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Review Article

Anticonvulsant Herbal Drugs Have the Least Negative Drug Interactions and Side Effects:A Review

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ABSTRACT
Epilepsy is the second most common neurologic disorder after stroke. Approximately 1% of the world's population has epilepsy, is a condition where the patient suffers from recurrent seizures. Control to seizures numerous conventional drugs came into existence. Most of the epileptic patients need polytherapy of conventional anticonvulsants and still not 100% cured. The major drawback due to these agents is their chronic side effects and drug interactions which restrict its use. On the other hand nature has provided us plants to be used as natural remedy for diseases with least side effects and insignificant drug interactions. This has motivated the researchers towards herbal remedy for antiepileptic activity. In this review herbal and nonherbal drugs have been discussed with more emphasis on the research advancements of traditional or herbal anticonvulsants.

Keywords: Anti-convulsant, Tonic clonic seizures, Barbiturates, Epilepsy.

INTRODUCTION

The conventional therapy permits control of seizures in 80% of the patients but millions still suffer from uncontrolled epilepsy. Epilepsy is the disorder that is associated with significant psychological and social consequences[1]. It is a untidy state of C.N.S characterized by paroxysmal cerebral dysrhythmia and having brief episodes of loss or disturbance of consciousness with or without characteristic body movement. [2] Existing anti seizure drugs provide adequate seizure control in about 2/3 of patients. A fraction of the antiepileptic population is resistant to all available drugs. Single therapy is often not responsive in treating most of the epileptic patients, so combination of the drugs are given, which leads to more severe adverse effects.

Until 1990, approximately 16 antiseizure drugs were available and 13 were divided into quite similar groups i.e. barbiturates, hydantoin, oxazolidinediones, succinimide and acetylureas. Numerous choices of antiepileptic drugs are available to treat various types of seizures. The conventional antiepileptic drugs commonly used like barbiturates, carbamazepine and phenytoin fail to fully control seizure activity in few patients so combination with newer antiepileptic drugs (AED) are given, which further enhances the frequently caused side effects[3]. Antiepileptic drugs act by mainly 3 mechanisms[4]

Enhancement of GABA action

Phenobarbitone and Benzodiazepine enhance the action of GABA receptors thus facilitating GABA mediated opening of chloride channels. Vigabatrin acts by inhibiting the enzyme GABA transaminase which is responsible for inactivating GABA. Tiagabine inhibits GABA uptake thereby increasing the action of GABA as inhibitory transmitter.

Inhibition of Sodium channel function
Phenytoin, Carbamazepine, Valproate affect membrane excitability by an action on voltage dependent sodium channels which are necessary for generation of action potential.

Inhibition of Calcium channel function
Ethosuximide specifically blocks the T type calcium channels, activation of which is believed to play a role in rhythmic discharge associated with absence seizures. The table (01) shows the side effects of commonly used conventional drugs[5]. Apart from the side effects, vast number of drug interactions is seen with almost all current antiepileptic drugs[6]. Few of the interactions are mentioned in the table [02].

Table 1: Side effects of commonly used conventional drugs

DRUG	SIDE EFFECTS
Diazepam	Sedation, thromboflebitis, lowering of blood pressure, respiratory depression
Carbamazepine (iminostilbene)	Dizziness, ataxia, drowsiness, hallucinations, dermatologic sweating, abdominal pain, genitourinary albuminaria, hypotension, liver dysfunction, urticaria, diplopia etc.
Phenobarbitone, Mephobarbitone	Dizziness, lethargy, hypotension, apnoea, megaloblastic anemia, Liver damage , ataxia, hypoventilation etc.
Phenytoin, Ethotoin	Nausea, skin rashes blood dyscarasias, hyperglycemia cardiac arrhythmias, Steven Johnson syndrome, .
Gabapentin	Mild sedation, tiredness, dizziness and unsteadiness.

Table 2: Drug interactions of current antiepileptic drugs

Antiepileptic drug	Other drugs	Interactions
Barbiturates	Caffeine	Reduces or abolishes the hypnotic effect of pentobarbitone
	Cimetidine /Ranitidine	Pentobarbitone reduces the absorption of cimetidine while cimetidine increases metabolism of pentobarbitone
	Codeine	Increases serum level of pentobarbitone.
	Felbamate	Increases serum level of pentobarbitone.
	Miconazole	Reduce in the activity of rifampicin by increase in the clearance.
	Rifampicin	Reduce in the activity of rifampicin by increase in the clearance.
	Sodium valproate	Decrease in serum Phenobarbitone level.
Carbamazepine	Allopurinol	Increase in serum levels of carbamazepine.
	Cholestyaramine/ Colestipol	Reduction in absorption of carbamazepine.
	Cimetidine / Ranitidine	Marked increase in serum carbamazepine levels leading to toxicity
	Diuretics	Marked increase in serum carbamazepine levels leading to toxicity
	Isoniazid Metronidazole Primidone	Carbamazepine levels are reduced leading to its poor seizure control
Phenytoin	Antacids	Reduced serum phenytoin levels and thus loss of seizure control.
	Chlorpheniramine	Phenytoin intoxication.

Phytomedicine consists of many chemical constituents with complex pharmacological effects on the body. They have been used continuously for many decades in a way different from those of nonherbal medicine prescribing. It is true that many nonherbal drugs or their precursors are derived from plants, but still there is a fundamental difference between administering a pure chemical and the same chemical in plant matrix[7]. Advancements in Herbal Anticonvulsants are described below:

Aqueous extract of *Leonotis leonurus* L possessed anticonvulsant activity against PTZ (90 mg/kg), Picrotoxin (8 mg/kg), N-methyl, DL aspartic acid (400 mg/ kg) and Bicuculline (20 mg/kg) induced seizures[8]. Ethanol extract and aqueous fraction of *Delphinium denudatum* showed anticonvulsant activity against MES, PTZ, Bicuculline and Picrotoxin induced seizures[9]. The ethanolic extract of leaves of *Bauhinia* showed anticonvulsant effect on MES and PTZ induced seizures in albino male mice at different dose levels: 100, 250, 500 mg/kg I.P[10].

Mucuna pruriens from Fabaceae family has anticataleptic and antiepileptic activity in its ethanolic extract. *Mucuna pruriens* at a dose of 100mg/kg has significant anticataleptic and antiepileptic activity in Haloperidol induced catalepsy, MES and Pilocarpine induced status epilepticus (PISE). [11] A study with methanolic and aqueous extracts of leaves of *Anacardium occidentale* reported its anticonvulsant activity against MES and PTZ induced convulsions in mice. This study further demonstrated that 500 mg/kg body weight of both methanolic and aqueous extract of *Anacardium occidentale* significantly reduce the onset and duration of seizures induced by MES and also protected animals from PTZ induced tonic seizures[12]. *Nigella sativa* seeds have anticonvulsant effect against PTZ. The study claimed that *Nigella sativa* has thymoquinone, responding for its anticonvulsant activity. Thymoquinone at a dose of 40 mg/kg & 80 mg/kg prolong the onset of seizures induced by PTZ, not MES. [13] Essential oils are of great importance. This has been proved by fruits of *Pimpinella anisum* which suppressed the tonic clonic convulsions in mice induced by PTZ & MES[14].

The rhizomes of *Smilax china* Linn, mentioned in Ayurveda, Siddha and Unani system of medicine have been used to treat epilepsy, insanity, syphilis, colic disease and skin disease. The study revealed the anticonvulsant effect of ethanolic extract of rhizomes of *Smilax china* against seizures induced by MES & PTZ. It was reported that the duration of hind leg extension in MES test was reduced significantly by ethanolic extract at dose level of 400 mg/kg & ethyl acetate fraction at 200 & 400 mg/kg. In PTZ model, the seizure latency was prolonged by all test groups[15].

Pretreatment with methanolic extract of roots of *Moringa oleifera* caused significant protection against strychnine & PTZ induced convulsions[16]. Aqueous methanolic extract of *Lavandula stoechas* flowers significantly reduced the severity of convulsions induced by PTZ at a dose of 600 mg/kg. Further it was reported that it caused a dose dependent (0.1 mg/ml) relaxation of spontaneous contraction, suggesting Ca +2 channel blockade[17]. Stem bark of *Mitragyna africanus* showed anticonvulsant effect against Strychnine (2 mg/kg) induced convulsions in rats. It

caused protection by increase in period of onset of convulsions & simultaneously reduced number of episodes of spam[18]. *Holorrhena antidysenterica* is a plant common in the forests of tropical Himalayas, Assam, Uttar Pradesh & Travancore. The plant has various uses like diarrhea, blood dysentery, diabetes, haematemesis, acute rheumatism, astringent, and convulsions. The study revealed that ethanolic extract of 250 & 500 mg/ kg p.o significantly reduced the duration of seizures induced by MES & also protected animals from tonic seizures induced by PTZ. Further it significantly delayed the onset of tonic seizures induced by PTZ. [19] *Cleome rutidosperma* Linn is found in the tribal areas of Salipur (India) and is used as stimulant, antihelmintic, antiscorbutic, rubifacient, vesicant, anticonvulsant and carminative. Different solvents like ethanol, petroleum ether, diethyl ether, ethyl acetate, n-butanol were used to prepare extract of different aerial parts of the plant for anticonvulsant activity. It was concluded that all except ethanol extract were able to reduce strychnine induced tonic convulsions.

Ocimum gratissimum is a small shrub known as scent leaf, tea bush and is used in the treatment of diarrhea, febrifuge, antimalarial, insect repellant skin infections & conjunctivitis. The study reported that the extracts and fraction increased the latency of tonic clonic seizures induced by PTZ. Open field test performance showed reduced frequency of line crossing, center square entries, rearing against wall. They reported that the extracts of the plant possess anticonvulsant properties[21].

Embelia ribes showed a significant inhibition of seizures induced by electroshock and PTZ in dose dependent manner and activity was comparable to phenytoin and diazepam. A CNS depressant activity was observed[22]. Table (03) and (04) shows few marketed brands available for conventional drugs and herbal drugs respectively[23, 24].

Table 3: Few marketed brands available for conventional drugs

SALT	BRANDS	COMPANY
Sodium Valproate	Epilex	Abbott
	Valparin alkalets	Torrent
Carbamazepine	Mazetol	Sarabhai Piramel
	Tegretal	Torrent
Clonazepam	Clotrin	Stadmed
	Epitril	Novartis
Phenytoin sod	Eptoin	Abbott
	Epsolin	Cadila Healthcare
Phenobarb	Luminal	Bayer
	Gardenal	Nicholas

Table 4: Few marketed brands available for herbal drugs

BRAND	COMPANY	INGREDIENTS
APSA	IMIS	Withania somnifera, Hemamakshika Blasma, Rajatha Blasma, Extract of Rasona Vacha, Atimadhura, Mandukaparni, Kushta, Jatamansi, Parasika Yavani, Brahmi, Shatavari, Sarpagandha, Triphal, Jeeraka, Krishana Beeja,Shirisha Beeja,Guduchi And Apapajitha
Ned forte	Charak	Akika Bhasma, Mass Extracts of Yashthimadhu, Brahmi, and Vacha
Zandopa	Zandu	Mucuna Pruriens
Raswatarishta	Baidyanath	Brahmi, Shatavar, Vidara, Haritaki, Ushri, Sontha, Saunf, Nishoth, Laung Papal. Ashvagandha Bahera Giloe, Vidanga, Dachini, Dhataki, Jaggery (Gud).
Chaturbhuj Ras	Baidyanath	Ras Sindoor, Kasturi, Swarna Blasma, Manashila and Hartal, Ghrit Kumari
Chaturmukha Ras.	Baidyanath	Parad, Gandhak, Lauha, Bhasma, Abhrak, Bhasma, Swarna Bhasma

Drug Withdrawal

After a period of atleast 2-3 years free from seizures, withdrawal of antiepileptic drug therapy can be considered. Some seizures are known to remit spontaneously like benign epilepsy and petit mal whereas others never remit like juvenile myoclonic epilepsy. In many types of epilepsy the outlook is less certain and only general indicators are available. The following factors can be important:

1. Type of seizure disorder: major seizures are more easily controlled.
2. Time for remission: early remission carries a better outlook.
3. Number of drugs required to induce remission: rapid remission on a single drug is favorable indicator for successful withdrawal.
4. Presence of underlying lesions: control is difficult.
5. Presence of an associated neurological deficit: control is difficult.

It is generally recommended that antiepileptic drugs be withdrawn over a period of 6 months. If a fit occurs during this time, a full therapy must be resumed again until patient has been free from seizures for further 2-3 years[25].

Overdose

Anticonvulsant drugs are central nervous system depressants but are rarely lethal. Overdoses are life threatening: only when very high blood levels are reached. Most dangerous effect of antiseizure drugs after large doses is respiratory depression, which may be potentiated by other agents like alcohol. Treatment of antiseizure drug overdoses is supportive and stimulants should not be used. [26]

CONCLUSION

Convulsive activities lead to neuronal cell loss, therefore right treatment is mandatory. Now antiepileptic drugs are available in the market and are being used left and right especially as polytherapy. This has invited various drug interactions and side effects. Nature has given us plants to be used efficiently as a natural therapy for various ailments with fewer side effects and lesser drug interactions. This review has explored various interactions and side effects of nonherbal drugs and simultaneously emphasizing the role of various plant parts as anticonvulsants. Thus it may be concluded that herbal drugs make anticonvulsant treatment more rational and patient friendly.

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