Review Article

PHYTOMEDICINE: INDIAN MEDICINAL PLANTS AS A SOURCE OF ANTICONVULSANT

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ABSTRACT

Medicinal plants have contributed considerably to the ethnotherapeutics and drug development all over the world, provides potential leads to find active and therapeutically useful compounds. From ancient times to the present day in India plants have been used as a source of medicine. Epilepsy is a chronic neurological disorder it affects people of all ages, currently available antiepileptic drugs has some adverse effects therefore phytomedicine provides idea for producing new antiepileptic drugs. This review summarizes medicinal plants used to prevent epilepsy or those possess anticonvulsant properties some of the plants are used as singly while others are multiherbs. The search for new and better compounds is constantly ongoing, but the ideal high-efficacy/low- frequency of adverse-effect drugs still need to be identified.

Keywords: Epilepsy, Anticonvulsant, Phytomedicine, Antiepileptic drugs.

BACKGROUND

Epilepsy is one of the most common chronic neurological disorders characterized by recurrent seizures with a worldwide prevalence of 0.5 - 5%.[1] Approximately, 45-100 million people worldwide suffer from active epilepsy.[2] The prevalence rate of epilepsy in India varies between 4.15 and 7.03 per 1000 population. The results from India were higher, and reached 60·0 per 100 000 person-years.

Epilepsies are classified five ways

First cause or etiology.

Observation manifestation.

Location in the brain where the seizures originate.

Identifiable medical syndromes.

Events that triggers the seizures.

Anything that disturbs the normal pattern of neuron activity from abnormal brain development to trauma to illness leads to seizures. Epilepsy has many possible causes. Seizures are classified into two groups focal seizures begin in one area of the brain are due to abnormal neuronal activity on both sides of the brain. In some cases the seizures are clearly linked to infection, head trauma, brain tumors, stroke or other identifiable problems. However seizures have also been reported to be precipitated by a wide range of drugs including antidepressants, antibiotics, levodopa, antipsychotics, thiazide diuretics.[3] The cause or etiology of epilepsy still remains somewhat unclear. India has a rich history of medicinal herbs used for treating various diseases. India is known as the emporium of Medicinal plants due to the occurrence of several thousands of medicinal plants in the different bioclimatic zone. Ayurveda and siddha systems of medicine are the traditional heritage of India. Many times tested drugs from medicinal plants cures for various diseases and disorders to which there is no answer in modern medicine till today, more than half of the patients treated with established antiepileptic drugs (AEDs) in monotherapy will experience adverse effects.[4] We discuss a list of Indian medicinal plants used for the treatment of epilepsy or those posses anticonvulsant properties.

METHODOLOGY

A literature search was carried from Science Direct and various other journals following were the keywords used: Indian medicinal plants used to treat epilepsy, anticonvulsant, phytotherapy, herbs possess anticonvulsant properties. Several Indian Medicinal plants books were also searched.[5-7]

INDIAN MEDICINAL PLANTS POSSES ANTICONVULSANT ACTIVITY

Ethanolic root extract of *Carissa carandas* (Apocynaceae) are shown in Figure 1 (200 and400 mg/kg) significantly reduced the duration of seizures induced by maximal electroshock (MES) on the mice and also protected animals from pentylenetetrazole-induced tonic seizures and significantly delayed the onset of tonic seizures produced by picrotoxin and N-methyl-dl-aspartic acid. The extract had no effect on bicuculline-induced seizures.[8]

Aqueous leaf extract of *Rauvolfia vomitoria* (Apocynaceae) are shown in Figure 2 (100 and 200 mg/kg, i.p) was tested for its anticonvulsant activity against strychnine, picrotoxin and pentylenetetrazole induced seizures. The extract, at a dose of 200 mg/kg, prolonged the onset of seizures in the male albino mice.[9]

Balanites roxburghii (Zygophyllaceae) are given in Figure 3 is a medicinal herb, found in Bengal, drier parts of India and Myanmar Thirupathi *et al*. studied the anticonvulsant effect of methanolic extract from the pericarpium of *Balanites roxburghii* (100 or 300 mg/kg) orally administrated on maximal electroshock (MES) or Pentylenetetrazole (PTZ) in male mice. The extract at 300 mg/kg dose suppressed hind limb tonic extensions (HLTE) induced by MES and also exhibited protector effect in PTZ-induced seizures.[10]

Unmadnashak Ghrita (UG) is an ayurvedic formulation containing powdered dried gum resin of *Ferula narthex* (6 g), dried leaves of *Gardenia gummifera* (6 g), fruits of *Ellataria cardamom* (6 g) and aerial parts of *Bacopa monneri* (6 g) were shown in (Figure 4,5,6 & 7) were mixed and cow's ghee (clarified butter fat) (76 g) and Achliya *et al*., tested for its anticonvulsant activity of Unmadnashak Ghrita' (UG) (100, 200, 300 and 500mg/kg p.o.) against Pentylenetetrazole and Maximal electroshock induced seizures. The formulation inhibited Maximal electroshock and Pentylenetetrazole induced seizures in mice.[11]

Hosseinzadeh and Parvardeh was investigated for anticonvulsant effects of thymoquinone, the major constituent of *Nigella sativa* (Ranunculaceae) (Figure 8) seeds against pentylenetetrazole (40 and 80 mg/kg) and maximal electroshock induced seizure models. In pentylenetetrazole induced seizure model prolonged the onset of seizures and reduced the duration of myoclonic seizures and in maximal electroshock failed to reduce the duration of seizure, whereas exhibited a complete protection against mortality.[12]

Anticonvulsant activity of methanolic extract of *Moringa oleifera* (Figure 9) was studied significant protection against pentylenetetrazole (80 mg/kg, i.p.) and strychnine (2 mg/kg, i.p) induced animals. The extract protected potentiated significantly the sleeping time induced by pentobarbitone sodium and diazepam. Central Nervous System depressant nature of methanolic extract was reported. Further studies are necessary analyse the potential effectiveness of extract.[13]

Ngo Bum *et al.,* found that the decoction of *Mimosa pudica* (Fabaceae) (Figure 10) leaves given intraperitoneally at dose of 1000–4000 mg/kg protected mice against pentylentetrazol and strychnine-induced seizures and had no effect against picrotoxin-induced seizures NMDA prevents mice from turning in a dose-dependent fashion: 12.5%, 37.5% and 62.5% of the animals did not show turning behavior at the doses of 1000 mg/kg, 2000mg/kg and 4000 mg/kg i.p but non-protected animals, the time to the onset of the turning behavior was delayed significantly only at dose of 2000 and 4000 mg/kg.[14]

Aqueous extract of *Centella asiatica* (Mackinlayaceae) are shown in Figure 11 (100 and 300 mg/kg) was tested for its anticonvulsant activity against pentylenetetrazole (30 mg/kg i.p). The extract at the dosage of 300 mg/kg orally decreased the PTZ kindled seizures and improvement in the learning deficit and low dose (100 mg/kg) failed to improve the seizure, it improved only the learning deficit.[15]

Kasture *et al*., reported ethanol extracts of leaves of *Albizzia lebbeck* (Fabaceae) (Figure 12) and flowers of *Hibiscus rosasinesis* (Malvaceae) (Figure 13) and the petroleum ether extract of flowers of *Butea monosperma* (Fabaceae) (Figure 14) (100 mg/kg i.p) possess anticonvulsant activity against maximum electroshock and pentylenetetrazole induced convulsions in mice but the fractions failed to protect animals from strychnine induced convulsion.[16]

Anticonvulsant activity of petroleum ether extract of *Morinda tinctoria-Roxb* (Rubiaceae) (Figure 15) was evaluated in albino mice (200,400 and 600 mg/kg i.p) against seizure induced by electroshock (42 MA, 0.2 sec) and pentylenetetrazole (80 mg/kg). The extract showed significant delay on the onset of convulsion on a dose depended manner.[17]

Balamurugan *et al*., reported aqueous root extract of *Withania somnifera* (Solanaceae), leaves of *Bacopa monnieri*, *Chlorophytum borivillianum* (Agavaceae), rhizomes of *Curcuma longa* (Zingiberaceae), *Glycyrrhiza glabra* (Fabaceae) and barks of *Terminalia arjuna* (Combretaceae) (500 mg/kg i.p) are shown in Figure 16,17,18,19 & 20 protected rats from convulsion induced by maximum electroshock which proves polyherbal extract was providing a beneficial effect in controlling MES induced seizures. The levels of biogenic amines such as dopamine, noradrenaline and serotonin in the forebrain regions were restoration was observed in the polyherbal extract treated animals.[18]

An alcoholic extract of aerial parts of *Capparis deciduas* (Capparaceae) (Figure 21) including flowers and fruits, significantly inhibited the pentylenetetrazole-induced convulsions and a decrease in the percentage of animals developing convulsions was reported by Manoj Goyal *et al*.,.[19]

Tumeric is a rhizomatous herbaceous perennial plant of the ginger family, Zingiberaceae. It is native to tropical south asia. Curcumin is the principal curcuminoid present in this curcumin was studied for its anticonvulsant activity (50, 100 and 200 mg/kg, orally (p.o) against increasing electroshock test, elevated plus maze and actophotometer in mice.[20]

Bharal *et al*., found that curcumin in a dose of 100 mg/kg significantly increased the seizure threshold in ICES test on both acute and chronic administration, whereas the same dose on acute administration showed anxiogenic effect on elevated plus maze and actophotometer test but later disappears on chronic administration.[21]

Benkara malabarica are indicated in Figure 22 root's methanol extract was unable to protect against strychnine induced convulsion but protection was

observed against isoniazide induced convulsion group was reported by Nibha Mishra *et al*.,.[22]

Figure 1: ***Carissa carandas***

Figure 2: ***Rauvolfia vomitoria***

Figure 3: ***Balanites roxburghii***

Figure 4: ***Ferula narthex***

Figure 5: ***Gardenia gummifera***

Figure 6: ***Ellataria cardamom***

Figure 7: ***Bacopa monneri***

Figure 8: ***Nigella sativa***

Figure 9: ***Moringa oleifera***

Figure 10: ***Mimosa pudica***

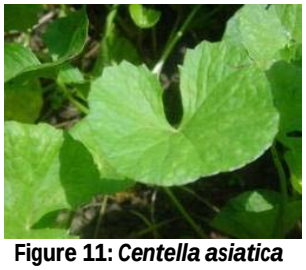

Figure 11: ***Centella asiatica***

Figure 12: ***Albizzia lebbeck***

Figure 13: ***Hibiscus rosasinesis***

Figure 14: ***Butea monosperma***

Figure 15: ***Morinda tinctoria-Roxb***

Figure 16: ***Withania somnifera***

Figure 17: ***Chlorophytum borivillianum***

Figure 18: ***Curcuma longa***

Figure 19: ***Glycyrrhiza glabra***

Figure 20: ***Terminalia arjuna***

Figure 21: ***Capparis deciduas***

Figure 22: ***Benkara malabarica***

Figure 23: ***Drosera burmannii***

Figure 24: ***Wedelia chinesis***

Figure 25: *Sphaeranthus indicus*

The oral administration of ethanol extract of *Drosera burmannii* are shown in Figure 23 (300 mg/kg and 500mg/kg) delayed the onset of seizures and decreased the duration of seizures. Hence *Drosera burmannii* exhibited anticonvulsant activity. [23]

Mishra *et al* reported the ethanolic extract (250,500 mg/kg) and aqueous extract (250, 500 & 700mg/kg) of *Wedelia chinesis* (Figure 24) showed anticonvulsant activity against pentelyenetetrazole and Maximum electroshock induced convulsion but found less significant than standard drug.[24]

Hydroalcoholic extract of *Sphaeranthus indicus* (Figure 25) showed anticonvulsant activity against pentelyenetetrazole and maximum electroshock, 500 mg/kg of *Sphaeranthus indicus* was found to significantly decrease the duration of the hind limb tonic extensor phase in MES-induced seizures whereas the lower dose(100 and 200 mg/kg) has not give any protection (100, 200 and 500 mg/kg). In PTZ induced seizure dose dependents reduction in the duration of the first clonic convulsion in mice was seen.[25]

Novel approach to find out antiepileptic drug target is to consider the protein product of genes associated with epilepsy syndromes in animals and humans. The genes associated with epilepsy syndromes mostly encode ion channels. [26, 27]

Table 1: Voltage-Gated Na^+ channels, Genes involved in epilepsy syndromes

Gene	Channel Subunit	Epilepsy Syndromes
SCN1A	$Na_v1.1$	Severe Myoclonic Epilepsy of Infancy, generalized epilepsy with febrile seizures plus.
SCN2A	$Na_v1.2$	Generalized epilepsy with febrile seizure type 2 benign familial neonatal infantile seizures
SCN1B SCN8A	$Na_v1.6$	Generalized epilepsy with febrile seizures type 1

Table 2: Voltage-Gated Ca^{2+} channels, Genes involved in epilepsy syndromes

Gene	Channel Subunit	Epilepsy Syndromes
CACNA1S	$Ca_v1.1$	
CACN1C	$Ca_v1.2$	
CACNA1D	$Ca_v1.3$	
CACNA1F	$Ca_v1.4$	
CACNA1A	$Ca_v2.1$	Absence epilepsy with ataxia episodic ataxia type 2 with epilepsy
CACNA1B	$Ca_v2.2$	
CACNA1E	$Ca_v2.3$	
CACNA1G	$Ca_v3.1$	
CACNA1H	$Ca_v3.2$	
CACNA1I	$Ca_v3.3$	
CACNH2D1	α2- δ subunit	
CACNH2D2		
CACNB1-4	β subunit	
CACNG1-7	γ-subunit	
EFHC1	Ca_v 2.3	
SNAP25	High voltage activated	Juvenile Myoclonic epilepsy

Table 3: Voltage-Gated K^+ channels, Genes involved in epilepsy syndromes

Gene	Channel Subunit	Epilepsy Syndromes
KCNA1	$K_v1.1$	Episodic ataxia type1with myokymia and partial seizures
LGI1		
KCNAB2	$K_v1.1$,$K_V1.4$,$K_V\beta$ $K_V\beta_2$ assembles with K_V1	Autosomal dominant lateral temporal lobe epilepsy with auditory features.
$KCNQ_2$	K_v 7.2	Benign familial neonatal convulsion
$KCNQ_3$	K_v 7.3	Absence
KC_1 NJ3	K_v 3.1	Genetic association but no functional effects of mutation
KCNJ6	K_v 3.2	
KCNJ1O	K_v 4.1	Tonic-clonic seizures
KCNJ11	K_v 6.2	Generalized epilepsy with paroxysmal dyskinesia Childhood absence
KCNMA1	K_{ca} 1.1	
KCNKG	TASK3	

Table 4: Seizures in animal models were induced by several methods

Pentylenetetrazole [PTZ] induced seizures
Maximum Electric Shock [MES] induced seizures
Picrotoxic or Strychine induced convulsions
Lithium Pilocarpine induced status epileptics
Isonicotinic hydrazide acid [INH] test
Bicuculline or N-methyl-d-aspartic acid [NMDA]

Table 5: Adverse effects of Antiepileptic Drugs[28]

Drug name	Indications	Adverse Effects
Phenobarbital	Focal + generalized seizures	Allergic reactions, Sedation ataxia, Impotence, Confusion, Irritability, Depression, Facial Coarsening, Vitamin D Deficiency
Phenytoin	Focal + generalized seizures	Sedation, Ataxia, Confusion blooddyscrasis, Hepatitis, Renal failure, Osteomalacia gingival hypertrophy, Facial coarsening, Neuropathy, Hypertension
Carbamazepine	Focal + generalized seizures	Visual blurring, ataxia,sedation, skin rash, abnormal liver function tests toxic effects of expoxide psychiatric reactions.
Valporic acid	Focal + generalized seizures	Liver failure, Metabolic coma, Hair loss, Pancreatitis, Hepatitis thrombo and Pancytopenia, Weight increase.
Oxcarbazepine	Focal onset	Nausea and vomiting, rash, Dizziness, Somnolence, Hyponatermia.
Lamotrigine	Focal + generalized adjunctive	Nausea, Erythema, Headache, Insomnia, Drowsiness, Dizziness, Ataxia tremor, Agitation, Confusion, Hallucinations and Psychosis.
Gabapentin	Focal onset, adjunctive	Dizziness, ataxia, nystagmus, headache, tremor, rhinitis, nausea and vomiting, fatigue.
Lavetiracetam	Focal onset, adjunctive	Dizziness, aggression, headache, asthenia, weight gain.
Pregabalin	Focal onset, adjunctive	Sedation, dizziness, ataxia, asthenia, weight gain, tremor blurred vision, dry mouth, myoclonus.

RESULTS

Only from *Curcuma longa*, curcumin the bioactive constituents was tested *in vivo* hence in future the isolation of bioactive compounds from the above mentioned plants have to be isolated. All plants used singly some has been used in combination. Especially Unmadnashak Ghrita include: *Ferula narthex*, leaves of *Gardenia gummifera*, fruits of *Ellateria cardamom* and aerial parts of *Bacopa monnieri*. Same way aqueous root extracts of *Withania Somnifera*, leaves of *Bacopa monnieri* and *Chlorophytum borivillianum*, rhizomes of *Curcuma longa*, *Glycyrrhiza glabra* and barks of *Zerminalia arjuna*. Various methods has been used to induce epilepsy on animal model, the most common methods used to induce seizure in animal models was given in Table 4. The present review revealed the anticonvulsant activity of Indian medicinal plants.

Table 5. Summarizes adverse effects caused by the drugs used for epilepsy *in vivo* studies revealed all the plants possess anticonvulsant activity. Few literatures reported medicinal plants possess anticonvulsant activity.[29] Plants that have been tested for their anticonvulsant activity by *in vivo*/*in vitro* studies have also been reported earlier.[30] Already reviews have been conducted by spontaneous excitatory postsynaptic currents (EPSCs) sustained repetitive fixing (SRF) *in vitro* studies. [31, 32]

CONCLUSION

The present review revealed the anticonvulsant activity of Indian medicinal plants those have been tested *in vivo*. Crude extracts was used for *in vivo* studies, the bioactive components from all those plants have to be isolated and tested *in vivo*/*in vitro*, molecular interactions with various epileptic targets have to be studied which provides vital results. Therefore in future more number of Indian medicinal plants that possess anticonvulsant activity is still remained to be studied. Herbal medicine will provide better treatment for epilepsy with lesser adverse effects. Thus, this review will be useful to isolate new bioactive compounds from these plants which serve as new antiepileptic drug with better results.

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