs for intractable epilepsy. Besides, nature is a rich source of biological and chemical diversity and a number of plants in the world have been used in traditional medicine remedies, including anticonvulsant one. The present review gives an account of medicinal plants showing anticonvulsant properties which when used alone or along with other synthetic anticonvulsant drugs may help to manage epileptic conditions as exemplified by the vast literature cited. Further, the chemical structure of the chief bioactive constituents presented in this article may help in understanding the structural requirements for a compound to be active against epilepsies as well as may help in designing new AEDs based on these structures. It can be concluded that studies with species from a range of families have been shown anticonvulsant properties against various types of experimental models of epilepsies used. Academic institutions should encourage these types of studies with medicinal plants as well as the design of new compounds resembling their active chemical constituents so as to get novel, safer and effective alternate to the available antiseizure drugs.

Acknowledgements: Authors are thankful to the Head, Department of Pharmaceutical Sciences, Mohanlal Sukhadia University, Udaipur, Rajasthan, for providing facilities for the present work.

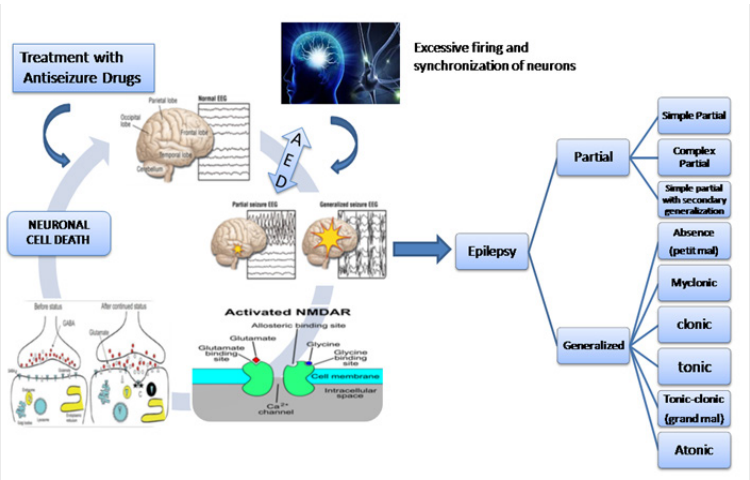
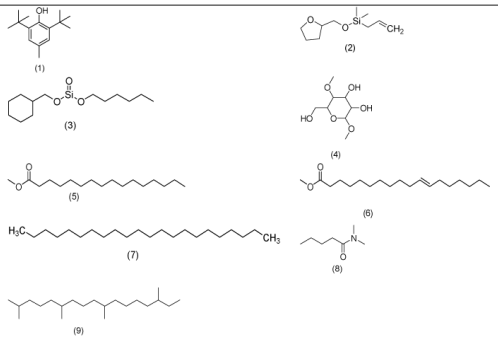
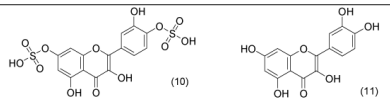
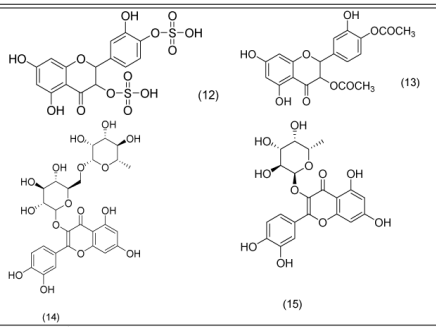
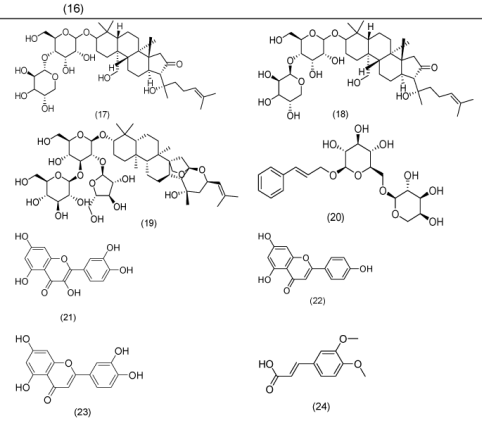
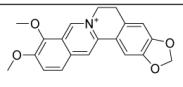
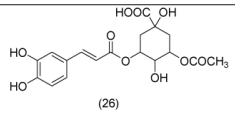
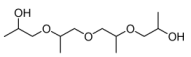
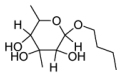
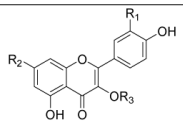
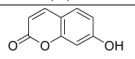
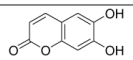
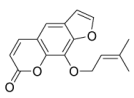
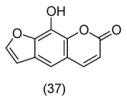
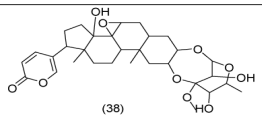
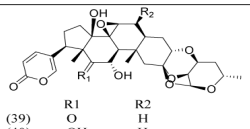
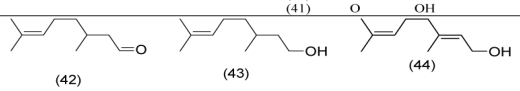
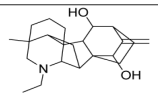
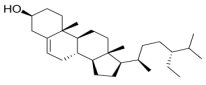
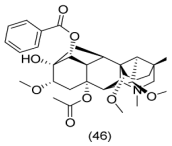
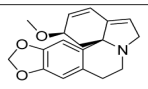
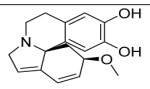
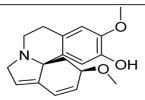
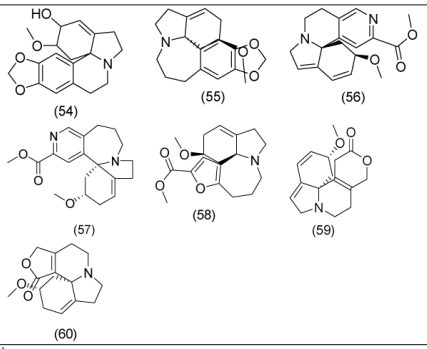
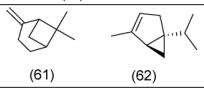
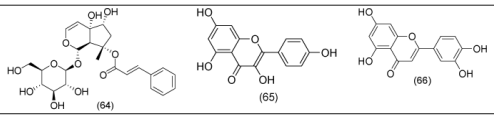
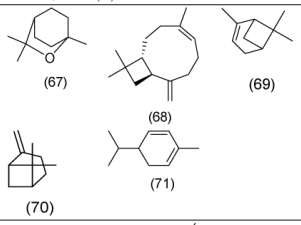
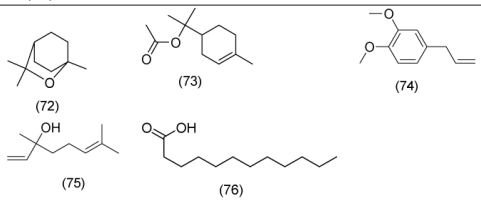
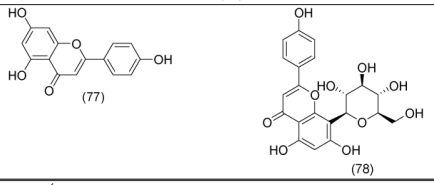
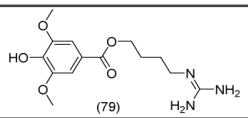
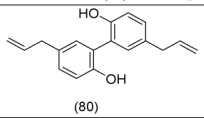
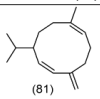
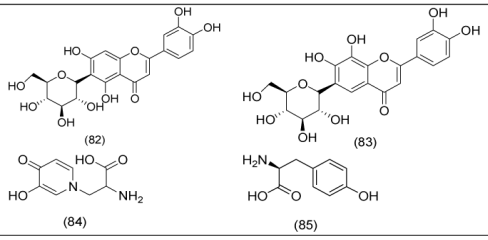


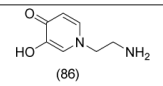
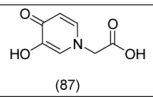
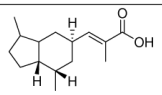
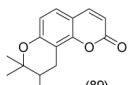
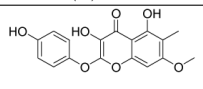
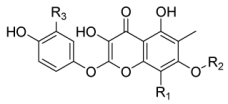
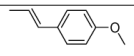
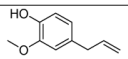
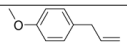
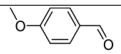
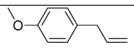
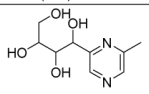
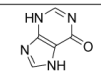
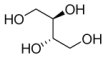
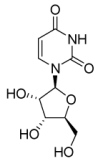
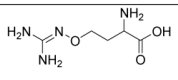
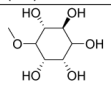
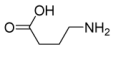
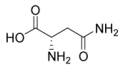
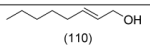
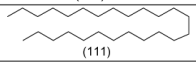
Figure 1. Seizures: Initiation, Types, Biochemical changes involved and action of Antiepileptic Drugs (AEDs) on them

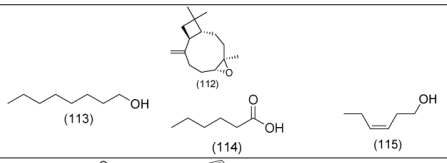
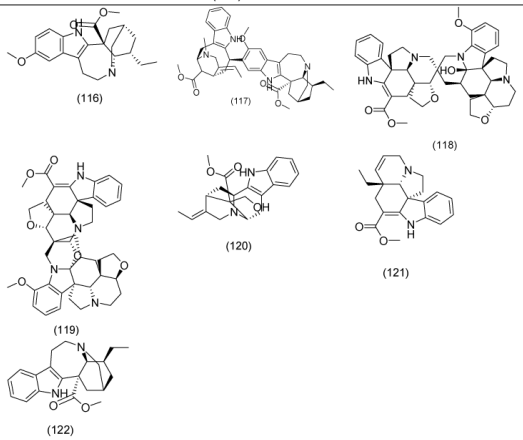
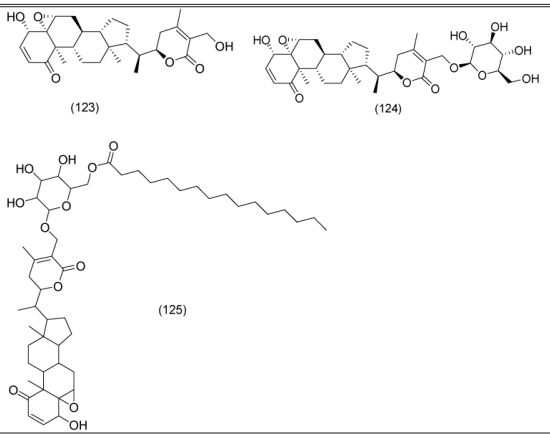
Table 1. List of herbal antiepileptic remedies along with their major bioactive constituents and methods used to evaluate their antiepileptic potential

S. No.	Name of the plant and family/ compound	Major bioactive constituent(s)	Chemical structure of chief constituent(s)	Part Used for evaluation	Model used for evaluation*	Ref
1.	*Acanthus montanus* (Acanthaceae)	(1). 2,6-bis(1,1-dimethylethyl)4-methyl phenol (2). Allyl(2tetrahydrofurylmethoxy) dimethylsilane (3). Sulfurous acid, cyclohexylmethyl hexyl ester (4). alpha-Methyl-4-methylmannoside (5). Hexadecanoic acid methyl ester (6). 11-Octadecenoic acid methyl ester (7). Docosane (8). N,N-Dimethylvaleramide (9). 2,6,10,15-Tetramethyl heptadecane		Whole plant	PTZ MES PIC STR	[19, 58]
2.	*Alchornea laxiflora* (Euphorbiaceae)	(10). Quercetin-7,4′-disulphate (11). quercetin (12). quercetin-3′,4′-disulphate (13). quercetin-3,4′-diacetate (14). rutin (15). quercetrin		Whole plant	MES PTZ PIC STR NMDA STR	[19, 59]
						
3.	*Alpha terpineol* (monoterpene)	(16). ± α-Terpineol		± α-Terpineol as an emulsion	MES PTZ	[20]
4.	*Bacopa monnieri (Bramhi)* (Scrophulariaceae)	(17). Bacoside A (18). Bacoside B (19). BacosideA_3 (20). Rosavin (21). Quercetin (22). Apigenin (23). Luteolin (24). 3,4-Dimethoxycinnamic acid		leaves	MES PTZ STR LPHE	[21, 60]
5.	*Berberine* (Isoquinoline Alkaloid)	(25). Berberine		Berberine hydrochloride solution	PTZ MES KA	[22]

6.	*Carissa edulis* (Apocyanaceae)	(26). 3-*O*-acetyl chlorogenic acid (27). kaempferol 3-*O*-b-D glucopyranoside (28). quercetin-3-*O*-b-D glucopyranoside (29). rhamnetin-3-*O*-b-D glucopyranoside (30). isorhamnetin-3-*O*-b-D-glucopyranoside (31). Isorhamnetin-3-*O*-b-D-glucopyranoside-(2"-1"')-rhamnopyranoside (32). Caredulis, 1-[1-[2-(2 hydroxypropoxy) propoxy] propan-2-yloxy] propan-2-ol (33). (+) butyl-*O*-α-L-rhamnoside	 (26)  (32)  (33)  R1 R2 R3 27 H OH Glu 28 OH OH Glu 29 OH OMe Glu 30 OMe OH Glu 31 OMe OH Glu(2---1)Rha	root bark	PTZ MES	[26, 61]
7.	*Casimiroa edulis* (Rutaceae)	(34). umbelliferone (35). esculetin (36). imperatorin (37). xanthotoxol	 (34)  (35)  (36)  (37)	leaves	MES PTZ	[27, 62]
8.	*Cotyledon orbiculata* (Crassulaceae)	(38). Cotyledoside C (39). Orbicusides A (40). Orbicusides B (41). Orbicusides C	 (38)  (39) R1 O R2 H (40) OH H (41) O OH	Whole plant	PTZ BIC PIC NMDA	[28, 63]
9.	*Cymbopogan winterianus* (Poaceae)	(42). Citronellal (43). Citronellol (44). Geraniol	 (42) (43) (44)	Essential oil from leaves	PTZ PIC STR	[30]
10.	*Delphinium denudatum* (Ranunculaceae)	(45). Denudatine (46). Delphinine (47). β-Sitosterol	 (45)  (47)  (46)	Whole plant	MES PTZ BIC STR PIC	[64]
11.	*Erythrina velentina and Erythrina mulungu* (Fabaceae)	Erythrinane alkaloids – (48). Erythraline (49). Erysopine (50). Erysovine (51). Erysodine (52). Schelhammeridine (53). Erythramine (54). Erythratine	 (48)  (49)  (50)	Stem bark	PTZ STR	[31, 65]

			 (54) (55) (56) (57) (58) (59) (60)			
12.	*Ferula gummosa* (Apiaceae)	(61). Pinene (62). α-thujene	 (61) (62)	Seed acetone extract	MES PTZ	[32, 36]
13.	*Ficus platyphylla* (Moraceae)	(63). Saponins	N.A.	Methanol extract of Stem bark	MES PTZ STR	[33]
14.	*Harpagophytum procumbens* (Pedaliaceae)	(64). Harpagoside (65). Kaempferol (66). Luteolin	 (64) (65) (66)	secondary root aqueous extract	PTZ PIC BIC	[34]
15.	*Hyptis spicigera* (Lamiaceae)	(67). cineole (68). caryophyllene (69). α-pinene (70). β-pinene (71). α-phellandrene	 (67) (68) (69) (70) (71)	Whole plant decoction	PTZ STR PIC	[19, 35]
16.	*Laurus nobilis* (Lauraceae)	(72). Eucalyptol (73). terpinyl acetate (74). methyleugenol (75). α- and β-pinenes (76). lauric acid	 (72) (73) (74) (75) (76)	leaf essential oil	PTZ MES	[36]
17.	*Leonotis leonurus* (Lamiaceae)	(77). Apigenin (78). Apigenin-8-C-β-glucoside (79). Leonurine	 (77) (78)	Whole plant aqueous extract	PTZ PIC BIC NMDA	[37, 38]
			 (79)			
18.	*Magnolia grandiflora* (Magnoliaceae)	(80). Magnolol	 (80)	ethyl ether and hydro-alcoholic extract of seeds; bark	MES PTZ	[39, 66]
19.	*Microglossa pyrifolia* (Asteraceae)	(81). Germacrene-D	 (81)	Leaf essential oil	MES PTZ PIC INH NMDA STR	[19, 40]
20.	*Mimosa pudica* (Leguminosae)	(82). 5, 7, 3', 4'-tetrahydroxyl-6-C-beta- D-glucopyranosyl flavones (83). 7,8,3',4'-tetrahydroxyl-6-C-beta-D-glucopyranosyl flavones (84). Mimosine (85). Tyrosine (86). Mmimosinamine (87). Mimosinicacid	 (82) (83) (84) (85)	Leaf decoction	PTZ STR PIC NMDA	[41, 42]

			 (86)  (87)			
21.	*Nardostachys jatamansi* (Valerianaceae)	(88). Nardin (89). pyranocoumerin	 (88)  (89)	Ethanol extract of roots	MES PTZ	[45, 67]
22.	*Piliostigma reticulatum* (Caesalpiniaceae)	(90). piliostigmol (91). 6,8-di-*C*-methylquercetin-3,30,7-trimethyl ether (92). 6,8-di-*C*-methylquercetin-30-dimethyl ether, (93). 30,6,8,-tri-*C*-methylquercetin-3,7-dimethyl ether, (94). 6-*C*-methylquercetin-3-methyl ether (95). 6,8-di-*C*-methylkaempferol-3-methyl ether (96). 6-*C*-methylquercetin-3,30 ,7-trimethyl ether	 (90) 	**R1** **R2** **R3** (91) CH_3 OCH_3 OCH_3 (92) CH_3 OH OCH_3 (93) CH_3 OCH_3 CH_3 (94) H OH OH (95) CH_3 OH OH (96) H OCH_3 OCH_3	Whole plant decoction	PTZ STR NMDA	[19, 46]
23.	*Pimpinella anisum* (Umbelliferae)	(97). *trans*-anethole (98). Eugenol (99). methylchavicol (100). anisaldehyde (101). estragole	 (97)  (98)  (99)	Fruit essential oil	MES PTZ	[47, 68]
			 (100)  (101)			
24.	*Rhizoma Pinelliae* (Araceae)	(102). pedatisectine F (103). hypoxanthine (104). erythritol (105). uridine	 (102)  (103)  (104)  (105)	Ethanol extract of tuber	NKTM	[49, 69]
25.	*Sutherlandia frutescens* (Fabaceae)	(106). L-canavanine (107). Pinitol (108). GABA (109). Asparagines	 (106)  (107)  (108)  (109)	shoot aqueous extract	PTZ PIC BIC	[50, 70]
26.	*Taxus wallichiana* (Taxaceae)	(110). (E)-2-octen-1-ol (111). n-pentacosane (112). caryophyllene oxide	 (110)  (111)	methanol leaf extract	PTZ	[51, 71]

		(113). 1-octanol (114). hexanoic acid (115). (Z)-3-hexenol				
27.	*Voacanga africana* (Apocynaceae)	(116). voacangine (117). voacamine (118). vobtusine (119). amataine (120). akuammidine (121). tabersonine (122). coronaridine		Whole plant	PTZ NMDA STR PIC	[19, 53]
28.	*Withania somnifera* (Solanaceae)	(123). Withaferin A (124). Sitoindoside IX (125). Sitoindoside X		alcoholic extract of plant	MES PTZ	[54, 55]

References:

1. Tripathi K. Essentials of Medical Pharmacology. New Delhi: Jaypee Brothers,Medical Publishers Pvt. Limited; 2013.
2. Jefferys JG. Basic mechanisms of focal epilepsies. Experimental Physiology 1990;75: 127-162.
3. Kandel ES, JH. Jessell, TM. . Principles of neural science. New York: McGraw-Hill, Health Professions Division; 2000.
4. Ferriero DM. Protecting neurons. Epilepsia 2005;46 Suppl 7: 45-51.
5. Fujikawa DG, Itabashi HH, Wu A, Shinmei SS. Status epilepticus-induced neuronal loss in humans without systemic complications or epilepsy. Epilepsia 2000;41: 981-91.
6. McKeown MJ, McNamara JO. When Do Epileptic Seizures Begin? Neuron 30: 1-3.
7. Litt B, Esteller R, Echauz J, D'Alessandro M, Shor R, Henry T, Pennell P, Epstein C, Bakay R, Dichter M, Vachtsevanos G. Epileptic seizures may begin hours in advance of clinical onset: a report of five patients. Neuron 2001;30: 51-64.
8. Macdonald RL, Kelly KM. Mechanisms of action of currently prescribed and newly developed antiepileptic drugs. Epilepsia 1994;35 Suppl 4: S41-50.
9. Stepien K, Tomaszewski M, Czuczwar SJ. Profile of anticonvulsant activity and neuroprotective effects of novel and potential antiepileptic drugs--an update. Pharmacol Rep 2005;57: 719-33.
10. Trojnar MK, Malek R, Chroscinska M, Nowak S, Blaszczyk B, Czuczwar SJ. Neuroprotective effects of antiepileptic drugs. Pol J Pharmacol 2002;54: 557-66.
11. Kneen R, Appleton RE. Alternative approaches to conventional antiepileptic drugs in the management of paediatric epilepsy. Arch Dis Child 2006;91: 936-41.
12. Schachter SC. Currently available antiepileptic drugs. Neurotherapeutics 2007;4: 4-11.
13. 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. J Ethnopharmacol 2001;78: 73-8.
14. Browning R. The electroshock model, neuronal network and antiepilep-tic drugs. Boca Raton, FL, : CRC Press, ; 1992.
15. Rho JM, Sankar R. The Pharmacologic Basis of Antiepileptic Drug Action. Epilepsia 1999;40: 1471-1483.
16. Loscher W, Fassbender CP, Nolting B. The role of technical, biological and pharmacological factors in the laboratory evaluation of anticonvulsant drugs. II. Maximal electroshock seizure models. Epilepsy Res 1991;8: 79-94.
17. McNamara JO. Drugs effective in the therapy of the epilepsies. . New York, U.S.A.: Permagon Press; 2001.
18. Meldrum BS. Update on the mechanism of action of antiepileptic drugs. Epilepsia 1996;37 Suppl 6: S4-11.
19. Bum EN, Taiwe GS, Nkainsa LA, Moto FC, Seke Etet PF, Hiana IR, Bailabar T, Rouyatou, Seyni P, Rakotonirina A, Rakotonirina SV. Validation of anticonvulsant and sedative activity of six medicinal plants. Epilepsy Behav 2009;14: 454-8.
20. de Sousa DP, Quintans L, de Almeida RN. Evolution of the Anticonvulsant Activity of α-Terpineol. Pharmaceutical Biology 2008;45: 69-70.
21. Kaushik D, Tripathi A, Tripathi R, Ganachari M, Khan SA. Anticonvulsant activity of Bacopa monniera in rodents. Brazilian Journal of Pharmaceutical Sciences 2009;45: 643-649.
22. Nechepurenko I, Salakhutdinov N, Tolstikov G. Berberine: Chemistry and biological activity. Chem. Sustain. Dev 2010;18: 1-23.
23. Imanshahidi M, Hosseinzadeh H. Pharmacological and therapeutic effects of Berberis vulgaris and its active constituent, berberine. Phytother Res 2008;22: 999-1012.
24. Bhutada P, Mundhada Y, Bansod K, Dixit P, Umathe S, Mundhada D. Anticonvulsant activity of berberine, an isoquinoline alkaloid in mice. Epilepsy & Behavior 2010;18: 207-210.
25. Nedi T, Mekonnen N, Urga K. Diuretic effect of the crude extracts of Carissa edulis in rats. J Ethnopharmacol 2004;95: 57-61.
26. Ya'u J, Yaro AH, Abubakar MS, Anuka JA, Hussaini IM. Anticonvulsant activity of Carissa edulis (Vahl) (Apocynaceae) root bark extract. J Ethnopharmacol 2008;120: 255-8.
27. Navarro Ruiz A, Bastidas Ramirez BE, Garcia Estrada J, Garcia Lopez P, Garzon P. Anticonvulsant activity of Casimiroa edulis in comparison to phenytoin and phenobarbital. J Ethnopharmacol 1995;45: 199-206.
28. Amabeoku GJ, Green I, Kabatende J. Anticonvulsant activity of Cotyledon orbiculata L. (Crassulaceae) leaf extract in mice. J Ethnopharmacol 2007;112: 101-7.
29. Cassel E, Vargas RM. Experiments and modeling of the Cymbopogon winterianus essential oil extraction by steam distillation. Journal of the Mexican Chemical Society 2006;50: 126-129.
30. Quintans-Junior LJ, Souza TT, Leite BS, Lessa NM, Bonjardim LR, Santos MR, Alves PB, Blank AF, Antoniolli AR. Phythochemical screening and anticonvulsant activity of Cymbopogon winterianus Jowitt (Poaceae) leaf essential oil in rodents. Phytomedicine 2008;15: 619-24.
31. Vasconcelos SM, Lima NM, Sales GT, Cunha GM, Aguiar LM, Silveira ER, Rodrigues AC, Macedo DS, Fonteles MM, Sousa FC, Viana GS. Anticonvulsant activity of hydroalcoholic extracts from Erythrina velutina and Erythrina mulungu. J Ethnopharmacol 2007;110: 271-4.
32. Sayyah M, Mandgary A, Kamalinejad M. Evaluation of the anticonvulsant activity of the seed acetone extract

of Ferula gummosa Boiss. against seizures induced by pentylenetetrazole and electroconvulsive shock in mice. J Ethnopharmacol 2002;82: 105-9.
33. Chindo BA, Anuka JA, McNeil L, Yaro AH, Adamu SS, Amos S, Connelly WK, Lees G, Gamaniel KS. Anticonvulsant properties of saponins from Ficus platyphylla stem bark. Brain Res Bull 2009;78: 276-82.
34. Mahomed IM, Ojewole JA. Anticonvulsant activity of Harpagophytum procumbens DC [Pedaliaceae] secondary root aqueous extract in mice. Brain Res Bull 2006;69: 57-62.
35. Ladan Z, Amupitan J, Oyewale O, Okonkwo E, Ladan E, Odjobo B, Habila N. Chemical composition and biological activity of the volatile oils of Hyptis spicigera against Trypanosoma brucei brucei,(Tbb) found in Northern Nigeria. African Journal of Pure and Applied Chemistry 2011;5: 53-58.
36. Sayyah M, Valizadeh J, Kamalinejad M. Anticonvulsant activity of the leaf essential oil of Laurus nobilis against pentylenetetrazole- and maximal electroshock-induced seizures. Phytomedicine 2002;9: 212-216.
37. Mazimba O. Leonotis leonurus: A herbal medicine review. Journal of Pharmacognosy and Phytochemistry 2015;3.
38. Bienvenu E, Amabeoku GJ, Eagles PK, Scott G, Springfield EP. Anticonvulsant activity of aqueous extract of Leonotis leonurus. Phytomedicine 2002;9: 217-23.
39. Bastidas Ramirez BE, Navarro Ruiz N, Quezada Arellano JD, Ruiz Madrigal B, Villanueva Michel MT, Garzon P. Anticonvulsant effects of Magnolia grandiflora L. in the rat. J Ethnopharmacol 1998;61: 143-52.
40. Mukazayire MJ, Tomani JC, Chalchat JC, Stévigny C, Duez P. Chemical composition, antimicrobial and antioxidant activities of the essential oil of Guizotia scabra and Microglossa pyrifolia from Rwanda. Planta Med 2009;75: PI38.
41. Azmi L, Singh MK, Akhtar AK. Pharmacological and biological overview on Mimosa pudica Linn. International Journal of Pharmacy & Life Sciences 2011;2.
42. Ngo Bum E, Dawack DL, Schmutz M, Rakotonirina A, Rakotonirina SV, Portet C, Jeker A, Olpe HR, Herrling P. Anticonvulsant activity of Mimosa pudica decoction. Fitoterapia 2004;75: 309-14.
43. Indurwade NH, Biyani KR. Evaluation of comparative and combined depressive effect of Brahmi, Shankhpushpi and Jatamansi in mice. Indian J Med Sci 2000;54: 339-41.
44. Dixit VP, Jain P, Joshi SC. Hypolipidaemic effects of Curcuma longa L and Nardostachys jatamansi, DC in triton-induced hyperlipidaemic rats. Indian J Physiol Pharmacol 1988;32: 299-304.
45. Rao VS, Rao A, Karanth KS. Anticonvulsant and neurotoxicity profile of Nardostachys jatamansi in rats. J Ethnopharmacol 2005;102: 351-6.
46. Babajide OJ, Babajide OO, Daramola AO, Mabusela WT. Flavonols and an oxychromonol from Piliostigma reticulatum. Phytochemistry 2008;69: 2245-50.
47. Pourgholami MH, Majzoob S, Javadi M, Kamalinejad M, Fanaee GH, Sayyah M. The fruit essential oil of Pimpinella anisum exerts anticonvulsant effects in mice. J Ethnopharmacol 1999;66: 211-5.
48. Maki T, Takahashi K, Shibata S. An Anti-Emetic Principle of Pinellia ternata Tuber. Planta Med 1987;53: 410-414.
49. Wu XY, Zhao JL, Zhang M, Li F, Zhao T, Yang LQ. Sedative, hypnotic and anticonvulsant activities of the ethanol fraction from Rhizoma Pinelliae Praeparatum. J Ethnopharmacol 2011;135: 325-9.
50. Ojewole JA. Anticonvulsant property of Sutherlandia frutescens R. BR. (variety Incana E. MEY.) [Fabaceae] shoot aqueous extract. Brain Res Bull 2008;75: 126-32.
51. Nisar M, Khan I, Simjee SU, Gilani AH, Obaidullah, Perveen H. Anticonvulsant, analgesic and antipyretic activities of Taxus wallichiana Zucc. J Ethnopharmacol 2008;116: 490-4.
52. Tan PV, Penlap VB, Nyasse B, Nguemo JD. Anti-ulcer actions of the bark methanol extract of Voacanga africana in different experimental ulcer models in rats. J Ethnopharmacol 2000;73: 423-8.
53. Hussain H, Hussain J, Al-Harrasi A, Green IR. Chemistry and biology of the genus Voacanga. Pharm Biol 2012;50: 1183-93.
54. Mishra LC, Singh BB, Dagenais S. Scientific basis for the therapeutic use of Withania somnifera (ashwagandha): a review. Alternative medicine review 2000;5: 334-346.
55. Raju SK, Basavanna P, Nagesh H, Shanbhag AD. A study on the anticonvulsant activity of Withania somnifera (Dunal) in albino rats. National Journal of Physiology, Pharmacy and Pharmacology 2017;7: 17-21.
56. Bialer M. New antiepileptic drugs that are second generation to existing antiepileptic drugs. Expert Opinion on Investigational Drugs 2006;15: 637-647.
57. Bialer M, Johannessen SI, Kupferberg HJ, Levy RH, Loiseau P, Perucca E. Progress report on new antiepileptic drugs: a summary of the Fifth Eilat Conference (EILAT V). Epilepsy Res 2001;43: 11-58.
58. Igwe OU, Nnaji JC. Chemical Characterization and Investigation of the Bio-effects of the Leaves of Acanthus montanus (Acanthaceae) on Some Selected Microorganisms.
59. Ogundipe OO, Moody JO, Houghton PJ, Odelola HA. Bioactive chemical constituents from Alchornea laxiflora (benth) pax and hoffman. Journal of Ethnopharmacology 2001;74: 275-280.
60. Zhou Y, Shen Y-H, Zhang C, Zhang W-D. Chemical constituents of Bacopa monnieri. Chemistry of Natural Compounds 2007;43: 355-357.
61. Al-Youssef HM, Hassan WHB. Chemical constituents of Carissa edulis Vahl. Arabian Journal of Chemistry 2017;10: 109-113.
62. Awaad AS, Al-Jaber NA, Soliman GA, Al-Outhman MR,

Zain ME, Moses JE, El-Meligy RM. New Biological Activities of Casimiroa edulis Leaf Extract and Isolated Compounds. Phytotherapy Research 2012;26: 452-457.
63. Botha C. Potential Health Risks Posed by Plant-Derived Cumulative Neurotoxic Bufadienolides in South Africa. Molecules 2016;21: 348.
64. Nizami Q, Jafri M. Unani drug, Jadwar (Delphinium denudatum Wall.)—a review. 2006.
65. Soto-Hernández RM, García-Mateos R, San Miguel-Chávez R, Kite G, Martínez-Vázquez M, Ramos-Valdivia AC. Erythrina, a Potential Source of Chemicals from the Neotropics. In: Bioactive Compounds in Phytomedicine: InTech; 2012.
66. Chen CR, Tan R, Qu WM, Wu Z, Wang Y, Urade Y, Huang ZL. Magnolol, a major bioactive constituent of the bark of Magnolia officinalis, exerts antiepileptic effects via the GABA/benzodiazepine receptor complex in mice. British Journal of Pharmacology 2011;164: 1534-1546.
67. Chatterjee A, Basak B, Datta U, Banerji J, Neuman A, Prange T. Studies on the chemical constituents of Nardostachys jatamansi DC (Valerianaceae). 2005.
68. Shojaii A, Abdollahi Fard M. Review of Pharmacological Properties and Chemical Constituents of Pimpinella anisum. ISRN Pharmaceutics 2012;2012: 510795.
69. Wang R, Wen Y, Yang L, Qin W. Chemical constituents of rhizoma Pinelliae pedatisecta. Zhongguo Zhong Yao Za Zhi 1997;22: 421-3, 447-8.
70. https://www.sutherlandia.org/chemistry.html. In.
71. Khan M, Verma SC, Srivastava SK, Shawl AS, Syamsundar KV, Khanuja SPS, Kumar T. Essential oil composition of Taxus wallichiana Zucc. from the Northern Himalayan region of India. Flavour and Fragrance Journal 2006;21: 772-775.