EPILEPSY

Epilepsy is a brain disorder characterized by occurrence of more than one epileptic seizure with a continuing predisposition to generate more epileptic seizures associated with neurobiological, cognitive, psychological, and social disturbances (Raol and Brooks-Kayal, 2012). Epilepsy is one of the most prevalent neurological disorder after stroke, and it is estimated that approximately 0.8% of the population worldwide is affected by some form of epilepsy (Browne and Holmes, 2001). Recent studies both in the developing and in the developed world revealed that if properly treated up to 70 % of people with this condition could live productive and fulfilling lives, free from seizures. It has to be acknowledged that more than 80 % of people with epilepsy live in developing countries, where the condition remains largely untreated (Boer et al., 2008). The reasons for the unavailability of treatment include, inadequate health delivery systems, lack of trained personnel, essential drugs, traditional beliefs and practices that often do not consider epilepsy as a treatable condition (Boer et al., 2008). It often carries with it a high economic and social burden resulting from high healthcare costs and from loss of earnings, productivity, social interaction, self-esteem and independence (Gilliam, 2005). The unpredictable nature of epileptic seizures, usually involving loss of consciousness, tends to impose an intense psychosocial burden and leads to restrictions in normal daily activities (Gilliam, 2005). The epileptic seizure is an event consisting of a sudden and transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain (Raol and Brooks-Kayal, 2012). An epileptic seizure can be as subtle as a momentary lapse of attention to very obvious involving violent and involuntary contractions of muscles (Elger and Schmidt, 2008). The phenotype of each seizure is determined by the point of origin of the hyperexcitability and its degree of spread in the brain. By convention, the diagnosis of epilepsy requires that the patient has had at least two unprovoked

seizures (Elger and Schmidt, 2008). However, a person with isolated nonrecurrent, externally provoked seizures that are also caused by excessive discharge of cerebral neurons is not thought to have epilepsy as long as the seizures are not recurrent and each seizure is preceded by a provocation (e.g., substance abuse, fever, exposure to alcohol combined with lack of sleep) (Elger and Schmidt, 2008).

Classification of epilepsy

Having seizure and epilepsy classifications are exceedingly important for the clinicians, care teams, patients and families, and researchers. Classifications for seizures and epilepsy, proposed by the International League Against Epilepsy (ILAE) is constructed on basis of seizure type and relies on clinical and EEG criteria (Ohtsuka et al., 1993) A modification allows classification of seizures on purely clinical grounds and is suitable when facilities for investigation are limited (Commission on epidemiology and prognosis; ILAE, 1993) as obtainable in most developing countries including Nigeria. Seizures are classified as partial or generalized based on the extent of neuroanatomic involvement and as simple or complex based on their effects on awareness (Fisscher et al., 2005).

Focal seizures

A seizure should be classified as focal when there is either clinical or EEG evidence of (focal) onset (Geiger and Harner 1978), it starts in one part of the brain and may affect a large part of one hemisphere or just a small area in one of the lobes. This type, occurs with or without impairment of awareness, except that atonic and epileptic spasm seizures usually do not show obvious impairment of awareness.

- **Focal Aware -** A seizure is "focal aware" if awareness is intact, even if the person is unable to talk or respond during the seizure. This replaces the term simple partial seizure.

• **Focal Impaired Awareness** - A seizure is classified as "focal impaired awareness" if awareness is impaired at any time during the seizure. This replaces the term complex partial seizure.

Focal onset seizures can be further divided into following categories.

• **Focal automatisms seizure:** A seizure with automatic fumbling behavior, such as lip-smacking, hand-rubbing, picking at objects, walking in circles, repeating meaningless phrases, or undressing.

• **Focal atonic seizure:** Focal, for example in one arm or leg, sudden loss of muscle tone and strength, resulting in a transiently limp limb.

• **Focal clonic seizure:** Sustained rhythmical jerking of one part of the body or face.

• **Focal epileptic spasms:** Sudden flexion or bending of the trunk with flexion or extension of the limbs lasting less than a few seconds. These often occur in clusters. The term infantile spasms applies to epileptic spasms occurring during infancy. Video-EEG monitoring and a brain MRI may be needed to determine whether onset of epileptic spasms is focal or generalized.

• **Hyperkinetic seizure:** A seizure with vigorous thrashing or pedaling movements. Even though both sides of the body are usually involved with these seizures, the EEG often shows a focal and frontal lobe origin. Some people used to call these hypermotor seizures.

• **Focal myoclonic seizure:** Irregular and brief lightning jerks of limbs or face on one side of the body.

• **Focal tonic seizure:** Stiffening of arm, leg, or neck producing a forced posture during the seizure.).

• **Focal autonomic seizure:** A seizure whose primary effect is on autonomic nervous system functions, such as heart rate, blood pressure, sweating, skin color, piloerection, and gastrointestinal sensations.

• **Focal behavior arrest seizure:** In this seizure type, movement stops, sometimes called a freeze or a pause. A seizure should only be classified as a focal behavior arrest seizure if the behavior arrest is the main feature through the entire seizure.

• **Focal cognitive seizure:** This type of seizure refers to impaired cognition during a seizure. The impairment might affect language, spatial perception, ability to calculate math, or other cognitive functions. Do not count loss of awareness or memory (unless only memory is impaired) as a focal cognitive seizure, because awareness is used to describe other seizure types.

• **Focal emotional seizure:** This seizure type begins with spontaneous fear, anxiety, or less often joy. There may be involuntary laughing or crying, each of which might or might not be accompanied by a subjective emotion. Gelastic and dacrystic seizures would fit into this group.

• **Focal sensory seizure:** Sensory seizures can consist of tingling or numbness, visual symptoms, sounds, smells, tastes, tilting or vertigo, and hot-cold feelings.

Generalized onset seizures

Generalized onset seizures are characterized by widespread involvement of both cerebral hemispheres (Woermann et al., 1998). Typically, the seizure starts with abrupt alteration of consciousness without warning. EEG discharges are bilateral, grossly synchronous and symmetrical over both cerebral hemispheres. It is further classified into following categories.

• **Generalized tonic–clonic:** Immediate loss of awareness, with stiffening of all limbs (tonic phase), followed by sustained rhythmic jerking of limbs and face (clonic phase). Duration is typically 1 to 3 min. The seizure may produce a cry at the start, falling, tongue biting, and incontinence.

• **Generalized clonic:** Rhythmical sustained jerking of limbs and/or head with no tonic stiffening phase. These seizures most often occur in young children.

• **Generalized tonic:** Stiffening of all limbs, without clonic jerking.

• **Generalized myoclonic:** Irregular, unsustained jerking of limbs, face, eyes, or eyelids. The jerking of generalized myoclonus may not always be left–right synchronous, but it occurs on both sides. Myoclonus may be part of a seizure or a non-epileptic motor disorder.

• **Generalized myoclonic–tonic–clonic:** This seizure is like a tonic–clonic seizure, but it is preceded by a few myoclonic jerks on both sides of the body. Such seizures are commonly seen in people with the syndrome of juvenile myoclonic epilepsy.

• **Generalized myoclonic–atonic:** This seizure presents with a few myoclonic jerks, followed by a limp drop. These seizures may be seen in children with Doose syndrome.

• **Generalized atonic:** This is an epileptic drop attack, with sudden loss of muscle tone and strength and a fall to the ground or a slump in a chair. Atonic seizures usually last only seconds.

• **Generalized epileptic spasms:** Brief seizures with flexion at the trunk and flexion or extension of the limbs. Video-EEG recording may be required to determine focal versus generalized onset.

• **Generalized typical absence:** Sudden cessation of activity with a brief pause and staring, sometimes with eye fluttering and head nodding or other automatic behaviors. In the more severe seizures, awareness and memory are impaired and recovery is immediate. The EEG during these seizures always shows generalized spike-waves.

• **Generalized atypical absence:** Like typical absence seizures, but may have slower onset and recovery and more pronounced changes in tone. Atypical absence seizures can be difficult to distinguish from focal impaired awareness seizures, but absence seizures usually recover more quickly and the EEG patterns are different.

• **Generalized myoclonic absence:** A seizure with a few jerks and then an absence seizure.

• **Generalized eyelid myoclonia:** Eyelid myoclonia represents jerks of the eyelids and upward deviation of the eyes, often precipitated by closing the eyes or by light. These may be associated with absence seizures in people with Jeavon's syndrome.

Unknown Onset Seizures:

- Clinicians using the classification will identify a seizure as focal or generalized onset if there is about an 80% confidence level about the type of onset. This means that there is significant confidence on the seizure onset and type.
- Seizures without enough confidence about onset are labeled of unknown onset. The most important seizures of unknown onset are tonic-clonic, epileptic spasm, and behavior arrest (which could be either a focal impaired awareness or absence seizure).
- If a seizure onset becomes clarified at a later date, the type will change.

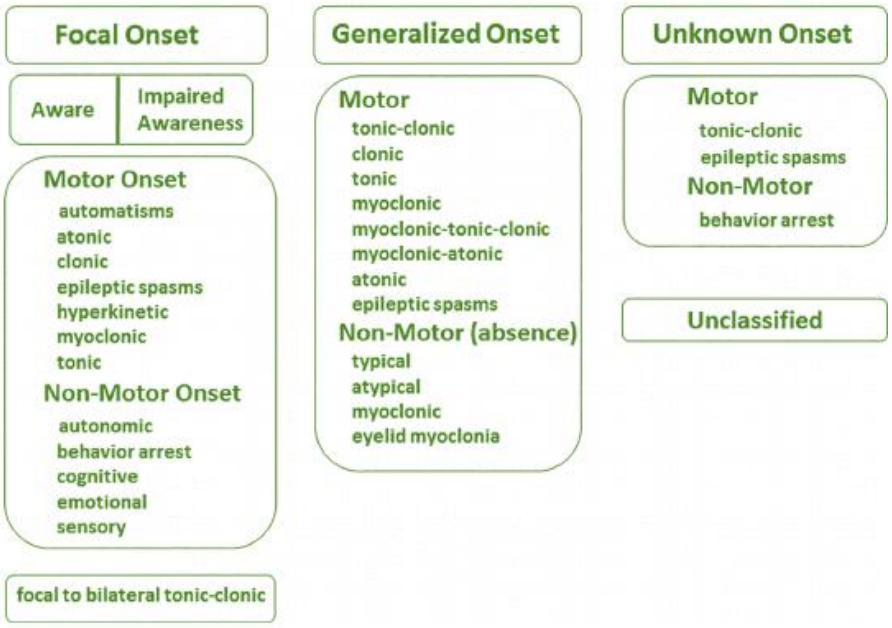


Fig.1 ILAE 2017 classification of seizure types expanded version.

Pathophysiology of epilepsy

The underlying mechanisms of seizure pathogenesis have been proven to be complex and are not completely understood; several other molecular mechanisms are involved, including oxidative stress, inflammation, neuronal apoptosis, reduced neurogenesis, loss of GABA-ergic neurons, glutamate excitotoxicity and calcium overload (Wang and Quin 2010). A variety of different electrical or chemical stimuli can easily give rise to a seizure in any normal brain. The epileptic seizure always reflects abnormal hypersynchronous electrical activity of neurons caused by an imbalance between excitation and inhibition in the brain (Goldenberg 2010). Neurons are interconnected in a complex network in which each individual neuron is linked through synapses with hundreds of others. A small electrical current is discharged by neurons to release neurotransmitters of synaptic levels to permit communication with each other (Pannasch and Rouach 2013). More than hundred neurotransmitters or neuromodulators have been shown to play a role in neuronal excitation. However, the major excitatory neurotransmitter in the brain is L-glutamate and the major inhibitory neurotransmitter in the brain is gamma-amino butyric acid (GABA). An abnormal function of either of these could result in a seizure (Davis and Wu 2001). An excited neuron will activate the next neuron whereas an inhibitory neuron will not. A normal neuron discharges repetitively at a low baseline frequency, and it is the integrated electrical activity generated by the neurons of the superficial layers of the cortex that is recorded in a normal electroencephalogram. If neurons are damaged, injured or suffer electrical or metabolic insult, a change in the discharge pattern may develop. In the case of epilepsy, regular low-frequency discharges are replaced by bursts of high-frequency discharges usually followed by periods of inactivity. An epileptic seizure is triggered when a whole population of neurons discharges

synchronously in an abnormal way. This abnormal discharge may remain localized or it may spread to adjacent areas, recruiting more neurons as it spreads (Fabricius et al., 2008).

Role of GABA and glutamate in the pathogenesis of epilepsy

It is important to mention the role of neurotransmitters especially, γ-amino butyric acid (GABA) and glutamate in epileptogenesis, since they are the major inhibitory and excitatory transmitters in the central nervous system, respectively, and the fact that generation of seizures has been accredited to imbalance between excitatory and inhibitory neurotransmission in epileptic brains. GABA plays an important role in regulation of neuronal excitability and impairment of GABA function produces seizures (Allen et al., 2004)). Compounds that facilitate GABA- mediated inhibition are convulsants (Holland et al., 1992). GABA exerts its major inhibitory effect via $GABA_A$ receptor (which is a ligand-gated ion channel) by increasing neuronal membrane conductance for chloride ions causing membrane hyperpolarization resulting in reduced neuronal excitability and most rapid inhibition in brain (Olsen and Avoli 1997). $GABA_A$ receptor is target for many important neuroactive drugs including antiepileptic drugs benzodiazepines and barbiturates (Olsen and Avoli 1997). $GABA_A$ receptor consists of five subunits that form a chloride ion channel (Macdonald and Mascagni 2001). The subunits consist of various subtypes and pharmacological studies have shown that individual subunits and subtypes confer different sensitivities to agents acting on $GABA_A$ receptors (Neelands et al., 1999). It is postulated that exposure of GABA to postsynaptic receptors for a brief period of time results in generation of Inhibitory Post-Synaptic Currents (IPSCs) (Hill et al., 1998). $GABA_A$ receptor-mediated miniature IPSCs play important physiological role in preventing the development of neuronal hyper excitability (Salin and Prince 1996). Decrease in $GABA_A$ from receptor-mediated IPSCs is observed in cells from hippocampi of animals with chronic experimental epileptic seizures and

humans with chronic intractable temporal lope epilepsy (Isokawa, 1996). Glutamate is the most important excitatory neurotransmitter in all rapidly conducting relay pathways of the motor and sensory systems of the outer tube of the central nervous system. It produces fast or prolonged synaptic excitation and triggers various calcium dependent processes in the target cells, including production of nitric oxide (Bienvenu et al., 2002). Glutamate is a transmitter in the corticospinal, corticostriatal pathways, intrahemispheric and interhemispheric association pathways, hippocampal circuits, primary afferents, and somatosensory and special sensory pathways, cerebellar afferents and excitatory inter-neurones. Glutamate acts via two types of receptors, ionotropic glutamate receptors (iGluR) which are ligand-gated cation specific channels and metabotropic glutamate receptors (mGluR) which are G-protein-coupled receptors. Ionotropic glutamate receptors are classified according to their prototype agonists: NMDA (N-methyl-D-aspartate), kainite and AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid). Practically all agonists are able to induce epileptic seizures and brain damage whereas antagonists have been shown to be anticonvulsant (Mares et al., 2004). The role played by metabotropic glutamate receptors depends on the type of receptors: activation of type I is proconvulsant and convulsants, whereas activation of type II and III is anticonvulsant (Moldrich et al., 2003).

Epilepsy may arise as a consequence of a dramatic release of glutamate from central nerve terminals. Sustained seizures of the limbic system in experimental animals result in brain damage that resembles that due to glutamate toxicity. Similar changes are seen at autopsy in patients with intractable epilepsy. In animals such seizure-related brain damage may be reduced by the administration of non-competitive NMDA receptor antagonists, but it would appear that not all seizure activity is suppressed by drugs (Leonard, 2003). The precise mechanism whereby persistent seizure activity results in neuronal degeneration is not completely understood. It seems

possible that repetitive depolarization and repolarization of the nerve membrane eventually leads to an energy-deprived state within the cell, thereby preventing the restoration of the cell membrane potential. Each depolarization will also lead to an influx of calcium ions and efflux of potassium ions, which if prolonged, can result in cell death. The reduced efficiency of glial cells to remove potassium ions, and the ability of high extracellular concentration of potassium ions to depolarize neurons and cause neurodegenerative changes also play a critical role in causing the degenerative changes that are a feature of status epilepticus and intractable epilepsy (Leonard, 2003). Recent advances have indicated that $GABA_A$ receptors work synergistically with NMDA receptors to increase the influx of calcium ions into neuroblasts and immature neurons. This is essential for the modulation of early CNS development (DeLorey and Olsen 1999). It is evident that GABA is a critical inhibitory transmitter and seizures can rapidly be elicited by pharmacological disruption of GABAergic mechanism (Mohler 2007). Drugs have also been developed to modulate glutamic acid function. Reduction of excitatory glutaminergic neurotransmission is potentially important; AMPA receptor blockade probably contributes to the antiepileptic effect of drugs such as lamotrigine (Lee et al., 2008).

Oxidative stress and Epilepsy

Neuronal cells in the brain are highly vulnerable to oxidative stress; therefore, the prolonged excitation of neurons during seizures can lead to injury resulting from biochemical alterations and specifically to the role played by the oxidation state. Oxidative stress reflects an imbalance between the production of reactive oxygen species (ROS), reactive nitrogen oxygen (RNS), and the ability to readily detoxify the reactive intermediates in a biological system (Ho et al., 2015 2015). Reactive oxygen species (ROS) are short-lived and highly reactive molecules, excessive ROS generation can cause damage of neuronal cells inducing cell death via either an apoptotic or

a necrotic pathway (Redza-Dutordoir and Averill-Bates DA 2016). Recent evidence has suggested an intimate link between oxidative stress and mitochondrial dysfunction contribute to the neuropathology of human epilepsy, particularly in the hippocampus. Intrinsic mitochondrial apoptotic pathway includes bioenergetic failure and increased cytosolic calcium, oxidative stress (excessive free radical production and impaired synthesis of antioxidants, especially glutathione), mitochondrial permeability transition pore opening, and the release of key proteins into the cytosol triggering cell death pathways Oxidative stress associated with seizure activity can greatly reduce mitochondrial function and is widely accepted as a contributor to learning and memory deficits resulting from epileptic seizures (Chuang and Yu 2010). Compared to other organs, the brain is extremely susceptible to damage by free radicals due to its relatively high levels of oxidative metabolism and comparatively low levels of both free-radical scavenging enzymes and antioxidant molecules (Uttara et al., 2009). Glutathione (GSH) is one of the most important antioxidant defenses against oxidative stress (Valko et al.; 2007). The accumulation of malondialdehyde (MDA), an end product of lipid peroxidation, reflects the extent of oxidative stress in plasma. It is regarded as an indicator for the group with various neurological disorders like epilepsy, (Ramaekers et al., 1997).The inactivation of ROS can be accomplished by antioxidant enzymes. The enzyme SOD plays a key role in detoxifying the superoxide anions from hydrogen peroxide and oxygen (Fridovich, 1998). The hydrogen peroxide that is formed may be decomposed by CAT in water and oxygen. Oxidative stress injuries result in increased ROS formation and oxidative damage to proteins, lipids and mitochondrial DNA, which exacerbates mitochondrial dysfunction, reduces mitochondrial energy production and triggers apoptotic cell death through the activation of the caspase-3 pathway (Kovac et al., 2013). Those changes that affect neuronal calcium homeostasis may be factors that contribute to increase of susceptibility to epileptic

seizures associated with mitochondrial dysfunction (Waldbaum and Patel 2010) Hence, exogenous antioxidants may be safe and effective agents for seizure control and the prevention of cognitive decline.

Epilepsy and neurogenesis

Virtually all mammals, including humans, exhibit neurogenesis throughout life in the hippocampus, a learning and memory center in the brain. Numerous studies in animal models imply that hippocampal neurogenesis is important for functions such as learning, memory, and mood. Interestingly, hippocampal neurogenesis is very sensitive to physiological and pathological stimuli (Lazarov and Hollands 2016). Certain pathological stimuli such as seizures alter both the amount and the pattern of neurogenesis, though the overall effect depends on the type of seizures. Acute seizures are classically associated with augmentation of aberrant neurogenesis and migration of newly born neurons into ectopic regions such as the hilus and the molecular layer of the dentate gyrus. Additional studies suggest that abnormally migrated newly born neurons play a role in the occurrence of epileptogenic hippocampal circuitry characteristically seen after acute seizures, status epilepticus, or head injury (Ko et al., 2015). Recurrent spontaneous seizures such as those typically observed in chronic temporal lobe epilepsy are associated with substantially reduced neurogenesis, which, interestingly, coexists with learning and memory impairments and depression (Arabadzisz et al., 2005).

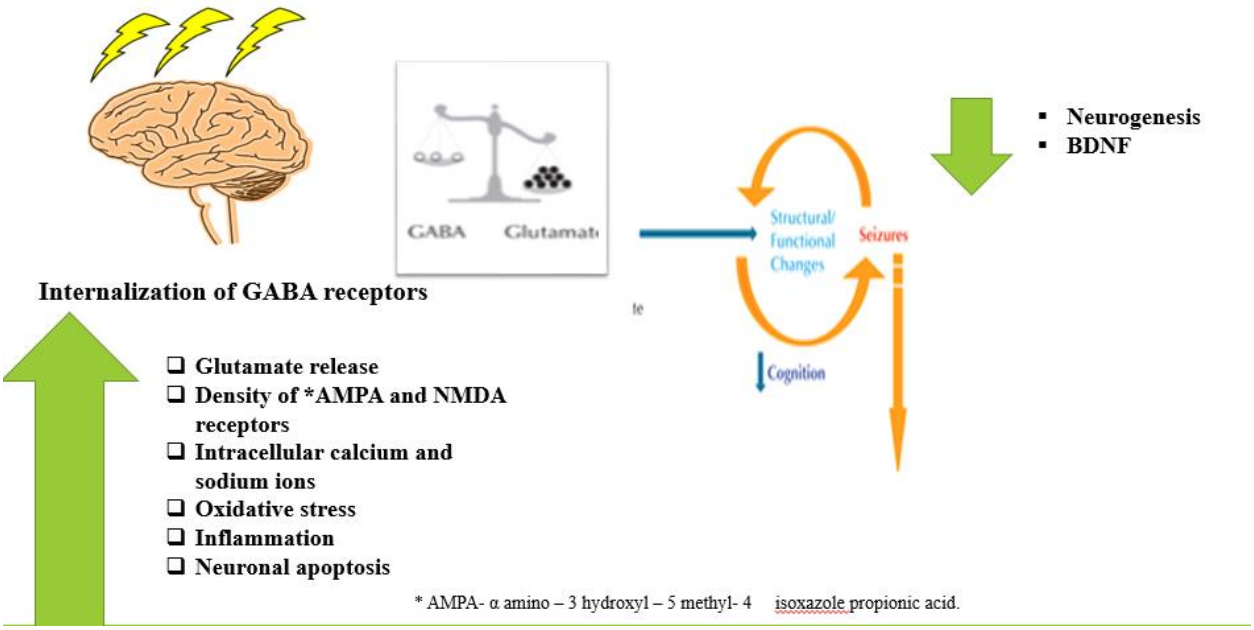


Fig.2 Structural and functional changes in brain after induction of epilepsy.

Epilepsy Etiology:

Epilepsy is a condition with recurrent seizures. These may be idiopathic or symptomatic. Epilepsy has no identifiable cause in about half the people with the condition. In the other half, the condition may be traced to various factors, including: (Harden 2002).

- **Genetic influence.** Some types of epilepsy, which are categorized by the type of seizure you experience or the part of the brain that is affected, run in families. In these cases, it's likely that there's a genetic influence. Researchers have linked some types of epilepsy to specific genes, but for most people, genes are only part of the cause of epilepsy. Certain genes may make a person more sensitive to environmental conditions that trigger seizures.

- **Head trauma.** Head trauma as a result of a car accident or other traumatic injury can cause epilepsy.

- **Brain conditions.** Brain conditions that cause damage to the brain, such as brain tumors or strokes, can cause epilepsy. Stroke is a leading cause of epilepsy in adults older than age 35.
- **Infectious diseases.** Infectious diseases, such as meningitis, AIDS and viral encephalitis, can cause epilepsy.
- **Prenatal injury.** Before birth, babies are sensitive to brain damage that could be caused by several factors, such as an infection in the mother, poor nutrition or oxygen deficiencies. This brain damage can result in epilepsy or cerebral palsy.
- **Developmental disorders.** Epilepsy can sometimes be associated with developmental disorders, such as autism and neurofibromatosis.

Mechanism of action of antiepileptic drugs:

Antiepileptic effects are produced by drugs that modulate ion channels, enhance inhibition mediated by $GABA_A$ receptors and/or glycinergic systems, the regionally specific transmitter systems (including monoamines such as catecholamines, serotonin and histamine, and neuropeptides such as opioid peptides, galanin and neuropeptide Y) and the inhibitory neuromodulator adenosine (Errington et al., 2005). In addition, blockade of glutamate receptors (including those of the NMDA, AMPA, kainate and group I metabotropic (mGluR1 and mGluR5 types) can also protect against seizures in animal models. In principle, it might be possible to prevent seizures by targeting any one or a combination of these systems (Rogawski, 2006). Consideration will be given to three of the major mechanisms of action of antiepileptic drugs: modulation of ion channels, enhancement of GABA inhibitory neurotransmission, and attenuation of glutamate mediated excitatory transmission (Kwan et al., 2001).

Modulation of ion channels

The intrinsic excitability of the nervous system is ultimately controlled by voltage-gated ion channels which regulate the flow of cations across surface and internal cell membranes. Voltage-gated sodium channel is arguably the most important ion channel responsible for depolarization of cell membranes. Modulation of the gating of brain sodium channels is believed to account, at least in part, for the ability of several AEDs to protect against generalized tonic-clonic and partial seizures (Deckers *et al.*, 2003). Phenytoin and carbamazepine are prototype sodium channel blockers and this mechanism is shared by the newer drugs lamotrigine, felbamate, topiramate oxcarbazepine and zonisamide (Remy *et al.*, 2003). By binding mainly to the inactivated state of the sodium channel these drugs produce a voltage- and frequency-dependent reduction in channel conductance, resulting in a limitation of repetitive neuronal firing with little or no effect on the generation of single action potentials (Kwan *et al.*, 2001). Their actions translate indirectly into reduced transmitter output at synapses (Leach *et al.*, 1986). AEDs might also act by blocking the persistent sodium current (current that flows due to the overlap between the voltage ranges for sodium channel activation and inactivation) (Taddese and Bean, 2002). It has been reported that phenytoin (Segal and Douglas, 1997), valproate (Taverna et al., 1998) and topiramate (Taverna *et al.*, 1999) inhibit the persistent sodium current at concentrations lower than those that block fast sodium current. The selective reduction of late, persistent sodium channel openings might contribute to the ability of these drugs to protect against seizures with minimal interference in normal function (Rogawski and Loscher, 2004). Voltage-gated calcium channels are also involved in depolarization. They are often recruited in response to initial sodium-dependent action potential generation. The N-, P- and Q-type calcium channels have been implicated in the control of neurotransmitter release at the synapse, whereas the T-type channel, expressed predominantly in

the thalamocortical relay neurons, is believed to play a role in the distinctive rhythmic discharges of generalized absence seizures (Kwan *et al.*, 2001). The efficacy of ethosuximide against generalized absence seizures is believed to be mediated by blockade of the T-type calcium channel. Evidence suggests that valproate may have similar effects (Deckers *et al.*, 2003). Lamotrigine has also been reported to limit neurotransmitter release by blockade of the N- and P- subtypes of voltage-sensitive calcium channel while gabapentin binds to the α2δ-subunit of the L-type channel (Kwan *et al.*, 2001). Potassium channels also play a major role in the control of resting membrane potential, responsiveness to synaptic inputs, spike frequency adaptation and neurotransmitter release. They are therefore potential targets for antiepileptic drugs. Genetic, molecular, physiological and pharmacological evidence supports a role of some K^+ channels in the control of neuronal excitability and epileptogenesis (Wickenden, 2002). Retigabine functions through its ability to activate potassium currents (Rundfeldt, 1997).

Enhancement of inhibitory neurotransmission

Potentiation of inhibitory neurotransmission mediated by GABA is a key mechanism of AED action. Compared to excitatory synapses, neurons that use GABA as their neurotransmitter represent only a small fraction of neurons in key regions implicated in epileptic activity, such as the neocortex, hippocampus and amygdala (Galarreta and Hestrin, 1998). These inhibitory connections are still capable of restraining the natural tendency of excitatory neurons from undergoing the transition into synchronized epileptiform discharges. Following synaptic release, GABA acts through $GABA_A$, $GABA_B$ and $GABA_c$ receptors to bring about neuronal hyperpolarization leading to synaptic inhibition. Potassium bromide, the first effective epilepsy treatment, augments $GABA_A$ receptor-mediated inhibition by enhancing the sensitivity of GABAA receptors to GABA and increasing $GABA_A$ receptor currents (Akaike *et al.*, 1989).

Bromide salts continue to be widely used for treating epileptic dogs and cats in veterinary medicine although clinically it has been replaced by less toxic agents (Lane and Bunch 1990). Drugs that act by interacting with $GABA_A$ receptors or by modifying the activity of enzymes and transporters typically have a broad spectrum of antiepileptic activity in human seizure disorders, although, with the exception of benzodiazepine receptor agonists, they are generally ineffective in absence seizures. The actions of valproate and gabapentin (by increasing GABA synthesis and turnover) overlap with drugs that interact with GABA systems. The antiepileptic activity of benzodiazepine-like agents occurs through positive allosteric modulation of $GABA_A$ receptors containing the α2 subunit, β1 subunit (necessary for seizures protection) and effects on tonic $GABA_A$ receptor currents, which originate from GABA acting on extrasynaptic receptors (Crestani *et al.*, 2000). Benzodiazepines have an important clinical role in the acute treatment of status *epilepticus* though sedation, muscle relaxation but development of tolerance and dependence limit their chronic use. Benzodiazepines, such as clonazepam have anti-absence activity by inhibiting the 3-Hz spike-and-wave activity believed to underlie the generalized absence seizures, in thalamocortical circuits) (Sohal *et al.*, 2003). Thalamic reticular neurons exert an inhibitory influence on thalamocortical relay neurons that is necessary for de-inactivation of the T-type calcium currents that underlie bursting. Benzodiazepines reduce the inhibitory output of the reticular neurons by effects on benzodiazepine-sensitive α3-containing $GABA_A$ receptors and therefore prevent absence seizure activity. Barbiturates such as phenobarbital also act as positive allosteric modulators of $GABA_A$ receptors to shift the relative proportion of openings to favor the longest-lived open state associated with prolonged bursting (brief openings in rapid succession), thereby increasing the overall probability that the channel is open (Macdonald and Olsen, 1994). In addition, barbiturates act on other ion channel systems, including calcium and sodium channels, and this probably contributes

to their therapeutic activity and might also be a factor in their side effects (ffrench-Mullen *et al.*, 1993). Felbamate (Rho et al., 1997) and topiramate (Gordey et al., 2000) might also act, in part, through positive modulation of $GABA_A$ receptors. The concentration of GABA in the brain is controlled by two pyridoxal-5′-phosphatedependent enzymes, glutamate decarboxylase (GAD) and GABA transaminase (GABAT). The AED vigabatrin (γ-vinyl GABA) elevates brain GABA by acting as an irreversible suicide inhibitor of GABAT (De Biase *et al.*, 1991). The AED tiagabine is a potent and selective competitive inhibitor of GABA transporter 1(GAT1) that binds with high affinity for the transporter and prevents GABA uptake without itself being transported (Suzdak and Jansen, 1995). By slowing the reuptake of synaptically released GABA, tiagabine prolongs inhibitory postsynaptic potentials (Thompson and Gahwiler, 1992).

Attenuation of excitatory neurotransmission

Glutamate is the principal excitatory neurotransmitter in the mammalian brain. Following synaptic release, it exerts its effects on both ionotropic (AMPA, kainate and NMDA) and metabotropic receptor types. The ionotropic glutamate receptors form ligand-gated ion channels permeable to sodium and depending on subtype and subunit composition, calcium ions. The AMPA and kainite subtypes are implicated in fast excitatory neurotransmission, whereas the NMDA receptor, quiescent at resting membrane potential, is recruited during periods of prolonged depolarization (Kwan *et al.*, 2001). NMDA receptors consist of NR1 subunits combined with one or more NR2 (A–D) subunits, which form channels that are permeable to sodium and calcium ions. The activity of NMDA receptors is regulated via a strychnine-insensitive glycine-binding site and other modulatory sites, such as polyamines, Zn2+ and H+. At resting membrane potentials, the pore of this receptor is blocked by magnesium ions, which are removed after membrane depolarization. The role of NMDA receptors in experimental epileptogenesis, neuroplasticity, seizures and

excitotoxicity has been firmly established (Delorenzo et al., 2005). Antagonists of NMDA receptors, such as dizocilpine or ketamine, inhibit seizures induced by pentylenetetrazole, pilocarpine, maximal electroshock or sensory stimulation. Furthermore, they delay the development of amygdala kindling but have a weaker effect on fully developed seizures in this model. Unfortunately, both competitive and non-competitive NMDA receptor antagonists show serious undesired effects, such as psychomotor, memory and cognitive disturbances, and psychotomimetic-like effects in experimental animals and in initial clinical studies. However allosteric modulators of NMDA receptors, especially modulators that interact with the strychnine-insensitive glycine-binding site and the polyamine-binding site, are more promising as potential AEDs. The partial agonist of the glycine binding site, D-cycloserine, exerts anticonvulsant activity most likely via the desensitization of NMDA receptors. This compound also augments the seizure suppressing effects of some AEDs and, in low doses, has a positive influence on memory processes. Beneficial effects in experimental models of seizures have been observed after the concomitant administration of glycine- and polyamine-binding site antagonists. In 2008 lacosamide (LCM), an antagonist of the glycine binding site on NMDA receptors, was registered as an AED Blockade of the NMDA subtype of glutamate receptor and AMPA receptors have also been reported to contribute to the antiepileptic effects of felbamate and topiramate respectively (Deckers *et al.,* 2003).

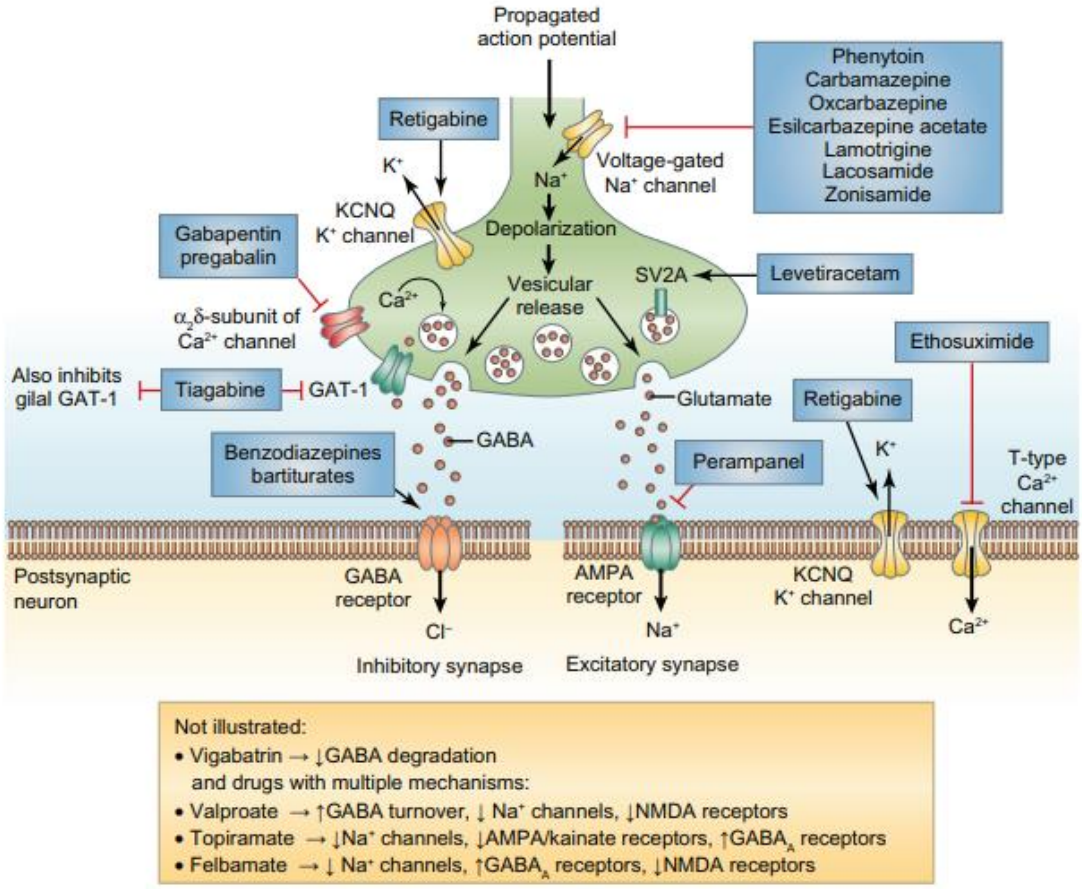


Fig.3 Mechanisms of action of antiepileptic drugs (Shih et al., 2013).

Experimental Models for Anticonvulsant screening

Acute models

The maximal electroshock (MES) test and the pentylenetetrazole (PTZ) seizure are conventional and most widely used animal models for detection of seizures and are often classified as acute animal models (Loscher, 2002). The prime important step in screening of potential anticonvulsant compounds is the classical maximal electroshock (MES) test in mice, introduced by Putnam and Merritt (Putnam and Merritt, 1937). This is the most acknowledged animal model in AED discovery, because seizure induction is simple and the predictive value for detecting clinically

effective AEDs is high (Loscher, 2002). A powerful detection system is ensured when the MES is combined with the pentylenetetrazole (PTZ) seizure test. These are the two primary bioassays employed in the in *vivo* screening of new anticonvulsant compounds (Raza *et al.*, 2001). AEDs such as phenytoin, carbamazepine, valproic acid, that inhibit the hind limb tonic extension phase (HLTE) of the electroshock seizure in MES are effective in the therapy of generalized tonic-clonic and partial seizures. AEDs that inhibit seizures induced by pentylenetetrazole (PTZ) in PTZ test e.g. ethosuximide and phenobarbitone are effective in the treatment of generalized myoclonic and absence seizures (Raza et al., 2001). The subcutaneous administration of bicuculline (BIC), picrotoxin (PTX) and strychnine (STR) are also valuable models to induce seizures and evaluate the effectiveness and mechanisms of anticonvulsant compounds (Raza et al., 2001). Clinically efficacious drugs have been discovered by these acute models including ethosuximide, trimethadone and valproate. These show similar anticonvulsant effects in different genetic models of absence epilepsy such as Genetic Absence Epilepsy Rats from Strasbourg (GAERS) or lethargic mice (Loscher, 2002).

Chronic models

Acute models might not detect all compounds with antiepileptic activity when used alone. The MES test preselects drugs with certain mechanisms, but misses others (Meldrum, 1997). Although the MES test is often considered a mechanism-independent model (Kupferberg, 2001), it is particularly sensitive to drugs blocking sodium channels (Meldrum, 1997). This means that several clinically efficacious AEDs which act by other mechanisms (such as levetiracetam, vigabatrin and tiagabin) and were initially not screened or detected by using MES test would have been missed using this model as the only drug discovery model (Loscher and Schmidt, 1994). Also, the PTZ test might not be able to detect all antiepileptic drugs against non- convulsive seizures (Loscher,

2002). This is due to the fact that lamotrigine, which is very efficacious against non-convulsive seizures in patients, is ineffective in the PTZ test, while vigabatrin and tiagabin, which are quite effective in the PTZ test, are ineffective in patients and even aggravate non-convulsive seizures (Loscher, 2002). In this case chronic seizure models including kindling, genetic models such as GAERS or lethargic mice have been used (Loscher, 2002). Also, even after the primary screening of anticonvulsants, advanced experiments on primate models and 'Kindling in rodents' which may follow include monkey models of absence (petit mal) seizures, aluminium hydroxide induced partial or secondary generalised (grand mal) seizures in monkeys, experimental temporal lobe epilepsy in monkeys and amygdala kindled seizures in rats. Also the pliocarpine induced status epilepticus which is a model of temporal lobe epilepsy is also widely used.

Electroencephelograph (EEG) and epilepsy:

When someone has had seizures, and it is thought that they might have epilepsy, there are various tests that their specialist might ask for. Two of these tests are the electroencephalogram (EEG) and MRI. Before we look at EEG in detail, we need to understand that neither of the tests will say for certain whether the person has epilepsy or not. But these tests, alongside other information, might help the specialist to decide if epilepsy is a likely cause of the seizures. (Sahu et al., 2011)

Electroencephalographs - EEGs

Not all seizures are due to epilepsy. There are other medical conditions that might cause someone to have a seizure for example, diabetes. The difference between epileptic seizures and other seizures is that epileptic seizures are caused by a disruption in the way the brain is working. The fact that epileptic seizures always start in the brain is important when considering the EEG. An EEG looks at what is happening in the brain – the activity of the brain cells. It does not look at the structure of the brain (how the brain is made up).

Brain waves and electrical signals

Brain cells (neurons) work by sending nerve impulses from one cell to another to transfer messages around the brain and the body. These messages, called action potentials, happen due to changes in the electrical charge of the cells. So when the brain is 'working' cells communicate using electrical signals, and when they do this they 'give off' electricity. It is this electrical activity, sometimes called 'brain waves', that is picked up on by EEG The electrical signals from the brain are picked up by small electrodes (about one centimeter across), which are placed on the person's head. The electrodes only record the electrical activity of the brain; they do not give out electricity. The electrodes cannot pick up the electrical signals from individual neurons – the cells are far too small and the electrical charge is also too small. Instead, they record the electrical activity from small areas of the brain. The EEG shows brain function, and looks for the presence or absence of specific brain activity in specific areas of the brain. The EEG cannot interpret what the messages are 'saying' (or what you are thinking!), only that brain activity is happening. Because the electrical signals are still quite small, they are amplified (made stronger) so that they can be recorded. The activity is recorded on an electroencephalograph either on paper or more usually on computer.

EEG waves:

The EEG recording shows different types of brain waves. A wave is any type of brain activity, which appears as a 'wave' shape on the EEG recording. There are different names for the brain waves which are put into bands according to their frequency or number of 'waves' per second (see below), and each type of wave looks different on the EEG. Some brain waves happen at particular times or in different areas of the brain.

- **Alpha waves** are at a frequency of 8-13 waves per second, and are the typical waves seen in adults who are relaxed with their eyes closed. These waves are clearest in the occipital lobes (the part of the brain responsible for our sight and seeing).
- **Beta waves** are at frequencies greater than 13 per second. These are often seen in people who are awake, with their eyes open or closed. They are often seen in the frontal lobes (responsible for conscious thought and movement) and in central areas of the brain.
- **Theta waves** happen between the frequencies of 4-7 waves per second, and are also called slow activity. Theta waves occur during sleep and in young children. They are not obvious in adults who are awake.
- **Delta waves** are at frequencies up to 4 waves per second. These are the slowest type of wave but have the highest amplitude (strongest signal). Delta waves are common in children under one year. They also happen during some parts of sleep.
- **Gamma waves** are at frequencies of 26-100 waves per second.
- Spikes are very fast waves and are called spikes because of their shape on the EEG. Each lasts less than 80 milliseconds (less than 1/12th of a second) and may be followed by slow delta waves. Spikes clearly stand out from other brain activity on the EEG.
- Polyspikes are a series of spikes that happen quickly.
- Spike waves happen when one or more brief spikes are followed by a slow wave, and this happens three times per second.
- Sharp waves happen over 80-200 milliseconds.

Medicinal Plants and Epilepsy

Medicinal plants are the oldest form of healthcare known to mankind. Since antiquity, plants have been used by mankind for their relieving and therapeutic abilities and still we rely on their healing properties (Tagarelli et al., 2013). Plants comprise of multitude of active constituent, which have a direct pharmacological action on our body including various organs. One such major complex organ is brain, so complex that still only few drugs are approved by drug authorities for ailments like epilepsy. In reality, current interest in traditional medicine has resulted in quick development and investigation of many remedies applied in various ethnic groups across the world. The screening of herbal extracts has been of great interest to the scientists for the discovery of new and effective drugs (Kosger et al., 2009). There are number of drugs being used in the traditional medicine for treatment of epilepsy and presently many of these drugs are being explored scientifically to ascertain their anticonvulsant activity. The data related to plants, methods employed, tested or reported for anticonvulsant properties is summarized in Table 1.

List of Plants from India and outside of India with anticonvulsant properties

Plant	**Family**	**Part used**	**Method**	**References**
Abelmoschus angulosus Wall.	Malvaceae	Aerial Parts	ACV	Bhakuni et al., 1988
Abrus precatorius L.	Leguminosae	Root	LIS, SIS	Adesina, 1982a
Abrus precatorius L.	Fabaceae	Root	MIS	Adesina, 1982a
Acanthus longifolius Poir.	Acanthaceae	Entire Plant	MIS, MES	Rousinov et al., 1966
Achillea millefolium E. Mey	Asteraceae	Aerial Parts	MES	Athanassova et al., 1965
Achyranthes aspera L.	Amaranthaceae	Root	MES, PTZ, Pic and Bic.	Gawande et al. 2017.
Achyranthes aspera L.	Amaranthaceace	Aerial parts	MES, PTZ, and NMDA	Viswanatha et al. 2017.
Aconitum species L.	Ranunculaceae	-	Bic	Ameri, 1997

Plant	Family	Part used	Method	References
Acorus calamus L.	Araceae	-	MIS	Chauhan et al., 1988
Acorus calamus L.	Araceae	Rhizome	ACV, MES, PTZ	Rousinov et al., 1966
Acorus gramineus Aiton.	Araceae	Rhizome	PTZ	Liao et al., 1998
Acosmium subelegans (Mohlenbr) Yakovlev.	Leguminosae	Aerial Parts	MES, PTZ	Vieira et al., 2002
Adonis vernalis L.	Ranunculaceae	-	AVC	Chauhan et al., 1988
Afraegle paniculata Engl.	Rutaceae	Root, Stem	LIS, ACV	Ameri, 1997
Afraegle paniculata Engl.	Rutaceae	Rootbark	ACV, MIS	Adesina & Ette 1982
Afrormosia laxiflora Harms.	Fabaceae	Root	MES, PIC	Haruna, 2000
Albizia glaberrimma Benth.	Fabaceae	Leaf	STN, PTX and PTZ.	Adebesin et al 2015
Albizia lebbek Benth.	Leguminosae	Leaf, Root	PIC, PTZ, MIS	Kasture et al., 1996
Albizia lebbek Benth.	Fabaceae	Leaf	MES, PTZ, PIC	Kasture et al., 1996
Albizia zygia J.F.Macbr	Leguminosae	Leaf	LIS, SIS	Adesina, 1982a
Allium ascalonicum L.	Liliaceae	Shallot	LIS	Adesina, 1982a
Allium ascalonicum L.	Liliaceae	Flower	MIS	Adesina, 1982a
Allium cepa L.	Liliaceae	Bulb	LIS, SIS	Adesina, 1982a
Allium cepa L.	Liliaceae	Bulb	MIS	Adesina, 1982a
Allium sativum L.	Liliaceae	Bulb	LIS	Adesina, 1982a
Allium sativum L.	Liliaceae	Bulb	ACV, MIS	Adesina, 1982a
Alstonia boonei Dewild	Apocynaceae	Stem	LIS	Adesina, 1982a
Alstonia boonei Dewild.	Apocynaceae	Stembark	MIS	Adesina, 1982a
Alstonia schoaris R. Br.	Apocynaceae	Stem	LIS	Adesina, 1982a
Altingia excelsa Noronha.	Hamamelidaceae	Entire Plant	ACV	Singh et al., 1985
Anagallis arvensis L.	Primulaceae	Entire Plant	MIS, SIS	Rousinov et al., 1966
Angelica pancicii Vandas.	Apiaceae	Aerial Parts	MIS	Rousinov et al., 1966
Annona diversifolia Saff.	Annonaceae	Leaf	ACV, PTZ	Gonzalez-Trujano, 1998

Plant	**Family**	**Part used**	**Method**	**References**
Annona muricata L.	Annonaceae	Flower	LIS, SIS	Adesina, 1982a
Annona muricata L.	Annonaceae	Leaf	PTZ	N'gouemo et al., 1997
Anthocleista djalonensis A.Chev	Genianaceae	Root bark	Biccuculine, PTX, Pliocarpine and PTZ.	Taiwe et al. 2017.
Antiaris toxicaria Lesch.	Moraceae	Stem bark.	PTZ kindling and Lithium pilocarpine	Mante et al. 2017.
Apium graveolens L.	Umbelliferae	-	ACV	Chauhan et al., 1988
Apium graveolens L.	Apiaceae	Seed	PTZ, MES, MIS	Kulshrestha et al., 1970
Areca catechu L.	Palmae	-	ACV	Lodge et al., 1997
Artemisia absinthium L.	Asteraceae	Aerial Parts	PTZ, MES, PILO	Athanassova et al., 1965
Artemisia verlotorum Lamotte	Asteraceae	Whole Plant	MES, PILO, 3-MCAIC	Lima et al., 1993
Artemisia vulgaris L.	Asteraceae	Leaf, Stem	PIC	Abdul-Ghani et al., 1987
Asarum heterotropoides F. Sehmidt	Aristolochiaceae	Whole Plant	ACV	Sun et al., 1991
Asarum himalaycum Hook.F	Aristolochiaceae	Whole Plant	ACV	Sun et al., 1991
Asarum ichangense C.P.Chen	Aristolochiaceae	Whole Plant	ACV	Sun et al., 1991
Asparagus officinalis L.	Liliaceae	Aerial Parts	LIS, MIS	Chauhan et al., 1988
Asparagus racemosus Willd.	Liliaceae	Root	PTZ kindling.	Pahwa and Goel 2016
Asparagus verticillatus L.	Liliaceae	Aerial Parts	MIS, SIS	Athanassova et al., 1969
Asperula odorata L.	Rubiaceae	Aerial Parts	MIS, SIS	Athanassova et al., 1969
Asplenium trichomanes L.	Aspleniaceae	Entire Plant	MES, MIS, SIS	Athanassova et al., 1965
Astragalus centralpinus Bnaun-Blanq	Leguminosae	-	HIC	Chauhan et al., 1988
Atractylodes lancea DC.	Asteraceae	Rhizome	MES	Yamahara et al., 1977

Plant	Family	Part used	Method	References
Atractylodes lancea DC.	Asteraceae	-	MIN, PTZ, PIC	Chiou et al., 1997
Baccharis serraefolia DC.	Asteraceae	Leaf	PIZ, SIS	Tortoriello et al., 1996
Basella alba L.	Basellaceae	Leaf, Stem	LIS, SIS	Adesina, 1982a
Basella ruba L.	Basellaceae	Leaf, Stem	LIS, SIS	Adesina, 1982a
Bauhinia outimouta Aubl.	Fabaceae	Whole Plant	PTZ	Quintans-Júnior et al., 2002
Berberis lyceum Royle.	Berberidaceae	Root	MES	Dhar et al., 1968
Boerhavia diffusa L.	Nyctaginaceae	Leaf	ACV, PTZ, MES, MIS	Akah & Nwambie, 1993
Bupleurum chinense DC.	Apiaceae	Entire Plant	ACV	Wu & Yu, 1984
Bupleurum falcatum L.	Apiaceae	Root	ACV	Narita et al., 1982
Butea monosperma Taub	Fabaceae	Flower	MES, PTZ, SIS	Kasture et al., 2000
Buthus martensii Sehult. & Sehult. F	Buthidae	Venom	ACV	Liu et al., 1989
Canscora decussata (Roxb.)Roem &Sehult.	Gentianaceae	Whole Plant	ACV	Harbison, 1975 Dikshit et al., 1972
Cassia siamea Lam.	Fabaceae	Leaf	MIS, SIS	Arunlakshana, 1949
Cerbera odollam Gaertn.	Apocynaceae	Entire Plant Leaf	PTZ	et al. 2002; De Lucia et al., 1997 Hien et al., 1991
Cadia rubra R.Vig.	Fabaceae	Leaf	PTZ	Pieretti et al., 1993
Caesalpinia bonduc (L.) Rox	Leguminosae	Root, Stem	LIS, SIS	Adesina, 1982a
Caesalpinia bonducella (L.)Fleming	Fabaceae	Leaf	MES, MIS, SIS	Adesina, 1982a
Calliandra portoricensis Benth.	Leguminosae	Root, Stem	LIS, MIS, SIS	Akah & Nwaiwu 1988
Cannabis sativa L.	Cannabinaceae	Whole Plant	ACV, PTZ, MES, KID	Dantas, 2005; Dwivedi &
Capparis badueca L.	Capparaceae	-	ACV	Adesina, 1982a
Capsella bursa-pastoris (L.)Medik	Brassicaceae	Entire Plant	MES, MIS	Rousinov et al., 1966
Capsicum annum L.	Solanaceae	Flower	LIS, SIS	Adesina, 1982a
Carica papaya L.	Caricaceae	Root	MES, LIS,	Chauhan et al., 1988

Plant	Family	Part used	Method	References
			SIS	
Carrisa edulis Vahl.	Apocynaceae	Root bark	PTZ, PTX, STN, NMDA, INZ and aminophylline.	Yau et al. 2015.
Carthamus tinctorius L.	Asteraceae	Flower	MIS	Kasahara et al., 1989
Casimiroa edulis La Lrave.	Rutaceae	Leaf	MES, MIS	Adesina 1982a
Centella asiatica (L.) Urb.	Apiaceae	Aerial Part,	LIS, PTZ, SIS	Chauhan et al., 1988; Sudha
Chaerophyllum bulbosum L.	Apiaceae	Aerial Part	MES, MIS, SIS	Rousinov et al., 1966
Chelidonium majus L.	Papaveraceae	Aerial Part	MES, PTZ	Mahe et al., 1978
Chrysanthemum indicum L.	Asteraceae	Flower, Stem	MÊS, SIS	Lashev et al., 1981
Cicer arientinum L.	Fabaceace	Seed	MES, PTZ and electrical kindling.	Sardari et al 2015.
Cimicifuga dahurica Maxim.	Ranunculaceae	Root	SIS	Nikol-Skaya & Shreter, 1961
Cimicifuga simplex (DC.)Wormsk.	Ranunculaceae	Rhizome	MIS, SIS	Shibata et al., 1980
Cinchona officinalis L.	Rubiaceae	-	ACV	Chauhan et al., 1988
Cinnamomum cassia (L.) J.Persi	Lauraceae	Bark	ACV	Narita et al., 1982
Cinnamomum loureirii Ness.	Lauraceae	Bark	ACV, MIS	Sugaya et al., 1978
Cinnamomum zeylanicum Blume.	Lauraceae	Bark	ACV	Sugaya et al., 1988
Cissampelos pareira L.	Menispermaceae	Root	MIS, LIS, SIS	Adesina, 1982a
Cissus quadrangularis L.	Vitaceae	Whole plant	Pilocarpine induced epilepsy.	Moto et al. 2018.
Cistus villosus var.tauricus L.	Cistaceae	Aerial Part	MES, MIS, SIS	Athanassova et al., 1969
Citrus aurantifolia Suuingle	Rutaceae	Peel, Flower	LIS, SIS	Adesina, 1982a
Citrus aurantium L.	Rutaceae	Peel	LIS, SIS	Adesina, 1982a
Citrus bergamia ssp. *vulgaris* Risso.	Rutaceae	Flower	PTZ	Occhiuto et al., 1995

Plant	**Family**	**Part used**	**Method**	**References**
Clausena anisate Hook.	Rutaceae	Root, Stem	MIS, PTZ, SIS	Makanju, 1983
Cleome cileata Sehumach.	Capparidaceae	Leaf	MES, PTZ	Akah et al., 1993; 1997
Clerodendrum colebrookianum Walp.	Verbenaceae	Leaf	SIS	Gupta et al., 1998
Cnestis ferruginea Vahl.	Verbenaceae	Rootbark	SIS	Declume et al., 1984
Cnestis glabra Lan.	Connaraceae	-	ACV	Chauhan et al., 1988
Cocculus hirsutus L.	Menispermaceae	Root, Stem	MES, MIS	Das et al., 1964
Cola acuminata Scholt.	Sterculiaceae	-	LIS, SIS	Adesina, 1982a
Colebrookea oppositifolia Sm.	Lamiaceace	Root	MES and PTZ.	Viswanatha et al. 2017
Connarus wightii Hook.	Connaraceae	Aerial Part	SIS	Dhar et al., 1973
Consolida orientalis (DC.) Gray.	Ranunculaceae	Aerial Part	MES, MIS, SIS	Athanassova et al., 1969
Convolvulus arvensis L.	Convolvulaceae	Aerial Part	ACV, MIS, SIS	Chauhan et al., 1988,
Convolvulus hirsutus M. Bieb.	Convolvulaceae	Aerial Part	MIS, SIS	Athanassova et al., 1969
Convolvulus pluricaulis Chorsy.	Convolvulaceae	Entire Plant	ACV, MES	Sharmaxvn et al., 1965
Convolvulus suendermannii Bornm.	Convolvulaceae	Aerial Part	MIS, SIS	Athanassova et al., 1969
Coptis chinensis Franch.	Ranunculaceae	Rhizome	ACV	Hong et al., 1988
Cornus mas L.	Cornaceae	Fruits	Penicillin induced convulsions	Tubas et al. 2017.
Corydalis cava L.	Papaveraceae	Aerial Part	MES	Athanassova et al., 1965
Cotyledon orbiculata L.	Crussalaceae	-	ACV, PIC, PTZ	Amabeoku et al., 2007
Crassostrea gigas Thunberg.	Ostreidae	-	ACV	Bac et al., 1998
Crinum jagus J. Thomps	Amaryllidaceae	Leaf	PTZ kindling	Taiwe et al. 2016.
Croton zehntneri Pax& K.Hoffm	Euphorbiaceae	Branches	ACV, PIC, SIS	Bernardi et al., 1991
Cryptotympana atrata Stal.	Cicadidae	Skin	PIC	Hsieh et al., 1991
Cucurbita pepo L.	Cucurbitaceae	-	LIS, SIS	Adesina, 1982a
Cuminum cyminum L.	Apiaceae	Fruit	MES, PTZ	Sayyah et al., 2002

Plant	Family	Part used	Method	References
Curcuma amada Roxburgh.	Zingiberaceae	Rhizome	MES	Bhakuni et al., 1969
Curcuma aromatica Salisb.	Zingiberaceae	Root	ACV	Li, 1987
Cuscuta chinensis Lam.	Convolvulaceae	Entire Plant	ACV	Akbar et al., 1985a
Cyathea nilgirensis Holttum.	Cyatheaceae	Aerial Part	MES	Dhawan et al., 1977
Cylista scariosa Roxburgh.	Fabaceae	Root	SIS	Dhar et al., 1968
Cymbopogon citratus (DC.) Stapf	Gramineae	Leaf	ACV	Carlini et al., 1986
Cynanchum otophyllum L.	Asclepiadaceae	Rhizome	ACV	Pei et al., 1981
Cynodon dactylon (L) Pers.	Gramineae	Leaf	MES, MIS, PTZ	Akah et al., 1997
Cyperus articulates L.	Cyperaceae	Rhizome	AVC	Ngo Bum et al., 1996
Cyperus rotundus L.	Cyperaceae	Root	LIS, SIS	Adesina, 1982a
Cystophora moniliformis J.Agardh.	Cystoseiraceae	Thallus	ACV	Spence et al., 1979
Cystoseira usneoides L.	Cystoseiraceae	Thallus	ACV	Vazquez-Freire et al., 1995
Delphinium consolida L.	Ranunculaceae	Aerial Parts	AVC, MIS, SIS	Nsour et al., 2000
Delphinium denudatum Wall.	Ranunculaceae	Root	ACV, PIC, PTZ, SIS	Raza et al., 2001
Desmodium adscendes (DA.)	Leguminosae	Leaf	PTZ	N'gouemo et al., 1996
Dictamnus albus L.	Rutaceae	Entire Plant	ACV	Athanassova et al., 1965
Digitalis ferruginea L.	Scrophulariaceae	Entire Plant	ACV, MES	Athanassova et al., 1965
Digitalis lanata Ehrh.	Scrophulariaceae	Entire Plant	ACV, MES	Athanassova et al., 1965
Dillenia indica L.	Dillenciaceae	Leaf	MES	Bhakuni et al., 1969
Diospyros kaki L.f.	Ebenaceae	Calix	ACV	Fukuda & Shibata, 1994
Diospyros peregrine Gurka	Ebenaceae	Entire Plant	ACV	Singh et al., 1985
Duboisia leichhardtii R.Br.	Solanaceae	-	AVC	Nsour et al., 2000
Dunaliella tertiolecta Teodoresco	Dunaliellaceae	-	ACV	Laguna et al., 1990
Elettaria cardamomum L.	Zingiberaceae	Seed	ACV	Dasgupta et al., 1984 Shukia et al., 1987
Echinacea purpurea L.	Asteraceae	-	AVC	Nsour et al., 2000

Plant	Family	Part used	Method	References
Echium vulgare L.	Boraginaceae	Aerial Parts	ACV, MES, MIS, SIS	Nsour et al., 2000,
Eclipta alba L.	Asteraceae	Leaf	PTZ acute and kindling models	Tambe et al. 2017.
Egletes viscosa L.	Asteraceae	Flower	PTZ	Souza et al., 1998
Elaeocarpus ganitrus Roxb.	Elaeocarpaceae	Entire Plant/Fruit	MES, MIS	Bhattacharya et al., 1975
Eryngium foetidum L.	Apiaceae	Leaf	PIC	Simon, 1986
Erythraea centaurium Rafm.	Gentianaceae	Aerial Parts	CZIZ	Athanassova et al., 1965
Erythrina mulungu Mart.	Fabaceae	Stem Bark	PTZ, SIS	Vasconcelos et al., 2007
Erythrina velutina Wild.	Fabaceae	Stem Bark	PTZ, SIS	Vasconcelos et al., 2007
Erythroxylum coca Lam.	Erythroxylaceae	Leaf	MIS	Adesina, 1982a
Euphorbia antiquorum L.	Euphorbiaceae	Whole Plant	MIS	Dey et al., 1968
Euphorbia dracunculoides Lam.	Euphorbiaceae	Entire Plant	ACV, MES	Bhakuni et al., 1969
Euphorbia hirta L.	Euphorbiaceae	Whole Plant	ACV	Lanhers et al., 1996
Euphorbia pilulifera L.	Euphorbiaceae	Whole Plant	ACV	Chauhan et al., 1988
Euphorbia tirucalli L.	Euphorbiaceae	Aerial Part	ACV, MIS	Dhar et al., 1968
Evolvulus nummularius L.	Convolvulaceae	Entire Plant	MES, MIS	Dey et al., 1968; Chatterjee 1964
Feretia apodanthera Del.	Rubiaceae	Stem bark	PTZ kindling	Taiwe et al 2015.
Ferula gummosa L.	Apiaceae	Seed	MES, PTZ	Sayyah et al., 2002
Ficus benghalensis L.	Moraceae	Root	PTZ and MES	Pandey and Rauniyar 2016.
Ficus platyphylla Del.	Moraceae	Stem bark	PTZ kindling	Chindo et al. 2015.
Ficus religiosa L.	Moraceae	Fruit	PTZ kindling	Singh et al. 2014.
Geranium rotundifolium L.	Geraniaceae	Aerial Parts	MES, MIS, SIS	1988, Hsieh et al., 2001 Athanassova et al., 1969
Galeopsis ladanum L.	Lamiaceae	Aerial parts	PTZ	Czarnecki et al., 1993

Plant	**Family**	**Part used**	**Method**	**References**
Galicia spp.	Galiaceae	-	ACV	Chauhan et al., 1988
Galium cruciate Opiz.	Rubiaceae	-	ACV	Chauhan et al., 1988
Galium sylvaticum L.	Rubiaceae	Aerial Parts	MIS, SIS	Chauhan et al., 1988,
Galphimia glauca Bartl.	Malpighiaceae	Aerial Parts	ACV, LIS, SIS	Tortoriello et al., 1992
Galphimia glauca Bartl.	Malpighiaceae	Aerial Parts	ACV	Tortoriello, 1993
Ganoderma lucidum Reishi.	Ganodermataceae	Fruit	PTZ, SIS	Kasahara et al., 1987
Garcinia mangostana L.	Clusiaceae	Fruit	ACV	Kurukawa et al., 1997
Gastrodia elata Blume.	Orchidaceae	-	ACV, KAI	Chen, 1977; Chauhan et al.,
Ginkgo biloba L.	Ginkgoaceae	Rhizome	ACV	Rodriguez, 1993
Ginkgo biloba L.	Ginkgoaceae	Leaf	Lithium pilocarpine	Mazumder et al. 2017.
Gleditsia officinalis Lam.	Fabaceae	Fruit	ACV	Yen, 1977
Glycyrrhiza glabra L.	Fabaceae	Rhizome	ACV	Hong et al., 1988
Grewia hirsute Vahl.	Tiliaceae	Entire Plant	SIS	Bhakuni et al., 1971
Gymnosporia falconeri Hook.f.	Celastraceae	Aerial Parts	MIS	Bhakuni et al., 1971
Haplophyllum perforatum (M.B.)	Rutaceae	Seed	CZIC, LIS	Chauhan et al., 1988
Hedera rhombea Seibold and Zucc.	Araliaceae	Leaf	SIS	Lee et al., 1992
Helianthus annuus L.	Asteraceae	Flower	CZIZ, MES	Athanassova et al., 1965
Heracleum sibiricum L.	Umbelliferae	-	MES, PTZ, CZIC, SIS	Chauhan et al., 1988
Heracleum vericillatum L.	Umbelliferae	-	MES, PTZ, CZIC, SIS	Chauhan et al., 1988
Herpestris monniera L.	Scrophulariaceae	-	PTZ	Chauhan et al., 1988
Hippeastrum vittatum L.(Herb)	Amarillydaceae	Bulbs		Silva et al., 2006
Holarrhena floribunda(G.Don)	Apocynaceae	Leaf	MES, PTZ	Akah et al., 1997
Hoslundia opposite Vahl.	Lamiaceae	Leaf	MES, PTZ	Akah et al., 1993
Humulus lupulus L.	Cannabaceae	-	PTZ	Lee et al., 1993

Plant	Family	Part used	Method	References
Hypericum perforatum L.	Hypericaceae	Whole Plant	PTZ	Ozturk et al., 1996
Hypericum perforatum L.	Hyperiaceae	Whole plant	Electrical kindling	Ivetic et al. 2011
Icacina trichantha Oliv.	Icacinaceae	Tuber	ACV, PTZ, SIS	Asuzu et al., 1990
Ipomoea stans Cav.	Convolvulaceae	Wood	MES, PTZ	Contreras et al., 1996
Iris kamaonensis Wall.	Iridaceae	Entire Plant	MES	Dhawan et al., 1977
*Jasminum multiforum (*Burm.f.)	Oleaceae	Leaf	Bic and PTZ	Addae et al. 2017.
Jatropha curcas L.	Euphorbiaceae	Root	LIS, SIS	Adesina, 1982a
Jatropha gossypiifolia L.	Euphorbiaceae	Root, Leaf	LIS, SIS	Adesina, 1982a
Juniperus macropoda Boiss.	Cupressaceae	Fruit	ACV	Mishra et al., 1989
Justicia spicigera Schltdl.	Acanthaceae	Aerial parts	MES and PTZ induced convulsions.	Trujano et al. 2017.
Kalanchoe crenata Adans.	Crussalaceae	Leaf	PTZ, SIS	Nguelefack et al., 2006
Kalanchoe pinnata Lam.	Crassulaceae	Stem and root	PTZ	Mora-Perez et al. 2016.
Khaya grandifoliola C.DC.	Meliaceae	Stembark	ACV	Awe te al., 1997
Kochia prostrate L.	Chenopodiaceae	-	SIS	Chauhan et al., 1988
Lactuca sativa L.	Asteraceae	Seed	PTZ	Said et al., 1996
Laggera aurita (L.f.)	Asteraceae	Leaf	PTZ, strychnine and PTX	Malami et al. 2016.
Lannea barteri Oliv.	Anacardiaceae	Stem bark	PTZ, STN, PTX and MES.	Garba et al. 2016.
Lantana camara L.	Verbenaceae	Root, Leaf	LIS, SIS	Chauhan et al., 1988
Lantana microphylla Franch.	Verbenaceae	Leaf	LIS, SIS	Adesina, 1982a
Laurus nobilis L.	Lauraceae	Leaf	ACV	Sayyah et al., 2002
Lavandula stoechas L.	Lamiaceae	Flower	PTZ	Gilani et al., 2000
Ledebouriella seseloides (Turcz.)	Apiaceae	Root	ACV	Yen, 1977
Leea indica (Burm.f.)	Leeaceae	Leaf	SIS	Dhar et al., 1968
Leonotis leonurus L.	Lamiaceae	Leaf	ACV	Beinvenu et al., 2002

Plant	Family	Part used	Method	References
Leonurus cardiac L.	Lamiaceae	Aerial Parts	ACV, MES, SIS	Adesina, 1982a
Lettsomia setosa Roxb.	Convolvulaceae	Aerial Parts	MES	Bhakuni et al., 1971
Licaria puchury-major (Mart.)	Lauraceae	Dried Seed	MES	Carlini et al., 1983
Lippia alba (Mill.)	Verbenaceae	Leaf	SIS, PIC	Barros Viana et al., 2000
Lobelia inflate L.	Campanulaceae	Leaf	ACV	Bhakuni et al., 1971
Lonchocarpus sericeus (Poir.) Kunth	Leguminosae	Root	LIS, SIS	Chauhan et al., 1988
Luvunga scandens Roxb.	Rutaceae	-	ACV	Mishra et al., 1988
Magnolia grandiflora L.	Magnoliaceae	Seed	MES	Ramirez et al., 1998
Magnolia obovate Thunb.	Magnoliaceae	-	SIS, PIC	Chauhan et al., 1988
Magnolia officinalis Rehder &Wilson.	Magnoliaceae	Bark	ACV	Watanabe et al., 1983
Maprounea africana Mull.Arg.	Euphorbiaceae	Leaf	ACV, MES, PTZ, PIC	N'gouemo et al., 1994a
Marrubium peregrinum L.	Lamiaceae	Aerial Parts	MES, MIS	Athanassova et al., 1965
Marrubium vulgare L.	Lamiaceae	Leaf, Flower	ACV, CZIC, MES	Chauhan et al., 1988,
Marsilea rajasthanesis K.M. Gupta	Marsileaceae	-	ACV	Chauhan et al., 1988
Matricaria chamomilla L.	Asteraceae	Flower	CZIC, MES, PIC	Athanassova et al., 1969
Matricaria recutita L.	Asteraceae	Flower	PTZ	Viola et al., 1995
Melia azedarach L.	Meliaceae	Root Bark	MIS, SIS	Adesina, 1982a
Melothria maderaspatana L.	Cucurbitaceae	Aerial Parts	ACV	Sinha et al., 1997
Mentha piperita L.	Lamiaceae	Leaf	ACV	Leslie, 1978
Mentha suaveolens Ehrh.	Lamiaceae	Leaf	ACV	Moreno et al., 2002
Mikania cordata (Burm.f.)	Asteraceae	Aerial Parts	MES	Moreno et al., 2002
Mitragyna Africana (Wild.)	Rubiaceae	Stembark	SIS	Aji et al., 2001
Momordica balsamina L.	Cucurbitaceae	Leaf	LIS, SIS	Adesina, 1982a

Plant	**Family**	**Part used**	**Method**	**References**
Momordica charantia L.	Cucurbitaceae	Leaf, Flower	LIS, SIS	Adesina, 1982a
Moringa oleifera Lam.	Moringaceae	Root	LIS, SIS	Adesina, 1982a
Moringa pterygosperma Gaertn.	Moringaceae	Root	MIS, SIS	Adesina, 1982a
Morus rubra L.	Moraceae	Fruits	Penicillin induced convulsions	Tubas et al. 2017.
Musa sapientum L.	Musaceae	Stem	MES, PTZ induced convulsions and PTZ kindling.	Reddy et al. 2018.
*Nardostachys jatamansi (*D.Don) DC.	Valerianaceae	Rhizome	ACV	Debelmas et al., 1976
Nelumbo nucifera Gaertn	Nelumbonaceae	Fruit	STN	Rajput et al. 2107.
Nepeta cataria L.	Lamiaceae	Leaf	PTZ, SIS	Massoco et al., 1995
Nerium oleander L.	Apocynaceae	Leaf	ACV	Zia et al., 1995
Newboldia leavis Seem.	Bignoniaceae	Leaf	MES, PTZ	Olajide et al., 1997
Nicotiana tabacum L.	Solanaceae	Leaf	LIS, MIS, SIS	Chauhan et al., 1988
Notopterygium incisum Ting.	Apiaceae	Root	ACV	Yen, 1977
Ocimum americanum L.	Lamiaceae	Leaf	LIS	Adesina, 1982a
Ocimum basilicum L.	Lamiaceae	Leaf	LIS	Adesina, 1982a
Ocimum canum Sims.	Lamiaceae	Leaf	SIS	Ketusingha et al., 1950
Ocimum gratissimum L.	Lamiaceae	Leaf	LIS, SIS	Adesina, 1982a
Ocimum sanctum L.	Lamiaceae	Entire Plant	ACV	Sakina et al., 1990
Oplopanax elatus Miq.	Araliaceae	Root	ACV	Qu et al., 1984
Patrina intermedia (Hornem.)	Valerianaceae	-	SIS	1996 Chauhan et al., 1988
Paeonia alba Pall.	Paeoniaceae	Root	ACV	Hung et al., 1983

Plant	Family	Part used	Method	References
Paeonia albiflora Pallas.	Paeoniaceae	Root	ACV	Narita et al., 1982
Paeonia albiflora Pallas.	Paeoniaceae	Root	PTZ	Sugaya et al., 1991
Paeonia emodi Wall.	Paeoniaceae	Root	MIES, MIS	Ahmad et al., 1981
Paeonia japonica var. *pilosa* Nakai.	Paeoniaceae	Root	PIC, SIS	Hong et al., 1979
Palisota ambigua C. B. Clarke	Commelinaceae	Leaf	PTZ	N'gouemo et al., 1994b
Panax ginseng Nees.	Araliaceae	Root, Leaf	MIS, PIC	Takagi, 1977; Mitra et al.,
Passiflora alata Curtis.	Passifloraceae	Dried Leaf	MIS	Oga et al., 1984
Passiflora incarnate L.	Passifloraceae	Leaf	PTZ	Speroni et al., 1988
Pausinystalia yohimbe (K.Schum.)	Rubiaceae	Bark	ACV	Chermat et al., 1979
Persea indica L.	Lauraceae	Leaf	PTZ	Mazzanti et al., 1993
Peucedanum alsaticum L.	Apiaceae	fruits	Zebrafish epilepsy model.	Koziol et al. 2018.
Phaeodactylum tricoenutum Bohlin.	Fragilaricaceae	-	PTZ	Laguna et al., 1990
Picnomon acarna L.	Asteraceae	-	ACV	Chauhan et al., 1988
Picrorhiza kurroa Royle.	Scrophulariaceae	Entire Plant	MIS	Debelmas et al., 1976
Pimpinella anisum L.	Apiaceae	Fruit	SZIC, MES	Athanassova et al., 1969
Pinellia ternate (Thunb.) Makino.	Araceae	Tuber	ACV	Narita et al., 1982
Piper guineense Schumach.	Piperaceae	Flower	MIS, NMDLAIC	Abila et al., 1993
Piper longum L.	Piperaceae	Fruit	ACV, MES, PIC, PTZ	Pei, 1983
Piper methysticum G.Forst.	Piperaceae	Flower	SIS	Klohs et al., 1959
Piper nigrum L.	Piperaceae	Flower	ACV, NMDLAIC	Hu & Davies, 1997
Pistacia integerrima J.L. Stewart.	Anacardiaceae	-	PTZ	Ansari et al., 1993
Pithecellobium saman F. Muell.	Leguminosae	-	PIC	Chauhan et al., 1988
Plectranthus amboinicus Lour.	Lamiaceae	Entire Plant	ACV	Buznego et al., 1999

Plant	**Family**	**Part used**	**Method**	**References**
Plumbago zeylanica L.	Plumbaginaceae	Root	LIS	Adesina, 1982a
Polygala sabulosa A.W. Benett	Polygalaceae	Whole Plant	PTZ	Duarte et al., 2007
Polypodium vulgare L.	Polypodiaceae	Root	MES, PTZ	Mannan et al., 1989
Portucala oleracea L.	Portulacaceae	Whole Plant	LIS, SIS	Adesina, 1982a
Prunus spinose	Rosaceae	Fruit	PTZ	Mannan et al., 1989
Psedospondia microcarpa (A. Rich.) Engl.	Anacardiaceae	Leaf.	PTZ, PTX, STN, 4-AP, Isoniazid, MES induced convulsions	Adongo et al. 2017.
Psidium guyanensis Pers.	Myrtaceae	Leaf	PTZ, PIC, SIS	Santos et al., 1997
Psidium pohlianum O. Berg	Myrtaceae	Leaf	PTZ	Santos et al., 1996
Psydrax subcordata (DC.) Bridson	Rubiaceae	Leaf	PTZ, MES, PTX, 4-AP, STN and Lithium Pilocarpine.	Danna et al. 2018.
Pterocarpus santalinus L.f.	Fabaceae	Stem	MES	Mehta et al., 1979
Pyrus pashia Buch. Ham. ex Don	Rosaceae	Fruits	MES and PTZ	Sharma et al., 2017
Rauvolfia ligustrina Willd.	Apocynaceae	Root, Aerial	PTZ, PIC, SIS	Kuang, 1993 Quintans-Júnior et
Rauvolfia schueli Speg.	Apocynaceae	-	ACV	al.,2002;2007 Adesina, 1982a
Rauvolfia serpentine L.	Apocynaceae	Root, Stem Bark	ACV	Adesina, 1982a
Rauvolfia tetraphylla L.	Apocynaceae	Entire Plant	MES	Bhakuni et al., 1969
Rauvolfia vomitoria Afzel.	Apocynaceae	Root	LIS, MIS, SIS	Sokomba et al., 1986
Rehmannia glutinosa Gaertn.	Scrophulariaceae	Root	ACV	Hong et al., 1988
Rheum officinale Baill.	Polygonaceae	Rhizome	ACV	Yen, 1977
Rhodiola rosea L.	Crassulaceae	-	SIS	Aksenova et al., 1966

Plant	Family	Part used	Method	References
Ricinus communis L.	Euphorbiaceae	Root	MIS, LIS	Adesina, 1982a
Rosmarinus officinalis L.	Lamiaceae	Entire Plant	PIC	Abdul-Ghani et al., 1987
Rosmarinus officinalis L.	Lamiaceae	Whole plant	Kainic acid induced epilepsy.	Naderali et al. 2018.
Roylea elegans Sm.	Lamiaceae	-	ACV	Chauhan et al., 1988
Rubus brasiliensis Mart.	Rosaceae	Entire Plant	ACV	Nogueira et al., 2000
Rubus ellipticus Sm.	Rosaceae	Leaf	MES	Rana et al., 1990
Ruta chalepensis L.	Rutaceae	Aerial Parts	PTZ	Aguilar-Santamaria et al., 1996
Ruta chalepensis L.	Rutaceae	Leaf	MES, PTZ	Aguilar-Santamaria et al., 1996
Ruta graveolens L.	Rutaceae	Aerial Parts	CZIC, MES	Athanassova et al., 1969
Salvadora persica L.	Salvadoraceae	Stem	ACV	Monforte et al., 2002
Salvia guaranitica	Lamiaceae	Aerial Parts	ACV	Viola et al., 1997
Salvia guaranitica A.St.	Lamiaceae	Aerial Parts	ACV	Viola et al., 1997
Salvia haematodes A.St.	Lamiaceae	Root	MES	Akbar et al., 1984a
Salvia nemorosa L.	Lamiaceae	Aerial Parts	MÊS, MIS, SIS	Athanassova et al., 1965
Salvia nemorsa L.	Lamiaceae	Leaf	ACV	Sugaya et al., 1988; 1997
Salvia sclarea L.	Lamiaceae	Aerial Parts	MIS, SIS	Athanassova et al., 1965
Salvia transsylvanica Sehar.	Lamiaceae	Aerial Parts	ACV, PTZ	Maklad et al., 1997
Sambugus niagra Wall.	Adoxaceae	Bark,fruit and leaf	MES and PTZ	Attae et al. 2016.
Sapindus trifoliatus L.	Sapindaceae	Seed	MES	Gupta et al., 1996
Satureja clinopodium Spem.	Lamiaceae	Aerial Parts	MÊS, MIS, SIS	Athanassova et al., 1965
Schisandra chinensis Tuxz.	Schisandraceae	Fruit	ACV	Baek et al., 2000

Plant	Family	Part used	Method	References
Scutellaria baicalensis Georgi	Lamiaceae	Root	ACV	Narita et al., 1982
Searsia chirindensis Baker f.	Anacardiaceae	Root	Kainic acid induced convulsion	Qulu et al. 2016.
Securidaca logependunculata Fresen.	Polygalaceae	Root	SIS and PIC	Adeyemi et al.,2010
Securidaca longepedunculata Fresen.	Polygalaceae	Leaf	LIS	Ojewole, 2000
Senecio fuchsia C.C.Gmel.	Asteraceae	Entire Plant	MIS	Stoyanov et al., 1981
Senecio jacobaea L.	Asteraceae	Entire Plant	MES, MIS	Athanassova et al., 1969
Senna spectabilis D.C.	Fabaceae	Leaf	MES, PTZ and Pilocarpine	Nkantchoua et al. 2018
Sesbania grandiflora L.	Fabaceae	Leaf	MES	Kasture et al., 2002
Solanum Americana Mill.	Solanaceae	Leaf, Flower	ACV, LIS	Adesina, 1982a
Solanum gilo Radii.	Solanaceae	Flower	LIS	Adesina, 1982a
Solanum indicum L.	Solanaceae	Entire Plant	LIS, MIS, SIS	Dey et al., 1968; Adesina, 1982a
Solanum khasianum C. B.	Solanaceae	Entire Plant	MES	Dhar et al., 1968
Solanum macrocarpon L.	Solanaceae	Leaf, Flower	LIS, SIS	Adesina, 1982a
Solanum melongena L.	Solanaceae	Leaf, Flower	LIS, SIS	Adesina, 1982a
Solanum nigrum L.	Solanaceae	Flower	PTZ, MIS, LIS, SIS	Adesina 1982a; Perez et al. 1998
Solanum torvum Sw.	Solanaceae	Flower	LIS	Adesina, 1982a
Sphencostylis stenocarpa E. Mey.	Fabaceae	Seed	LIS	Asuzu, 1986
Spondias mombin L.	Anacardiaceae	Flower	LIS, SIS	Adesina, 1982a
Stenochilaena palustris (Burm.f.)Bedd.	Blechnaceae	Entire Plant	SIS	Dhar et al., 1973
Swertia purpurascens Boiss.	Gentianaceae	Entire Plant	MES, MIS	Dhar et al., 1973
Symphytum officinale L.	Boraginaceae	Root	CZIC, MES	Athanassova et al., 1969

Plant	Family	Part used	Method	References
Syzygium cumini L.	Myrtaceae	Seed	PTZ	De Lima et al., 1998
Tetraselmis suecica Kylin(Butcher).	Chlamydomonadaceae	-	PTZ	Adesina & Sofowora, 1979 Laguna et al., 1993
Tabernaemontana pandacaqui Lam.	Apocynaceae	Stem	PTZ	Taesotikul et al., 1998
Talinum triangulare Willd.	Portulacaceae	Flower	LIS, SIS	Adesina, 1982a
Taraxacum spp	Asteraceae	-	ACV	Chauhan et al., 1988
Teclea simplifolia Engl.	Rutaceae	-	ACV	Chauhan et al., 1988
Ternstroemia pinglei K&S.	Theaceae	Flower	PTZ, SIS	Aguilar-Santamaria et al., 1996.
Tetrapleura tetraptera DC.	Fabaceae	Arillus, Fruit	LIS, MIS, PTZ	Nwaiwu & Akah, 1986.
Thalictrum hernandezii Tausch.	Ranunculaceae	-	ACV	Chauhan et al., 1988
Thalictrum thumbergii DC.	Ranunculaceae	-	ACV	Chauhan et al., 1988
Theobroma cacao L.	Sterculiaceae	Seed	ACV	Marcus et al., 1997
Thymus vulgaris L.	Lamiacea	Whole plant	MES	Wozniak et al 2018.
Tilia species	Tiliaceae	Aerial Parts	MES	Athanassova et al., 1969
Trema guineensis (S&T)	Ulmaceae	Leaf	PTZ, MÊS, PIC, KAI	N'gouemo et al., 1994a
Trema orientalis L.	Ulmaceae	-	MIS	Chauhan et al., 1988
Triticum aestivum L.	Poaceae	Seed	ACV	Tsuda et al., 1986
Uncaria rhynchophylla Miq.	Rubiaceae	-	KAI, PTZ	Hsieh et al., 1999
Uncaria sinensis Oliv.	Rubiaceae	-	ACV	Chauhan et al., 1988
Valeriana angustifolia Mil.	Valerianaceae	Leaf	MIS	Pfeifer et al., 1953
Valeriana fauriei Briq.	Valerianaceae	Root	ACV	Yoshitomi et al., 2000
Valeriana jatamansi DC.	Valerianaceae	Root	SIS	Debelmas et al., 1976
Valeriana latifolia M. martens.	Valerianaceae	Leaf	MIS	Pfeifer et al., 1953
Valeriana officinalis L.	Valerianaceae	Rhizome	ACV	Fehri et al., 1991
Valeriana sambucifolia Mikan.f	Valerianaceae	Root	MIS	Pfeifer et al., 1953
Vanda roxburghii R.Br.	Orchidaceae	Entire Plant	MES	Bhakuni et al., 1969
Veratrum viride Rohl.	Liliaceae	-	ACV	Chauhan et al., 1988

Plant	Family	Part used	Method	References
Vernonia gratiosa Hance.	Asteraceae	Aerial Parts	PIC, PTZ, SIS	Hyou et al., 2001
Vinca erecta Regel & Sch.	Apocynaceae	-	ACV	Chauhan et al., 1988
Viscum capense L.	Loranthaceae	Stem	PTZ	Amabeoku et al., 1998
Vitex negundo L.	Verbenaceae	Leaf	LIS, SIS	Gupta et al., 1990
Vithania ashvagandha Cors.	Solanaceae	Root	ACV	Prasad et al., 1968
Withania somnifera L.	Solanaceae	Entire Plant	ACV	Singh et al., 1985
Ximenia Americana L.	Olacaceae	Whole Plant	PTZ	Quintans-Júnior et al., 2002
Xylopia aethiopica D.	Annonaceae	-	LIS, SIS	Adesina, 1982a
Xylopia carminative Ar.	Annonaceae	-	LIS, SIS	Adesina, 1982a
Xylopia frutescens Aubl.	Annonaceae	-	LIS, SIS	Adesina, 1982a
Xylopia grandiflora A.St. Hill	Annonaceae	-	LIS, SIS	Adesina, 1982a
Xylopia sericea A.St. Hill	Annonaceae	-	LIS, SIS	Adesina, 1982a
Xylopia spp	Annonaceae	-	LIS, SIS	Adesina, 1982a
Zataria multiflora Boiss.	Lamiaceae	Aerial parts	PTZ kindling	Shansizadeh 2016.
Zea mays L.	Gramineae	-	LIS, SIS	Adesina, 1982a
Zingiber officinale R.	Zingiberaceae	Rhizome	ACV	Sugaya et al., 1978
Ziziphus jujube L.	Rhamnaceae	Fruit	PTZ	Tsuda et al., 1986

Table.1 List of Plants with anticonvulsant properties. **ACV**: Accidente Cerebrovascular; **LIS**: Lithium induced seizures; **MIS:** Metrazole induced seizures, **Pic:** Pilocarpine induced seizures; **MES**: Maximal electroshock induced seizures; **PTZ:** Pentylenetetrazole induced seizures; **PTX**: Picrotoxine induced seizures; **NMDA**: N methyl D aspartate induced seizures; **SIS**: Strychnine induced seizures; **CZIC**: Carbamazepine induced convulsion; **4-AP**: 4- Aminopyridine induced seizures.

Polyphenols and Epilepsy:

Phytochemicals are pleiotropic in nature. A number of ongoing scientific studies are isolating and characterizing the bioactive principles of the medicinal plants which can serve as "lead" compounds in drug development processes. It is a fact that the plant kingdom has been found to

be a rich source of bioactive compounds (Magaji et al., 2012), phytochemicals are pleiotropic in nature hence can interact with multiple targets (Sucher 2006). The metabolites possess various biological activities, including anti-inflammatory, cytostatic, antiviral properties and antinociceptive activity. Neuroprotective role of flavonoids polyphenolics, as natural antioxidant compounds, on excitability-related neurological disorders (like migraine and epilepsy) is well established. Flavonoids are naturally occurring polyphenolic compounds that are present in a variety of fruits, vegetables, cereals, tea, and wine, and are the most abundant antioxidants in the human diet. The phenylpropanoids derived from caffeic acid exhibit neuroprotective effects (Neto et al., 2009). Polyphenolics, the group of antioxidants containing a polyphenolic substructure, include flavonoid and nonflavonoid polyphenolics (Shin et al., 2014). Owing to their potent antioxidant activity, polyphenols have long been considered to be beneficial in ameliorating age-dependent disorders, such as atherosclerosis, cancer and neurodegenerative diseases. Recently polyphenolics have been given considerable scientific and therapeutic interest because they offer protection from free radicals damage (Ramalingam et al., 2013) Both natural and synthetic flavonoids affect neuronal activity and their pharmacological profile suggests a potential usefulness of these compounds in adjunctive treatment of epilepsy. Below is the list of some polyphenolic compounds with antiseizure activity (effective doses) in different models of seizures in rodents (Lason and Leskiewicz 2013)

PTZ-induced seizures: Resveratrol (20–80 mg/kg, i.p), Baicalein (5–20 mg/kg, i.p), Rutin (50 and 150 nM, i.c.v), Quercetin (25 and 50 mg/kg, p.o), Vitexin (100 and 200 mM, i.c.v), Linarin (10 and 20 mg/kg, p.o), Chrysin (5mg/kg, p.o.).

PTZ-induced kindling: Epigallocatechin-3-gallate (25 and 50 mg/kg, i.p) Rutin (50 and 100 mg/kg, i.p) Quercetin (50 mg/kg, i.p) Hesperidin (200 mg/kg, p.o)

Kainate-induced seizures: Resveratrol (15 mg/kg, p.o) Naringin (20–80 mg/kg, i.p), Apigenin (25 and 50 mg/kg, i.p)

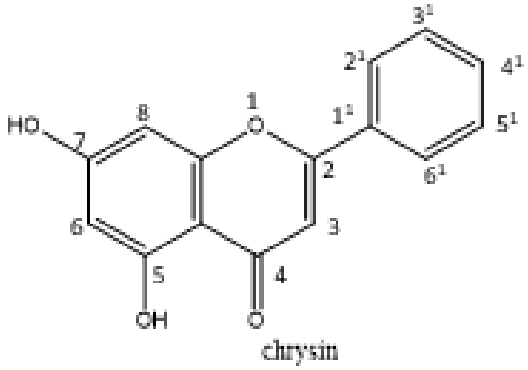
$FeCl_3$ -induced seizures: Resveratrol (20–40 mg/kg, i.p) Epigallocatechin-3-gallate Baicalein

Picrotoxin-induced seizures: Goodyerin (25 and 55 mg/kg, i.p)

Cocaine-induced seizures: NPC16377 (20–80 mg/kg, i.p)

Genetic model of epilepsy: Hispidulin (10 mg/kg, p.o.).

Chrysin: Chemistry and Neuropharmacology



chrysin

Fig 4: Structure of chrysin (5, 7 dihydroxyflavone)

Chrysin (5, 7-dihydroxyflavone or 5,7-dihydroxy-2-phenyl-4Hchromen- 4-one) belongs to the flavone class of the ubiquitous 15- carbon skeleton natural polyphenolic compounds collectively called flavonoids. The marked feature of flavones as evidenced in chrysin is the presence C2-C3 double bond in ring C and the lack of oxygenation at C-3. Unlike many flavonoids that possess

either one (most commonly at C-4́) or two hydroxyl (C3́, C4́-diortho hydroxyl) functional group in ring-B, chrysin lacks oxygenation in this ring. (Nabavi et al., 2015).

Physical and Chemical Properties

Colour	Yellow powder
Molecular weight	254.21g/mol
Melting point	285.5ºC
Boiling point	491.9ºC
Log P	3.52

Table. 2 Physical and chemical properties of chrysin.

Neuropharmacology

Chrysin is an important natural neuroprotective agent which is widely found in different fruits and vegetables as well as mushrooms. It has been reported that chrysin mitigates neurotoxicity and oxidative stress in the neural tissues. In addition, chrysin mitigates epilepsy, neuroinflammation as well as cognitive dysfunctions. The therapeutic role of chrysin as antidepressant compound has been previously assessed using animals subjected to chronic unpredictable mild stress (CUMS) (Filho et al., 2015). Mercer et al., 2005 has established the antiparkinsonian effects of chrysin. The neuroprotective efficacy of chrysin has also been evaluated in an experimental rat model of spinal cord injury (SCI) (Kandhare et al., 2014). (He et al., 2012; Yao et al., 2014) has reported that chrysin may represent a promising antidote to restore normal cellular homeostasis following ischemia/reperfusion (I/R) injury.

Plant profile

Overview

Pyrus pashia Hamilton ex D. Don belonging to family Rosaceae, also known as wild himalyan pear since it bears small pear-like fruits. It is a small to medium size deciduous tree of the small and oval shaped crown with ovate, finely toothed leaves, attractive white flowers.

Figure 5. Fruits of *Pyrus pashia*

Geographical Distribution

It is distributed across the Himalayas from Pakistan to Vietnam and from the southern provinces of China to the northern regions of India.

Taxonomical description

Kingdom: Plantae

Class: Angiosperms

Sub class: Eudicots

Order: Rosids

Super order: Rosales

Family: Rosaceae.

Species: *Pyrus pashia*

Vernacular names

Hindi: Mahal mol

Kashmiri: Tangi

Himachali: kainth

Kumaon: Mehol mol

Punjabi: Shegal

Assamese: Soh-shur, Soh-jhur, Chalthei

Botanical Description

Leaves are stipulate, petiolate, having 2 to 3.5 cm long petiole, crenate, reticulate crenate, ovate to lanceolate; apex, acute to acuminate; length, 4.5 to 11 cm; width, 2.5 to 4.2 cm. Leaves arise in alternate pattern on one-year-old shoots. On two-year-old branches, a single leaf, with a stipule, arises laterally on each node. A thorn is always present in the axil. The thorn also bears 2 to 30 alternate, pubescent leaves. In the case of older wood, 5 to 7 leaves are present on the fruiting spurs. Leaves, stipulate, petiolate, having 2 to 3.5 cm long petiole, crenate, reticulate crenate, ovate to lanceolate; apex, acute to acuminate; length, 4.5 to 11 cm; width, 2.5 to 4.2 cm. Leaves arise in alternate pattern on one-year-old shoots. On two-year-old branches, a single leaf, with a stipule, arises laterally on each node. A thorn is always present in the axil. The thorn also bears 2 to 30 alternate, pubescent leaves. In the case of older wood, 5 to 7 leaves are present on the fruiting spurs (Parmar and Kaushal, 1982). Fruit is a spherical berry. The size of the fruits varied from 1-2.5 cm in diameter. The surface of the fruit is dark greyish in color bearing numerous densely distributed

white and yellow spots. The fruit consists of fine wide radiating carpel chambers with one or two seeds attached in axile placentum (Hemaltha et al., 2016).

Traditional Uses

Traditionally, fruits and leaf crush is used in cuts, wounds and fungal infection in Mandi district of Himachal Pradesh (Sharma et al., 2013).Leaves, twigs, fruits and wood are used in treatment of mouth infection and eye complaints by the people of Mandi district Himachal Pradesh (Sharma et al., 2009). In folk medicine of Gharwal region, fruits of this plant are traditionally being used in treatment of digestive disorders (Kumar et al., 2011). It is well documented that ripend fruits are considered as edible by many tribes while tender leaves and twigs are used as fodder, leaf extract is used as a tonic for hair loss and woods are used as a major fuel source in the central Himalayan region (Arya. 2011) The leaves are consumed as tea beverages by the Monpa Community of Tawang, Arunachal Pradesh (India). Twigs of the tree are popularly being used in tooth ache problems by the indigenous people of Jammu Kashmir and Laddhak divisions of India (Gairola et al., 2014). Crushed fresh leaves are used as popular folk cosmetic by tribal communities of North-West Frontier Province, Pakistan for staining palms, feet and nails (Abbasi et al., 2010). Ripened fruits are used for treatment of constipation by tribal communities of Lesser Himalayas-Pakistan (Abbasi et al., 2010. Fruits are popular home remedy and are used as febrifuge, sedative and astringent in Khanbad village of Pakistan (Gorsi and Miraj 2002). Fruits are prescribed against asthma by the local vaidyas of Dronagiri, Uttaranchal (Arya 2002). Experimental study suggests that it has significant antimicrobial activity against *Klebsiella pneumonia*, *Shigella flexneri* and *Escherechia. Coli.* (Saklani and Chandra 2012). Ripened fruits are also used against nervous disorders such as epilepsy (Murad et al., 2011).

Phytochemical Review

Sl No	NAME	PART USED	PHYTOCONSTITUENTS	REFERENCES
1	*Pyrus pashia*	Stem	Hexacosanol, Hydroquinone, βsitosterol-β-D- glucoside, Luteolin glycoside. hentriacontanol, β-sitosterol, friedelin α-amyrin, Arborinol.	Bhakuni et al., 1971.
2	*Pyrus pashia*	Seedling leaves	Apigenin7-glucoside, Luteolin 7-glucoside, Luteolin 4 'glucoside, Chrysoenol 7-glucoside, Quercetin, Epicatechin,Catechin, Caffeoylcalleryanm, Caffeoylarbutin, p-Coumaroylarbutin, Arbutin, Acetylarbutin	Challice and Westwood. 1972.
3	*Pyrus pashia*	Branches and leaves	pashinin A, gastrodin-7-O-cis-caffeoyl ester, gastrodin-7-O-trans-caffeoyl ester, kaempferol-3-β-D-(6-O-trans-p-coumaroyl) glucopyranoside, kaempferol-3-β-D-(6-O-cis-p-coumaroyl) glucopyranoside, gastrodin-7-O-p-hydroxybenzoyl ester, arbutin, robustaside B, tormentic acid, euscaphic acid, quercetin-3-O-β-D-glucopyranoside, 2R,3R-dihydyoquercetin, luteolin-4-O-β-D-glucopyranoside, apigenin-4-O-β-D-glucopyranoside, 5,7,4-trihydroxyisoflavone-7-O-β-D-glucopyranoside, genistein, caffeic acid	Zhao et al., 2013.

Sl No	NAME	PART USED	PHYTOCONSTITUENTS	REFERENCES
4	*Pyrus pashia*	Branches and leaves	4-O-β-D-glucopyranosylbenzyl-benzoate ester, 3,5-dicaffeoylquinic acid, methyl 3,5- dicaffeoylquinate, methyl 5-O-caffeoylquinate, , 4- hydroxy-trans-cinnamomic acid 4-β-D-glucopyranosyloxybenzyl ester, 4-hydroxy-cis-cinnamomic acid 4-β-D- glucopyranosyloxybenzyl ester, p-hydroxyphenyl 6-O-trans-p-Coumaroyl-β-D-glucopyranoside, p-hydroxyphenyl 6-O-cis-p-Coumaroyl-β-D-glucopyranoside, 4-hydroxybenzoic acid, , 4-(methoxymethyl) phenyl-1-Oβ-D-glucopyranoside, 3,4-dihydroxyacetophenone, 3,4-dihytroxy benzaldehyde, p-hytroxy benzaldehyde, (–)-3-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone-3-O-βD glucopyranoside, picein, caffeic acid, trans-p-hydroxycinnamic acid, cedrusin, (+)-isolarisiresinol, , (-)-lariciresinol, 3-O- (β-D-glucopyranosyl)-1-(30 50 -dimethoxy-4-hydroxyphenyl-1-propanone, myzodendrone	Lia et al., 2015.

Sl No	NAME	PART USED	PHYTOCONSTITUENTS	REFERENCES
5	*Pyrus pashia*	Flowers	Uvaol, ursolic aldehyde, 4-hydroxybenzyl Me ether , 4-hydroxybenzyl Et ether, E-1-(4'-hydroxyphenol)-but-1-ene-3-one ,5,6β-epoxy-5β-sitostan-3β-ol , 5,6α-epoxy-5α-sitostan-3β-ol , stigmasta-5-en-3β,7α-diol , daucosterol palmitate , glycerol 1,3-di-(9Z,12Z-octadecadienoate) , linoleic acid) , daucosterol , β-sitosterol .	Chuan-shui et al, 2011.
6	*Pyrus pashia*	Flowers	2α, 3β, 27-trihydroxyolean-12-en-28-oic acid, (4α)-3-(5,5-dimethyltetrahydrofuranyl)-1-buten-3-ol 3-O-β-D-glucopyranoside, arjungenin, 2α,3α-dihydroxyolean-12-en-28-oic acid, 2α,3α,24-Trihydroxyolean-12-en-28-oic acid, 2α,3α, 19α,23-tetrahydroxyolean-12-en-28-oic acid, ursolic acid, corosolic acid, pomalic acid, tomentic acid, 3β-O-cis-p-coumaroyl-2α-hydroxy-urs-12-en-28-oic acid, , 3β-O-trans-p-coumaroyl-2α-hydroxy-urs-12-en-28-oic acid, 3-O-(Z)-p- coumaroyltormentic acid, 3-O-(E)-p-coumaroyltormentic acid, euscaphic acid, , 2α,3α,19α,23- tetrahydroxy-urs-12-en-28-oic acid, 2α,3α,19α,24-tetrahydroxy-urs-12-en-28-oic acid, swinhoeic acid, sachalinoide.	Lia et al., 2015.

Sl No	NAME	PART USED	PHYTOCONSTITUENTS	REFERENCES
7	*Pyrus pashia*	Flowers	4-O-Z coumaroylarbutin, 4-hydroxybenzaldehyde, 3,4-dihydroxybenzaldehyde, 4-methoxybenzoic acid, 4-methoxymethyl-phenol, 4-ethoxymethyl-phenol, E-1- (4′-hydroxyphenyl)-buten-1-en-3-one, 3,4-dihydroxyl cinnamic acid, p-hydroxyacetophenone, cynanoneside A, 4,4′-methylenediphenol, 3,3′,4-trihydroxydiphenylmethane, hydroquinone, arbutin, 6-Oacetylarbutin, 2-O-acetylarbutin, 5-O-p-cis-coumaroyl quinic acid methyl ester, 5-O-p-trans-coumaroyl quinic acid methyl ester, gastrodin, 2-methoxy-4-(2-propenyl) phenyl β-D-glucopyranoside, 3,5-O-caffeoylquinic acid, 3,5-O-caffeoylquinic acid methyl ether, 8-C-phydroxybenzyl apigenin, 3,5,7,4′-tetrahydroxy-8-methoxyflavone-3-O-β-D-glucopyranoside, kaempferol 3-rutinoside, apigenin, apigenin 4′-O-β-Dglucopyranoside, and apigenin 7-O-β-D-glucopyranoside.	He et al., 2015
8	*Pyrus pashia*	Fruits	Sitosterol, lupeol.	Khandelwal et al, 2008.
9	*Pyrus pashia*	Fruits	Chrysin	Sharma et al., 2017.

Table. 3 Phytochemical review of *Pyrus pashia*.

Pharmacological Review

Pyrus pashia Buch.-Ham. ex D. Don is a very less-explored plant in terms of pharmacological activities, as no detailed research exists on this plant. Therapeutic potential of *Pyrus pashia* fruits in cardiovascular, respiratory and gastrointestinal ailments has been established by (Janbaz et al., 2015). Recently (Ain and Khan 2019) documented that hydroethanolic extract of *Pyrus pashia* flowers and seeds showed their involvement with benzodiazepine receptors, and exhibited significant sedative and hypnotic effects in *in vivo* experimental models. Antioxidant potential of *Pyrus pashia* has been evaluated by (Siddiqui et al., 2015) using different methods such as,1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging activity, ferric reducing antioxidant power (FRAP) assay and total antioxidant activity by phosphomolybdenum complex. Antimicrobial activity of *Pyrus pashia* against *Klebsiella pneumonia, Shigella flexneri* and *Escherichia coli* has been reported by (Saklani and Chandra 2012). Triterpenoids from branches and leaves of *Pyrus pashia* have been reported to demonstrate cytotoxic activity (Lia et al., 2015).