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Herbal Approach in Treatment of Epilepsy

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Abstract:

Epilepsy is the second most common neurological disorder after stroke characterized by seizures of various types which result from episodic neuronal discharges. In Management of epilepsy the main target is to achieve the balance between the factors which alters the excitatory postsynaptic potential and postsynaptic potential. Although several antiepileptic drugs are available to treat epilepsy, the treatment of epilepsy is still far from adequate. Traditionally the herbal drugs can be an alternate source in treatment of epilepsy with improved safety and efficacy. The herbal drugs/remedies can make the anticonvulsant treatment more rationale and patient friendly due to less side effects, toxicity and drug interactions. In addition, more safety, tolerability, efficacy, and fewer expenses especially in long term therapy are other advantages with herbal anticonvulsants. This review article explains about the pathophysiology, management of epilepsy, various herbal drugs used in the treatment of epilepsy and their responsible phytoconstituents for producing significant effect in controlling seizures.

Keywords: *epilepsy, herbal drugs, seizures, herbal phytoconstituents*

Introduction

Epilepsy

Epilepsy is the second most common neurological disorder after stroke [1] characterized by seizures of various types which result from episodic neuronal discharges [2]. The prevalence rate of epilepsy is found to be 1–2% in the world [3]. In addition approx. 7 million people are suffering from epilepsy in India and 50 million people in whole world among them the 40% are women [4]. 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 and

most studies have given overall standardized mortality ratios between two and three times higher than that of the general population [5].

A seizure is a paroxysmal event due to abnormal, excessive, hyper-synchronous discharges from an aggregate of central nervous system (CNS) neurons [6].The seizures are found to occur from the cerebral cortex [7], of the brain which manage the behaviors in humans [8]. Seizures can be characterized into two major groups: partial and generalized (Figure 1). Partial (focal, local) seizures act locally in the brain while this phenomenon is missing in the case of the generalized seizures [9].

Pathophysiology of Epilepsy

Selected neurotransmitters (e.g., glutamate, aspartate, acetylcholine, norepinephrine, histamine, corticotrophin releasing factor, purines, peptides, cytokines, and steroid hormones) enhance the excitability and propagation of neuronal activity, whereas gamma-amino butyric acid (GABA) and dopamine inhibits the neuronal activity and propagation. Neuronal activity also depends on an adequate supply of glucose, oxygen, sodium, potassium, chloride, calcium, and amino acids. Systemic pH is also a keen factor in precipitating seizures. The different kinds of epilepsies arise from different neurophysiologic abnormalities [10, 11]. If neurons are damaged, injured or suffer chemical or metabolic insult, a change in the pattern of neurons discharge may develop. In addition, regular low frequency discharges are replaced by bursts of high-frequency discharges in epilepsy. This abnormal discharge may remain localized or it may spread to adjacent areas. An EEG recording may show a variety of atypical signs in epilepsy on which area of the brain is involved in producing abnormal discharge can be projected [12]. Glutamate is a principal excitatory amino acid neurotransmitter in the CNS mainly involved in epilepsy whereas γ-amino butyric acid is the major inhibitory amino acid neurotransmitter in the mammalian central nervous system [13, 14, 15]. Almost every area of brain contains GABA neurons [14]. GABA is essential for the overall balance between neuronal excitation and inhibition that is vital to normal brain function [16]. The major approach in treatment of epilepsy should be maintaining the balance between the factors which effect both the excitatory postsynaptic potential (EPSP) and postsynaptic potential (IPSP).The antiepileptic drugs can be grouped into sodium channel blockers, calcium current inhibitors, gamma-amino butyric acid (GABA) enhancers, glutamate blockers, carbonic anhydrase inhibitors, hormones, and drugs with unknown mechanisms of action [10].

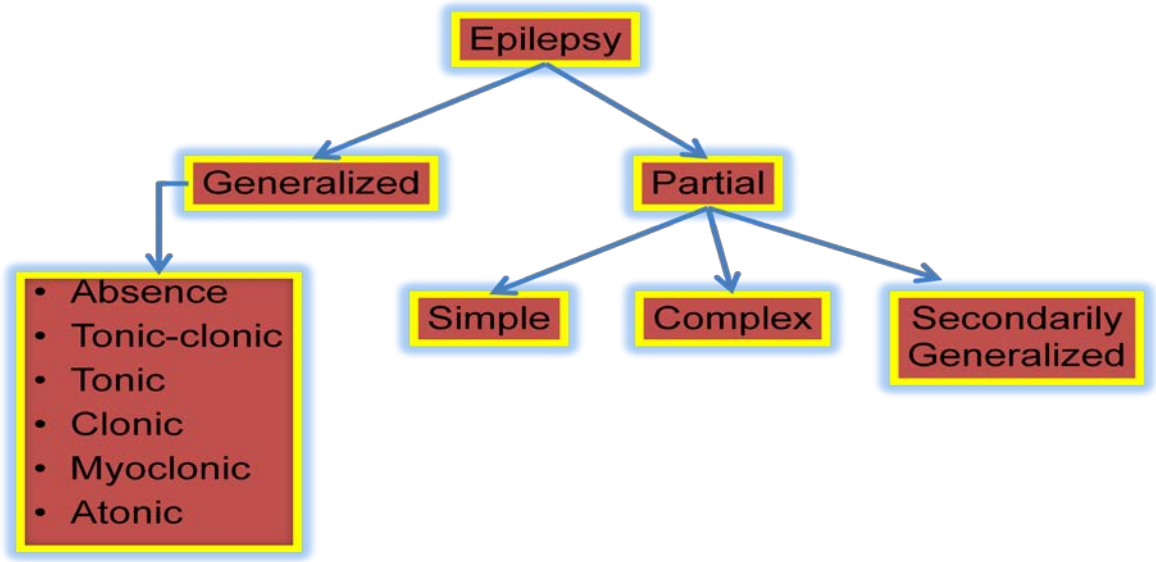


Fig. 1: *International Classification of Epileptic Seizures.*

Management of Epilepsy

Although several antiepileptic drugs (AEDs) are available to treat epilepsy, the treatment of epilepsy is still far from adequate [17]. Approximately in 70% of patients the symptoms of epilepsy are restricted by monotherapy with recent antiepileptic drugs (AEDs). In addition the epilepsy symptoms are not restricted with the use of newer available AEDs in over 20% of patients. As many as one-third of epilepsy patients continue to exhibit signs of seizure activity in spite of medical treatment with antiepileptic drugs (AEDs) [19]. The drawback of the existing therapy of epilepsy is that they possess fewer side effects, drug interactions and toxicity [20] (Table 1). However, the safety is now-a-days is a challenging factor for existing available AEDs [21]. In many cases even multi-drug therapy is not effective and neurosurgical procedures may be indispensable. Even with early onset of treatment and suppression of seizures, anticonvulsant drugs do not affect the progression or underlying natural history of epilepsy [22]. Besides, very high costs of new antiepileptic drugs have a major impact on overall expenses of epilepsy therapy. Drugs developed recently (gabapentin, lamotrigine, tiagabine, topiramate, vigabatrin, zonisamide) have failed to show significant clinical superiority [23].

Consequently a real need exists to develop new anticonvulsant compounds to cover seizures which are so far resistant to presently available drugs, i.e., drugs which prevent or treat epilepsy and not only its symptoms [24]. There is the need to explode the use of herbal therapy in treatment of epilepsy to attain the desired biological activity as the herbal therapy can act as potent AEDs with better safety and efficacy [25].

Table 1: *Adverse Effect of Synthetic Drugs having Antiepileptic Potential [5, 21].*

Drug	Side effects
Phenobarbital	Dizziness, lethargy, hypotension, aponea.
Phenytoin	Nausea, skin rashes, hyperglycemia, cardiac arrhythmia.
Sodium valproate	Hair loss, anorexia, drowsiness, nausea, vomiting.
Carbamazepine	Diplopia, drowsiness, headache, nausea, orofacial dyskinesia, arrhythmias, hallucinations, ataxia, liver dysfunction.
Clonazepam	Fatigue, drowsiness, ataxia.
Ethosuximide	Nausea, vomiting, headache, lethargy, drowsiness, euphoria, confusion, GI distress
Lamotrigine	Headaches, drowsiness, diplopia, ataxia, blurred vision.
Gabapentin	Headaches, drowsiness, diplopia, ataxia
Topiramate	Dizziness, drowsiness, nervousness, fatigue, weight loss
Vigabatrin	Drowsiness, dizziness, weight gain

Consequently a real need exists to develop new anticonvulsant compounds to cover seizures which are so far resistant to presently available drugs, i.e., drugs which prevent or treat epilepsy and not only its symptoms [24]. Plants may serve as the alternative sources for the development of new anticonvulsant agents. Many modern drugs are developed from phytochemical as such or taking phytochemical as lead molecules. The herbal drugs/remedies can make the anticonvulsant treatment more rationale and patient friendly due to less side effects, toxicity and drug interactions. In addition, more safety, tolerability, efficacy, and fewer expenses especially in long term therapy are other advantages with herbal anticonvulsants. The plants can act as an AEDS in treatment of epilepsy with better safety and efficacy [25].

Table 2: *Herbal Marketed Formulations of Epilepsy [25].*

HERBAL FORMULATIONS

Brand Name	Mfg company	Ingredients
APSA	IMIS	Withania somnifera, Hemamakshika Blasma, Rajatha Bhasma, Extract of Rasona, Vcha, Atimadhura, Mandukaparni, Jatamansi, Brahmi, Shatavari, Sarpagandha, Triphal, Jeerika, Guduchi
Ned forte	Chark	Akika bhasma, Mast extracts of Yashthimadhu, Brahmi, and Vacha
Zandopa	Zandu	Mucuna Pruriens
Raswatarishta	Baidyanath	Brahmi, Shatavar, Haritaki, Vidara, Ushri, Sauntha, Saunf, Laung Papal, Vacha, Ashvagandha, Bahera, Jaggery, Dachini
Chaturbhuj Ras	Baidyanath	Ras sindoor, Kasturi, Swarna Blasma, Manashila and Hartal, Ghrit Kumari
Chaturmukha Ras	Baidyanath	Parad, Gandhak, Lauha, Bhasma, Abhrak, Bhasma, Swarna Bhasma

(Vyawahare et al., 2007)

Plants As Anticonvulsants

The Plants -based medicines can be an alternate approach in treatment of epilepsy with improved safety profile when compared with the existing available AEDs [26]. Many drugs are developed with phytochemical or taking phytochemical as lead molecules. At present several herbal drugs have been reported to possess anticonvulsant property in animal experiments [27]. The herbal drugs/remedies can make the anticonvulsant treatment more rationale and patient friendly due to less side effects, toxicity and drug interactions. In addition, more safety, tolerability, efficacy, and fewer expenses especially in long term therapy are other advantages with herbal anticonvulsants [21]. Several plants used for the treatment of epilepsy in different systems of traditional medicine have shown antiepileptic activity when tested on animals' models (Table 2 and 3) and many such plants remain to be scientifically investigated. In past, attempts have been made to produce effective herbal AEDs from the plant origin but still the clinical trial has to be carried out in these drugs [17].

Table 3: *List of Plants Reported to Possess Anticonvulsant Property.*

Plant name	Family	Part used	References
Acosmium subelegans	Leguminosae	–	[28]
Afrormosia laxiflora	Leguminosae	Roots	[29]
Albizzia lebbeck	Mimosaceae	Leaves	[30]
Annona diversifolia	Annonaceae	Leaves	[31]
Artemisia dracunculus	Asteraceae	Aerial parts	[4]
Bixa orellana	Bixaceae	Leaves	[32]
Butea monosperma	Fabaceae	Flowers	[30]
Bryophyllum pinnatum	Lamiaceae	Leaf	[33]
Centella asiatica	Umbelliferae	Whole plant	[34]
Cestrum nocturnum	Solanaceae	Dried leaves	[35]
Citrus aurantium	Rutaceae	Flowers	[36]
Cotyledon orbiculata	Crassulaceae	Leaves	[37]
Crocus sativus	Iridaceae	Stigmas	[38]
Cymbopogon winterianus	Poaceae	Leaves	[39]
Cyperus articulates	Cyperaceae	Rhizomes	[40]
Delphinium denudatum	Ranunculaceae	Dried roots	[25, 26]

Desmodium adscendens	Papillionaceae	Leaves	[41]
Diospyros mespiliformis	Ebenaceae	Bark	[42]
Echinodorus berteroi	Alismataceae	Dried roots	[43]
Erythrina indica	Fabaceae	Leaves	[44]
Erythrina velutina,	Fabaceae	Stem bark	[45]
Eugenia caryophylla	Myrtaceae	Buds	[46]
Ferula gummosa	Apiaceae	Root	[47]
Ficus sycomorus	Moraceae	Stem bark	[48]
Gastrodia elata	Orchidaceae	–	[49]
Glycyhrrhiza glabra	Leguminosae	Roots	[50]
Heracleum crenatifolium	Apiaceae	Crushed seeds	[51]
Hibiscus rosa sinensis	Malvaceae	Flowers	[52]
Hoslundia opposite	Lamiaceae	Roots	[53]
Hypericum perforatum	Hypericaceae	Aerial parts	[54]
Hypoxis hemerocallidea	Hypoxidaceae	Corms	[55]
Kalanchoe crenata	Crassulaceae	Leaves	[56]
Laurus nobilis	Lauraceae	Leaves	[57]
Lavandula stoechas	Lamiaceae	Flowers	[58]
Leonotis leonurus	Lamiaceae	Leaves	[59]
Lippia alba	Verbenaceae	Aerial parts	[60]
Mimosa pudica	Mimosaceae	Leaves	[61]
Myristica fragrans	Myristicaceae	Seeds	[17]
Nardostachys Jatamansi	Valerianaceae	Roots	[62]
Nigella sativa	Ranunculaceae	Whole herb	[63]
Ocimum gratissimum	Lamiaceae	Leaves	[64]
Passiflora incarnata	Passifloraceae	Leaves	[65]
Persea Americana	Lauraceae	Leaves	[66]
Uncaria rhynchophylla	Rubiaceae	–	[67]
Vitex agnus castus	Lamiaceae	Fruit	[1]

Phytoconstituents with Anticonvulsant Potential

Many drugs are developed with phytochemical or taking phytochemical as lead molecules. Some phytoconstituents with anticonvulsant effects on different type of seizures are as follows:

Flavonoids

Flavonoids are made up of with the conjugation of phenyl-benzopyrones moiety with the glycone moiety available in plants [68]. 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 finding are supported by the available data which represents the change in the behavioral effects (anxiety, sedation and convulsion) in animals [16, 65]. Various flavonoids reported to have anticonvulsant effects are as follows:

Rutin

Rutin is a flavonoid of the flavonol type found in many plants such as buckwheat, apples and black tea [69]. 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 [65] (Figure 2A).

Apigenin

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 [68] (Figure 2B).

Goodyerin

It is a flavonol glycoside obtained from methanol extract of whole plant of *Goodyera schlechtendaliana* (Orchidaceae). It significantly prolonged the latency to 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 are still obscure [70].

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 [71].

Hispidulin

Hispidulin (4´, 5, 7-trihydroxy-6-methoxy-flavone) is obtained from the various species of *Artemisia* and *Salvia*. 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 [72] (Figure 2C).

Alkaloids

Sanjoinine A: It is one of the major alkaloid compounds from *Zizyphi spinosi* semen (Rhamnaceae) obtained in methanol extract whole plant. 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 [73] (Figure 2D).

Nantenine

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 [74] (Figure 2E).

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 might be through its interaction with benzodiazepine receptors [75].

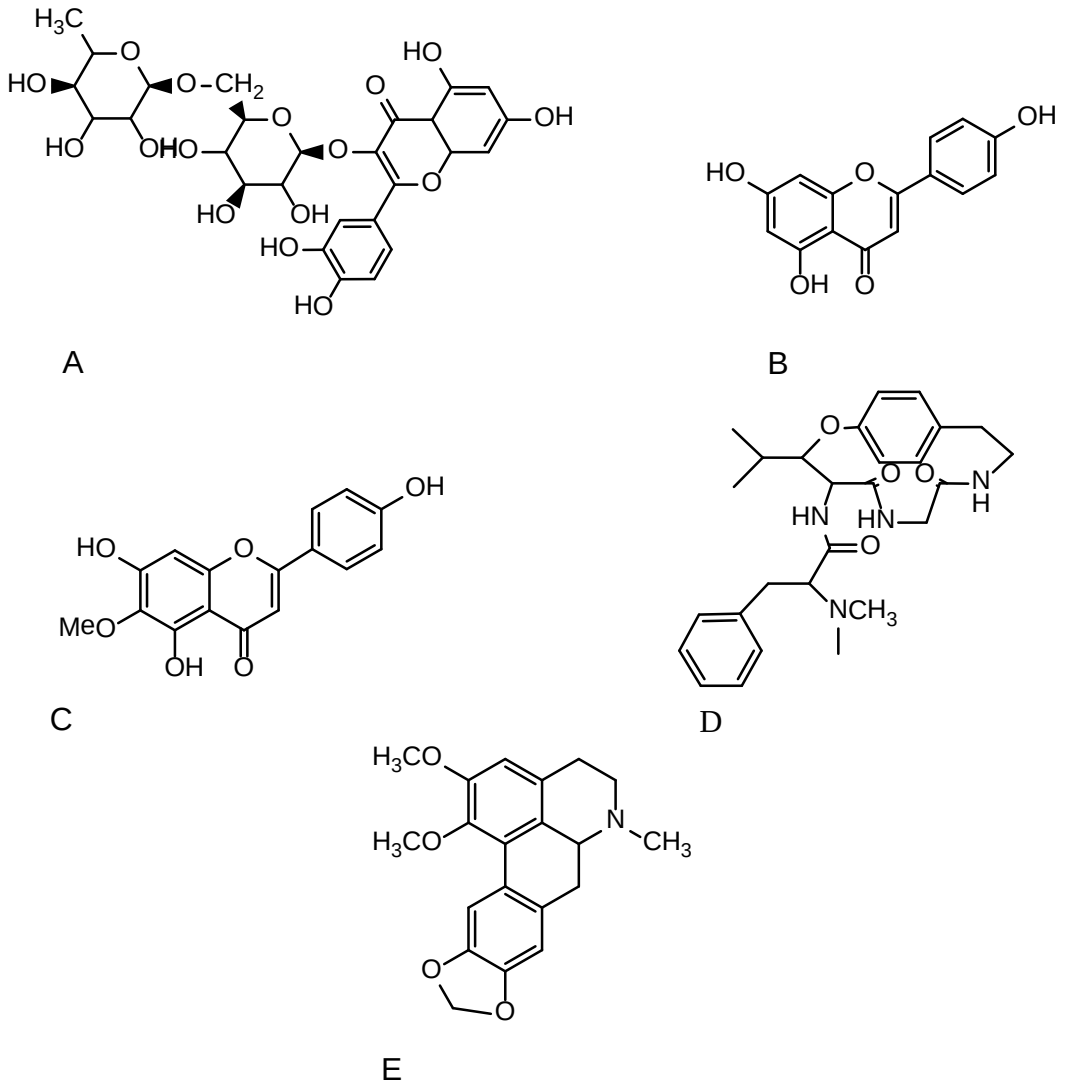


Fig. 2: *Structures of Alkaloids and Flavonoids with Anticonvulsant Activities.*

Terpenes

Betulin

It is a pentacylic triterpene alcohol with a lupane skeleton, also known as betulinol, betuline or betulinic alcohol. This is mainly present in the plants of family Marcgraviaceae which includes shrubs, small trees and lianas in tropical and Central America and West Indies. Betulin significantly antagonized 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 [76] (Figure 3A).

Safranal

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 [77, 78] (Figure 3B).

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 lessened lethality in mice. The anticonvulsant activity of ursolic acid may be mediated via the GABA-ergic system [79].

Linalool

It is a monoterpene compound reported to be present in essential oils of various aromatic species. Linalool showed a dose dependent non-competitive inhibition of [^{3}H] MK801 (a NMDA antagonist) binding but no effect on [^{3}H] muscimol (a $GABA_A$ agonist), which suggests that linalool directly interacts with NMDA receptor complex producing anticonvulsant effect [80].

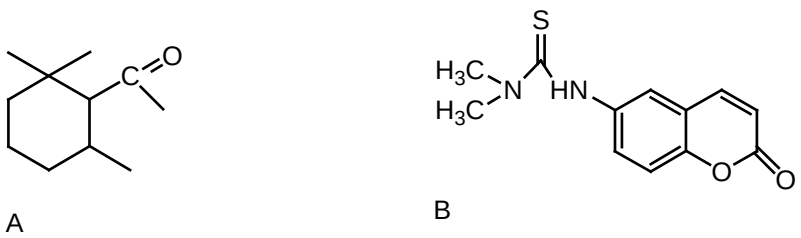


Fig. 3: *Structures of Terpenes with Anticonvulsant Activities.*

Lactones

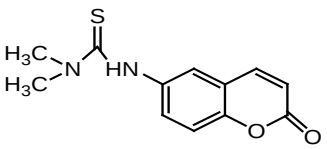
Lactones are common components in essential oil.

γ-decanolactone

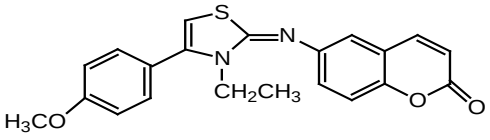
This lactone is present in the essential oil of *Aeollanthus suaveolens* (Lamiaceae). It showed marked anticonvulsant effect in PTZ induced convulsions and also prevented tonic convulsions in transcorneal electroshock induced seizures in mice [81] (Figure 4).

Coumarins

Some newly substituted coumarins tested for the anticonvulsant activity. These include coumarinylthiazolines, coumarinylthiazolidin-4-ones and chromenothiazoles. In PTZ test, among thioureas, *N*-ethyl thiourea (Figure 4A) showed maximum protection of 60% whereas the compound 3-ethyl-4-(4-methoxyphenyl)-2-(2-oxo-2H-chromen-6-ylimino)thiazoline (Figure 4B) 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 (Figure 4C) 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 [24].



A



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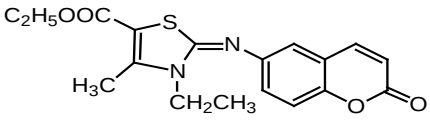

C

Fig. 4: *Structure of Some Coumarins Derivatives with Anticonvulsant Activities.*

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 (Figure 5A) and 6-chloro-2-((ethyl(2-hydroxyethyl)amino)methyl)-9H-xanthen-9-one (Figure 5B) showed anticonvulsant protection in mice. In PTZ test, compound (S)-chloro-2((1-hydroxypropan-2-ylamino) methyl-9H-xanthen-9-one (Figure 5C) 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 [82].

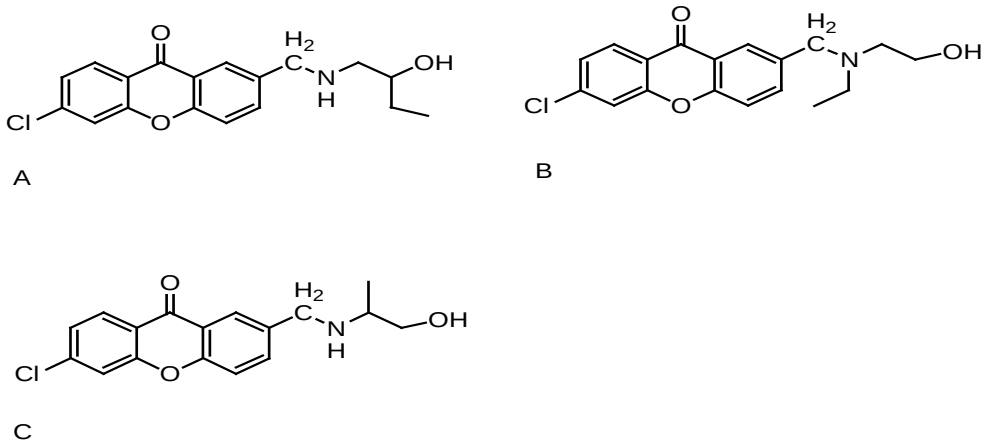

Fig. 5: *Structures of Some Xanthone Derivatives with Anticonvulsant Activities.*

Others

Vanillyl Alcohol

It is an analogue of vanillin and a component of *Gastrodia elata* (Orchidaceae} which is 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 [83] (Figure 6A).

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 [84] (Figure 6B).

Thymoquinone

It is the major constituent of *Nigella sativa* (Ranunculaceae) seeds. It prolonged the latency of myoclonic seizures in 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 [63]

(Figure 6C).

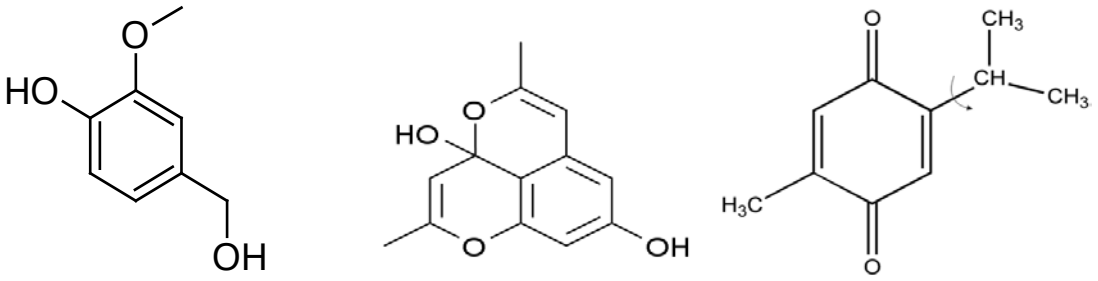

Fig. 6A: *Vanillyl Alcohol.* ***Fig. 6B:*** *Barakol.* ***Fig. 6C:*** *Thymoquinone.*

Fig. 6: *Structure of Other Compound having Antiepileptic Property.*

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