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Anticonvulsants From Nature

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ABSTRACT
Epilepsy is the second most common neurological disorder after stroke and shows a prevalence rate in 1-2% of the world population. Although several antiepileptic drugs are available, the treatment of epilepsy is still far from adequate. The current therapy of epilepsy with modern antiepileptic drugs is associated with side effects and drug interactions. Approximately 30% of the patients continue to have seizures with current drug therapy. Several plants used for the treatment of epilepsy in different systems of traditional medicine have shown antiepileptic activity in experimental animal models and many such plants claimed in the traditional system still remain to be scientifically investigated. In this review, we have compiled the reported herbal anticonvulsants with their research advancements.
KEYWORDS: Anticonvulsant, Convulsions, Epilepsy, Gamma amino butyric acid, Maximal electroshock, Pentylenetetrazole.

INTRODUCTION

Epilepsy is the second most common neurological disorder after stroke (1) and is characterized by seizures, which are of various types and result from episodic neuronal discharges. The type of the seizure depends on the part of the brain affected (2). A seizure is a paroxysmal event due to abnormal, excessive, hyper-synchronous discharges from an aggregate of central nervous system (CNS) neurons (3). The tendency to have recurrent attacks is known as epilepsy but a single attack does not constitute epilepsy (4).

Epilepsy shows a prevalence rate in 1-2% of the world population (5). It affects an estimated 7 million people in India and 50 million worldwide, approximately 40% of them are women. The prevalence of epilepsy is 0.7% in India and high in tropical countries particularly in South Africa. In developed countries, where drugs are easily available, epilepsy responds to treatment in up to 70% of the patients. However, in developing countries 75% of people with epilepsy do not receive the treatment (6, 7). It is estimated that up to 5% of people suffer at least one seizure in their lifetime. A minority of patients (20-30%) may develop chronic epilepsy, and in such cases, treatment is more difficult. There is an increased mortality in people with epilepsy; most studies have given overall standardized mortality ratios between two & three times higher than that of the general population (4).

Although several antiepileptic drugs (AEDs) are available to treat epilepsy, the treatment of epilepsy is still far from adequate. The current therapy of epilepsy with modern antiepileptic drugs is associated with side effects (Table I), dose related and chronic toxicity, teratogenic effects and approximately 30% of the patients continue to have seizures with current antiepileptic drug therapy (8,9). In addition, safety, tolerability, efficacy, expenses especially in long term therapy, serum drug monitoring are other limitations with synthetic antiepileptic drugs. Further, a large number of drug interactions (Table II) are seen with almost all current AEDs which make it more difficult to attain easy control on seizures (10). In many cases even multi-drug therapy is not effective and neurosurgical procedures may be indispensable (1). Consequently a real need exists to develop new anticonvulsant compounds to cover seizures which are so far resistant to presently available drugs (11).

Plants may serve as the alternative sources for the development of new anticonvulsant agents due to their biological activities. Several plants used for the treatment of epilepsy in different systems of traditional medicine have shown antiepileptic activity when tested on animal models and many such plants remain to be scientifically investigated (9). Many attempts have been made in the past to obtain anticonvulsant of plant origin and these efforts will continue till a satisfactory treatment becomes available (8). In this regards, a number of medicinal plants having anticonvulsant potential are reviewed.

Vitex negundo (Verbenaceae) is a large aromatic shrub found throughout India. Ethanol extract of leaf of *V. negundo* significantly potentiate the anticonvulsant activity of diphenylhydantoin and valproic acid in maximal electroshock (MES) and pentylenetetrazole (PTZ) induced seizures in albino rats and mice respectively. A significant post-ictal depression was observed against MES induced seizures. It also showed protection in clonic seizures. The extract may also be useful as an adjuvant therapy along with standard anticonvulsants. The extract may increase the level of gamma amino butyric acid (GABA) in PTZ induced seizures and therefore can be used in absence seizures (12).

Cissus quadrangularis (Vitaceae) is an edible plant found throughout the hotter parts of India, Malaya, West Africa and Ceylon (50). The aqueous extract of the stems of *C. quadrangularis* showed anticonvulsant activity against MES, PTZ, strychnine (STR), n-methyl-D-aspartate (NMDA) induced seizures. The extract protected mice against MES, PTZ and STR induced seizures and antagonized NMDA induced turning behavior. The inhibition of the STR and PTZ

Table 1: Side effect profile of Synthetic Anticonvulsants (2, 4, 48, 49)

Drug	Side effects
Carbamazepine	Diplopia, drowsiness, headache, nausea, orofacial dyskinesia, arrhythmias
Clonazepam	Fatigue, drowsiness, ataxia
Ethosuximide	Nausea, vomiting, headache, lethargy, drowsiness
Gabapentin	Headaches, drowsiness, diplopia, ataxia
Lamotrigine	Headaches, drowsiness, diplopia, ataxia
Phenobarbital	Fatigue, depression, poor memory, impotence, hypocalcaemia, osteomalacia, folate deficiency
Phenytoin	Ataxia, nystagmus, drowsiness, gingival hyperplasia, hirsutism, diplopia, folate deficiency, orofacial dyskinesia, asterixis
Sodium valproate	Dyspepsia, hair loss, anorexia, drowsiness, nausea, vomiting
Topiramate	Dizziness, drowsiness, nervousness, fatigue, weight loss
Vigabatrin	Drowsiness, dizziness, weight gain

Table 2: Drug interactions of major synthetic anticonvulsants (4, 49, 50)

AED	Drug implicated	Effect on plasma level
Carbamazepine (CBZ)	Phenytoin	Decreased CBZ
	Phenobarbital	Decreased CBZ
	Felbamate	Decreased CBZ
	Cimetidine	Increased CBZ
	Propoxyphene	Increased CBZ
	Erythromycin	Increased CBZ
	Isoniazid	Increased CBZ
	Fluoxetine	Increased CBZ
Lamotrigine (LTG)	Sodium valproate	Increased LTG
	Phenytoin	Decreased LTG
	Carbamazepine	Decreased LTG
	Phenobarbital	Decreased LTG
	Primidone	Decreased LTG
Phenytoin (PHT)	Carbamazepine	Decreased PHT
	Sodium valproate	Decreased PHT
	Vigabatrin	Decreased PHT
	Felbamate	Increased PHT
	Phenobarbital	Increased or Decreased PHT
	Propoxyphene	Increased PHT
	Chloramphenicol	Increased PHT
	Isoniazid	Increased PHT
	Disulfiram	Increased PHT
	Fluconazole	Increased PHT
	Amiodarone	Increased PHT
Valproic acid (VPA)	Carbamazepine	Decreased VPA
	Lamotrigine	Decreased VPA (slight)
	Phenobarbital	Decreased VPA
	Primidone	Decreased VPA
	Phenytoin	Decreased VPA
	Cimetidine	Increased VPA
	Salicylates	Increased free VPA

Table 3: List of plants reported to have anticonvulsant activity

Plant name	Part used	Extract	Dose	Animal models
Acosmium subelegans (Leguminosae) (51)	–	Ethanol extract	100, 500, 1000mg/kg, orally	PTZ, MES
Afrormosia laxiflora (Leguminosae) (52)	Roots	Aqueous extract	50, 100, 150, 200, 250, 300mg/kg, i.p.	PIC, MES
Albizzia lebbeck (Mimosaceae) (53)	Leaves	Ethanol extract	100mg/kg, i.p.	PTZ, MES, STR
Annona diversifolia (Annonaceae) (54)	Leaves	Ethanol extract	30mg/kg, i.p.	PCN
Artemisia dracunculus (Asteraceae) (55)	Aerial parts	Essential oil	0.1, 0.15, 0.2, 0.4, 0.8, 1.0 & 1.2ml/kg	MES, PTZ
Benincasa hispida (Cucurbitaceae) (10)	Fruit	Methanol extract	0.2, 0.4, 0.6 & 1.0g/kg i.p.	PTZ, MES, STR, PIC
Bixa orellana (Bixaceae) (56)	Leaves	Methanol extract	125, 250, 500mg/kg, p.o.	STR
Butea monosperma (Fabaceae) (57)	Flowers	Petroleum ether extract	10 – 150mg/kg, i.p.	MES, PTZ, PIC, STR, Li-Pilo
Bryophyllum pinnatum (Lamiaceae) (58)	Leaves	Aqueous extract	50,100,200 mg/Kg i.p. LD_{50}=64mg/kg	PIC, STR
Centella asiatica (Umbelliferae) (59)	Whole plant	Aqueous extract	100 & 300mg/kg orally	PTZ kindling
Cestrum nocturnum (Solanaceae) (60)	Dried leaves	Decoction	30% decoction i.p. (30 g/100ml water)	PIC, MES, INH
Citrus aurantium (Rutaceae) (61, 62)	Flowers	Percolation	120, 150, 175, 200, 300, 400mg/kg, i.p.	PTZ
Cotyledon orbiculata (Crassulaceae) (63)	Leaves	Aqueous and Methanol extracts	50, 100, 200 & 400mg/kg i.p.	PTZ, BCL, PIC, NMDA
Crocus sativus (Iridaceae) (64)	Stigmas	Ethanol and aqueous extracts	0.08-80 g/kg, i.p. & 0.2-2.0g/kg for aqueous & ethanol extracts resp.	PTZ, MES
Cymbopogon winterianus (Poaceae) (65)	Leaves	Essential oil	200 & 400mg/kg i.p.	PTZ, PIC, STR
Cyperus articulatus (Cyperaceae) (66)	Rhizomes	Methanol extract	200, 500, 1000 & 2000mg/kg i.p.	MES, PTZ, NMDA, STR, PIC, BCL, INH
Delphinium denudatum (Ranunculaceae) (9)	Dried roots	Ethanol & aqueous Extract	200, 400, 600 & 800mg/kg i.p.	MES, PTZ, BCL,PIC, STR
Desmodium adscendens (Papillionaceae) (67)	Leaves	Ethanol extract	50, 100, 300mg/kg, i.p.	PTZ, KA
Diospyros mespiliformis (Ebenaceae) (68)	Bark	Aqueous extract	100, 200mg/kg, p.o.	PTZ
Echinodorus berteroi (Alismataceae) (69)	Dried roots	Decoction	30%decoction i.p. (30 g/100ml water)	INH, PIC, MES
Erythrina indica (Fabaceae) (70)	Leaves	Ethanol, Ethyl acetate & chloroform extracts	50, 150, 250mg/kg, i.p.	PTZ, MES
Erythrina velutina and Erythrina mulungu (Fabaceae) (71)	Stem bark	Hydroalcoholic extract	200 & 400mg/kg i.p.	PTZ, STR
Eugenia caryophylla (Myrtaceae) (72)	Buds	Essential oil	0.025, 0.05, 0.075, 0.1ml/kg, i.p.	PTZ, MES
Ferula gummosa (Apiaceae) (73)	Roots	Acetone extract	50, 100, 300, 400, 500 & 750mg/kg i.p.	MES, PTZ
Ficus sycomorus (Moraceae) (74)	Stem bark	Aqueous extract	400 & 600mg/kg	PTZ, STR
Gastrodia elata	–	Hydroalcoholic	1g/mg, orally	KA

(Orchidaceae) (75)		extract		
Glychrrhiza glabra (Leguminosae) (76)	Roots and rhizomes	Ethanol extract	10, 30, 100 & 500mg/kg i.p.	MES, PTZ
Heracleum crenatifolium (Apiaceae) (77)	Crushed seeds	Essential oil	0.84ml/kg i.p.	MES
Hibiscus rosa sinensis (Malvaceae) (53)	Flowers	Ethanol extract	100mg/kg, i.p.	PTZ, MES
Hoslundia opposita (Lamiaceae) (78)	Roots	Chloroform extract	50, 100g/kg, orally	PTZ
Hypericum perforatum (Hypericaceae) (79)	Aerial parts	Aqueous and ethanol extracts	0.1, 0.4, 0.7 & 1.0g/kg i.p.	PTZ, MES
Hypoxis hemerocallidea (Hypoxidaceae) (80)	Corms	Aqueous extract	100, 200, 400, 800mg/kg, i.p.	PTZ, PIC, BCL
Kalanchoe crenata (Crassulaceae) (81)	Leaves	Methylene chloride:Methanol (1:1) extract	150 & 300mg/kg orally	PTZ, STR, TSC
Laurus nobilis (Lauraceae) (82)	Leaves	Essential oil	0.1, 0.125, 0.25, 0.5, 0.75, 1.0ml/kg, i.p.	PTZ, MES
Lavandula stoechas (Lamiaceae (83)	Flowers	Aqueous-methanolic extract	400, & 600mg/kg i.p.	PTZ
Leonotis leonurus (Lamiaceae) (84)	Leaves	Aqueous extract	100, 200, 400mg/kg, i.p.	PTZ, PIC, BCL
Lippia alba (Verbenaceae) (85)	Aerial parts	Hydroalcoholic extacts	20mg/ml	PTZ
Mimosa pudica (Mimosaceae) (86)	Leaves	Decoction	500, 1000, 2000 & 4000mg/kg, i.p.	PIC, PTZ, STR, NMDA
Myristica fragrans (Myristicaceae) (8)	Seeds	n-hexane fraction	10, 30 & 100mg/kg, i.p.	MES, PTZ, PIC, Li-Pilo
Nardostachys Jatamansi (Valerianaceae) (87)	Roots	Ethanol extract	50, 100, 200, 400, mg/kg, i.p. & 125, 250, 500mg/kg, orally	MES, PTZ
Nigella sativa (Ranunculaceae) (88)	Whole herb	Essential oil	–	PTZ kindling
Ocimum gratissimum (Lamiaceae) (89)	Leaves	Essential oil	0.5, 1.0g/kg, orally	PTZ, MES
Passiflora incarnate (Passifloraceae) (90)	Leaves, flowers, fruits	Hydro-alcoholic extract	0.05, 0.1, 0.2, 0.4mg/kg, i.p.	PTZ
Persea Americana (Lauraceae) (91)	Leaves	Aqueous extract	100, 200, 400, 800mg/kg, i.p.	PTZ, PCT, BCL
Pimpinella anisum (Apiaceae) (92)	Fruits	Essential oil	0.1, 0.25, 0.5 & 1.0ml/kg	PTZ, MES
Rhus chirindensis (Anacardiaceae) (93)	Stem bark	Aqueous extract	100, 200, 400 & 800mg/kg i.p.	PTZ, PIC, BCL
Rosa damascene (Rosaceae) (94)	Petals	Essential oil	250, 500, 750, 1000mg/kg, i.p.	PTZ
Salvadora persica (Salvadoraceae) (95)	Stem	Decoction	500mg/kg, orally	PTZ
Searsia dentate, Searsia pyroides (Anacardiaceae) (96)	Leaves	Ethanol extract	0.62, 1.67mg/ml	MCW
Sesbania grandiflora (Leguminosae) (97)	Leaves	Petroleum ether extract	25 – 200mg/kg, p.o.	PTZ, MES
Uncaria rhynchophylla, (Rubiaceae) (75)	–	Methanol extract	1.0g/kg, orally	KA
Valeriana edulis	Roots	Hydro-alcoholic	100, 300, 1000mg/kg,	PTZ

(Valerianaceae) (98)		extract	i.p.	
Viscum capense (Loranthaceae) (99)	Stem	Dichloromethane, Methanol, Aqueous Extracts	50, 100mg/kg, i.p.	PTZ, BCL, NMDA
Vitex agnus castus (Lamiaceae) (1)	Fruits	Hydrophilic extract	60, 120 & 180mg/kg, i.p.	Kindling

BCL = Bicuculline, INH= Isoniazid, KA= Kainic acid, Li-Pilo= Lithium sulphate-Pilocarpine nitrate, MCW = Mouse cortical wedge, MES = Maximal Electroshock, NMDA = n-methyl-D-aspartate, PCN= Penicillin, PIC = Picrotoxin, PTZ = Pentylenetetrazol, STR = Strychnine, TSC= Thiosemicarbazide

induced seizures suggests the involvement of glycine receptors and GABAergic neurotransmission (13).

Passiflora edulis (Passifloraceae) is an evergreen, flowering vine in tropical area of South America. Aqueous leaf extract of *P. edulis* significantly protected the mice against STR and PTZ induced seizures and NMDA induced turning behavior. The results suggested the involvement of glycine and NMDA receptors and it may not have any effects on the gamma amino butyric acid (GABAergic) neurotransmission (14).

Artemisia abrotanum (Asteraceae) is a shrub available abundantly in Nilgiri Hills. Essential oil obtained from the aerial parts of *A. abrotanum* showed anticonvulsant activity against PTZ induced seizures by significantly delaying the onset of myoclonic seizures in mice. The anticonvulsant activity of the plant may be due to the presence of terpenoids (6).

Casssia sophera (Caesalpiniaceae) is a shrub and an important drug of Unani system of medicine. Ethanol extract of *C. sophera* seeds produced significant reduction in the duration of the extensor phase and delayed the onset of myoclonic spasm and clonic convulsions in MES and PTZ induced seizures in albino rats respectively. Hence, the drug may be useful in epileptic conditions viz. Grand mal and Petit mal epilepsy (15).

Withania somnifera (Solanaceae) is widely used herb in the Ayurvedic system of medicine in India. It has been reported to be effective in alleviating epilepsy and other CNS disorders. It increases the PTZ seizure threshold for the onset of tonic extensor phase. Pretreatment of *W. somnifera* root extract with GABA (25mg/kg, i.p.) or diazepam (0.5mg/kg, i.p.) increases the seizure threshold in mice. The protective effect is conceived to be through GABAergic modulation (16).

Casimiroa edulis (Rutaceae) is a tree widely distributed throughout Mexico. Its aqueous extract of leaves showed anticonvulsant activity against MES and PTZ induced seizures in male wistar rats (17).

Sutherlandia frutescens (Fabaceae) is a well known, multipurpose shrub in South Africa and used as a remedy for an array of human ailments including epilepsy and convulsions. Chemical studies revealed that aerial parts of the plant contain gamma amino butyric acid (GABA). Aqueous leaf extract of the plant significantly delayed the onset of PTZ induced seizures and antagonized picrotoxin (PIC) induced seizures in mice. The LD_{50} value of extract was 1825±116mg/kg, proving it as a safer drug. It appeared that the extract produces its antiseizure effect directly by acting like GABA or indirectly by enhancing GABAergic neurotransmission and/or action in brain (18).

Heracleum persicum (Umbelliferae) is a perennial plant indigenous to Iran. Stem and seeds of this plant have been used for the treatment of epilepsy. Acetone extract showed a dose dependent protective effect in PTZ and MES seizure models in mice. It seems that the antiseizure profile of seed extract may be related to the presence of terpenoids, triterpenes and alkaloids (19).

Hippeastrum vittatum (Amaryllidaceae) is a herb found throughout South America and other continents. Ethanol extract of fresh bulbs showed anticonvulsant activity against PTZ induced seizures. It suppressed the clonic seizures induced by pentylenetetrazol in mice. The results indicate that montanine may act on the benzodiazepine site of the GABA receptor in the mouse's brain (20).

Ipomoea stans (Convolvulaceae) is a climbing plant and its aqueous infusions of roots have been used in Mexican traditional medicine for treating epileptic seizures. Studies showed the anticonvulsant effect produced by the root of this plant in MES and PTZ induced seizures. Ethyl acetate extract from the root of plant induced a protection of 71.43% in mice. It is probably that the effects are produced through central depressor mechanism by acting on the receptor-complex GABAergic or through modulation of GABAergic transmission (21).

Magnolia grandiflora (Magnoliaceae), a tall tree grows in the south-eastern states of US and Mexico has been reported to have beneficial effects on several ailments including epilepsy. It contains phytoconstituents magnolol and honokiol. Ethyl ether extract and hydroalcoholic extract of seeds showed anticonvulsant activity by exhibiting abolition of the extensor reflex against MES induced seizures in male wistar rats. The effect produced may be due to the presence of substances that act over the neurons of the hypothalamic area involved in sleep control, as both the extracts potentiated hypnosis (22).

Taxus wallichiana (Taxaceae) is a tall tree native to northern area of Pakistan. Traditionally, leaves of this plant are used to make herbal tea to treat indigestion and epilepsy. The methanol leaf extract of the plant significantly inhibited myoclonus and clonus in mice. The benzodiazepine site in the $GABA_A$ receptor and T-type Ca^{2+} currents may be responsible for the mechanism of action (23).

Harpagophytum procumbens (Pedaliaceae), is a weedy perennial herb which is one of the useful medicinal plants in South Africa. The anticonvulsant activity of secondary root extract (50-800mg/kg, i.p.) was examined against PTZ, PIC, and BCL induced seizures in mice. The aqueous extract significantly

delayed the onset of pentylenetetrazol induced seizures & antagonized PIC induced seizures, but only partially and weakly antagonized BCL induced seizures. So it could be used in both petit mal and grand mal epilepsy. The studies suggest that the extract might have inhibited or attenuated PTZ and BCL induced seizures in mice by enhancing or in some ways interfering with GABAergic neurotransmission. However, in PIC induced seizures model, the inhibition of seizures may be due to the opening of the chloride ion channels associated with $GABA_A$ receptors. The activity may be due to the presence of the iridoids harpagoside, harpagide and procumbide or due to its ability to depress CNS by one or more of the known mechanisms, such as altering of Na^+-K^+ ATPase expression, pyridoxamine-5-phosphate (PMP) metabolism and inhibition of expression of inducible nitric oxide (3, 24).

Natural products from folk remedies have contributed significantly in the discovery of modern drugs and can be an alternative source for antiepileptic drugs with novel structures and better safety and efficacy (25). Many drugs are developed with phytochemicals or taking phytochemicals as lead molecules. A list of plants responsible for anticonvulsant activity is given in Table III.

Some phytoconstituents with anticonvulsant potential on different type of seizures are as follows:

A. Flavonoids

Flavonoids are chemical phenylbenzopyrones which usually conjugated with sugars and are present in all vascular plants (26). Flavonoids possess neuroactive properties and many of these compounds are ligands for $GABA_A$ receptors in the central nervous system (CNS) and act as benzodiazepine-like molecules. These facts are supported by their behavioral effects in animal models of anxiety, sedation and convulsion (27, 28). Various flavonoids reported to have anticonvulsant effects are as follows:

1. *Rutin* (Fig. 1A): Rutin is a flavonoid of the flavonol type found in many plants such as buckwheat, apples and black tea (29). It showed dose dependent anticonvulsant activity against pentylenetetrazole induced minimal clonic and generalized tonic clonic seizures in rats. Rutin might exert its effect through $GABA_A$–benzodiazepine receptor complex (28).

2. *Apigenin* (Fig. 1B): This flavonoid was obtained from dried flowers of *Matricaria chamomilla* (Asteraceae) using methanol. It significantly reduced the latency in the onset of picrotoxin induced convulsions in rats. The anticonvulsant activity of apigenin may be due to its ability to reduce the GABA-activated chloride currents suggesting a selective activity at $GABA_A$ receptor level (30).

3. *Goodyerin*: It is a flavonol glycoside obtained from methanol extract of whole plant of *Goodyera schlechtendaliana* (Orchidaceae). It significantly prolonged the latency of onset of seizure and reduced the duration of seizures and exhibited complete protection against induced convulsions in rats. The mechanisms of action of goodyerin for inhibiting the CNS is still obscure (31).

4. *Wogonin*: This flavonoid is obtained from a Korean herb *Scuttellaria baicalensis* (Lamiaceae). Wogonin significantly decreased the seizure response induced by PTZ in male mice. It also decreased the intensity of electrogenic seizures induced with a convulsiometer. The mechanism involved in its anticonvulsant activity is potentiation of the activity of GABA (32).

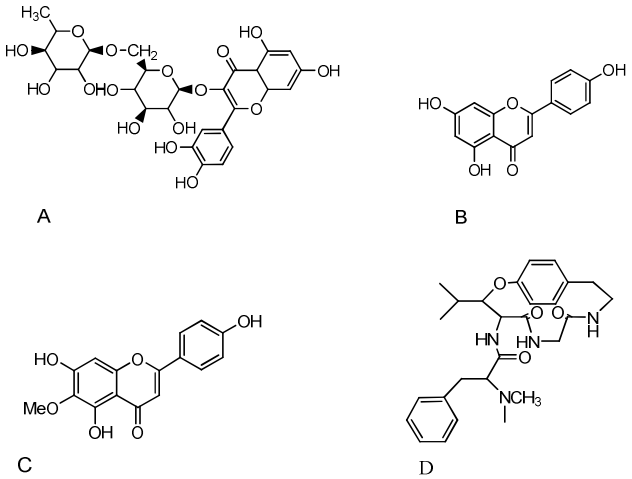
5. *Hispidulin* (Fig. 1C): Hispidulin (4´, 5, 7-trihydroxy-6-methoxy-flavone) is a naturally occurring flavone commonly found in several *Artemisia* and *Salvia* species. It markedly reduced the number of animals suffering from seizures induced by a standardized handling procedure in Mongolion gerbils (*Meriones unguiculatus*). The anticonvulsant effect of hispidulin suggested being through its interaction with benzodiazepine binding site (33).

B. Alkaloids

1. *Sanjoinine A* (Fig. 1D): It is one of the major alkaloid from *Zizyphi spinosi* semen (Rhamnaceae) obtained in methanol extract. Sanjoinine A significantly decreased seizure score and also increased the latency of seizure onset against NMDA elicited convulsions in mice. The anticonvulsant effect of the alkaloid may be due to the inhibition of intracellular calcium influx (34).

2. *Nantenine* (Fig. 1E): Nantenine is an aporphine alkaloid found in several vegetal species and was first isolated from fruit of *Nandina domestica*. It occurs abundantly in Papaveraceae family. It significantly reduced extensor/flexor ratio and mortality and showed an inhibition of 30, 60 and 90% tonic phase occurrence against MES and PTZ induced seizures in mice respectively. The alkaloid anticonvulsant effect could be attributable to stimulation of Na^+, K^+-ATPase and the resultant decrease of Ca^+-influx into the cell (35).

3. *Piplartine*: It is an amide alkaloid isolated from the roots of *Piper tuberculatum* (Piperaceae) by maceration with petroleum ether/ethyl acetate (1:1). It significantly decreased the latency to death against PTZ induced seizures in mice. The mechanism through which piplartine showed the anticovulsant activity is may be through its interaction with benzodiazepine receptors (36).



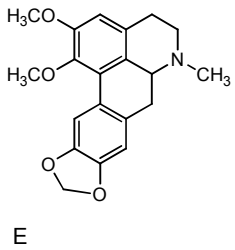


Figure 1: Structures of alkaloids and flavonoids with anticonvulsant activities

C. Terpenes

1. *Betulin* (Fig. 2A): It is a pentacylic triterpene alcohol with a lupane skeleton, also known as betulinol, betuline or betulinic alcohol. This is mainly present in family Marcgraviaceae which includes shrubs, small trees and lianas. Betulin significantly antgonised the BCL induced myoclonic jerks. The anticonvulsant property of betulin is due to its penetration into the mice brain and its direct binding to the $GABA_A$-receptor GABA site (37).

2. *Safranal* (Fig. 2B): Safranal (2, 6, 6-trimethyl-1, 3-cyclohexadiene-1-carboxyaldehyde) is a monoterpene aldehyde and an active constituent of *Crocus sativus* (Iridaceae), a perennial stemless herb. Peripheral administration of safranal induced a dose dependent decrease in minimal clonic seizure and generalized tonic-clonic seizure following PTZ administration after thirty minutes. Safranal exerted its anticonvulsant behaviour through $GABA_A$-benzodiazepine receptor complex and little role of opoid receptors may also be involved (38, 39).

3. *Ursolic acid*: It is a pentacyclic triterpenoid obtained from methanol extract of aerial parts of *Nepeta sibthorpii* (Lamiaceae), an aromatic plant. It showed anticonvulsant activity as it increased the latency period and decreased the number of clonic-tonic convulsions PTZ induced convulsions. It also lowers lethality in mice. The anticonvulsant activity of ursolic acid may be mediated via the GABA-ergic system (40).

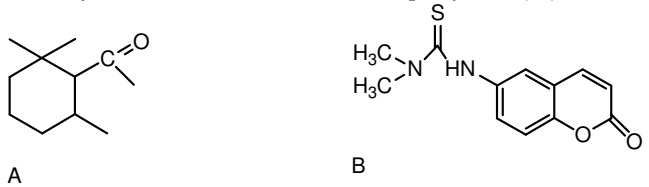


Figure 2: Structures of terpenes with anticonvulsant activities

D. Lactones

Lactones are common components in essential oil.

1. *γ-decanolactone*: This lactone is present in the essential oil of *Aeollanthus suaveolens* (Lamiaceae). It showed marked anticonvulsant effect in PTZ induced convulsions and also prevented tonic convulsions in transcorneal electroshock induced seizures in mice (41).

E. Coumarins

Some newly substituted coumarins tested for the anticonvulsant activity which includes coumarinylthiazolines, coumarinylthiazolidin-4-ones and chromenothiazoles. In PTZ test, among thioureas, *N*-ethyl thiourea (Fig. 3A) showed maximum protection of 60% whereas the compound 3-ethyl-4-(4-methoxyphenyl)-2-(2-oxo-2H-chromen-6-ylimino) thiazoline (Fig. 3B) showed more potent activity of 60% in comparison to other 3- substituted-4-(4-substituted phenyl)-2-(2-oxo-2H-chromen-6-ylimino)thiazolines. The compound thiazoline-5-carboxylic acid ethyl ester (Fig. 3C) also showed promising anticonvulsant activity of 80% against PTZ induced generalized convulsions in mice. In strychnine test, some derivatives of thiazolidinones, thiazolines and ethyl esters significantly increased the average survival time in mice against strychnine induced seizures. It might be possible that the compounds showed anticonvulsant effect in strychnine induced seizures by acting on glycine inhibitory mechanisms (11).

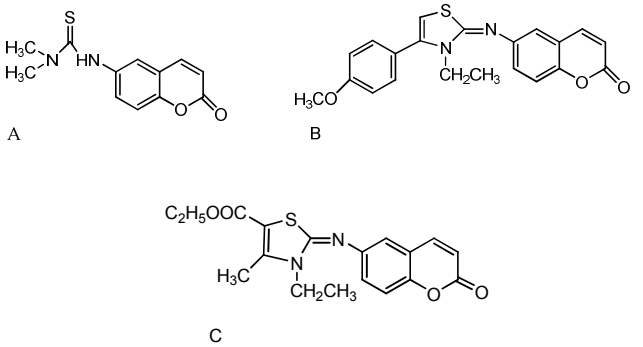


Figure 3: Structure of some Coumarins derivatives with anticonvulsant activities

F. Xanthones

Various xanthone derivatives reported to have anticonvulsant activity. In MES test, compounds (R,S)-6-chloro-2-(2-hydroxybutylamino)methyl)-9H-xanthen-9-one (Fig. 4A) and 6-chloro-2-((ethyl(2-hydroxyethyl)amino)methyl)-9H-xanthen-9-one (Fig. 4B) showed anticonvulsant protection in mice. In PTZ test, compound (S)-chloro-2((1-hydroxypropan-2-ylamino) methyl-9H-xanthen-9-one (Fig. 4C) showed protective activity in mice. In case of rats, compound (R,S)-6-chloro-2-(2-hydroxybutylamino) methyl)-9H-xanthen-9-one showed anticonvulsant activity in MES test. The anticonvulsant activity of these compounds may be due to their affinity to the benzodiazepine receptor and to the voltage-dependent calcium channel (42).

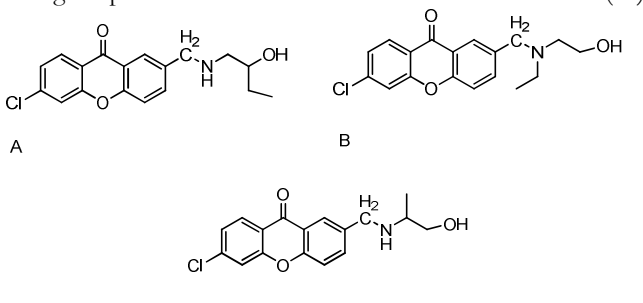


Figure 4: Structures of some xanthone derivatives with anticonvulsant activities

G. Others

1. *Vanillyl alcohol*: It is an analogue of vanillin and a component of *Gastrodia elata* (Orchidaceae), a traditional Chinese herb. Intraperitoneal injection of vanillyl alcohol significantly inhibited wet dog shakes induced by ferric chloride in rats. The anticonvulsant effect of vanillyl alcohol resulted mainly from its free radical scavenging activities (43).

2. *Barakol*: Barakol (3a, 4-dihydro-3a, 8-dihydroxy-2, 5-dimethyl-1, 4-dioxaphenalene) is a novel dioxaphenalene derivative from *Cassia siamea* (Ceasalpiniaceae). It prolonged the latency of clonic convulsion induced by picrotoxin in mice (44).

3. *Thymoquinone*: It is the major constituent of *Nigella sativa* (Ranunculaceae) seeds. It prolonged the latency of myoclonic seizures through a dose-dependent manner and also reduced the duration of myoclonic seizures induced by PTZ administration in mice. In case of MES test, it exhibited complete protection against mortality. Thymoquinone produced its effect through interaction with GABA-BZD receptor complex and κ-opoid receptors (45).

CONCLUSION

With the advent of allopathic system of medicine which is based on the fast therapeutic actions of synthetic drugs as in the case of epilepsy, herbal medicine gradually lost its popularity among people. The current antiepileptic drug therapy in the treatment of epilepsy is based upon the nature and type of epilepsy. Almost a century has passed and limitations of allopathic system have been witnessed. Herbal medicine has again gained the momentum and it is evident from the fact that certain herbal remedies peaked at par with synthetic drugs as it is shown in this review. The present review clearly revealed the anticonvulsant potential of herbal anticonvulsants that are now reported scientifically.

The rapid pace in research and development in herbal medicine has made it an interdisciplinary science. The Research and Development thrust in the Pharmaceutical sector is focused on development of new innovation/indigenous plant based drugs through investigation of leads from the traditional system of medicine. Due to better cultural acceptability, better compatibility with human body, wide biological activities, higher safety margin and lesser costs than the synthetic drugs, there is great demand of herbal medicines in the developed as well as developing countries. It is interesting to note that the value of animal testing to establish safety and toxicity is not so critical in botanicals if they are time tested and used widely in traditional forms. On the contrast synthetic molecules drug development requires about 12-15 years. The traditional medicine provides new functional leads to reduce time, money and toxicity- the three main hurdles in drug development (46, 47).

The golden triangle consisting of various traditional systems of medicines across the globe, modern medicine and science will converge to form a real discovery engine that can result in newer, safe, cheaper and effective therapies. Ayurveda and modern medicine techniques must be coupled in order to bring out high quality herbal products with rapid onset of action and good bioavailability. The possible mechanism of actions shown in this review can be exploited further for the identification of particular fraction and or active constituent which can provide more extensive results. The review also explored various herbal drugs mentioned in different traditional systems of medicine across the world that require more exploitation up to desired level, and these reports could be a better target for the development of alternatives to synthetic antiepileptic drugs.

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