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# HERBAL PLANTS USED IN THE TREATMENT OF EPILEPSY-PERSPECTIVES FOR THE FUTURE

**Sawhney Shalini K*, Singh Monika, Kumar S Sadish**

Affiliation: ITS College of Pharmacy, Muradnagar, Ghaziabad 201206, U.P. India

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Corresponding author:
Dr. Shalini K Sawhney, Associate Professor, , ITS college of Pharmacy, Muradnagar, Ghaziabad, U.P., India

**ABSTRACT**

Epilepsy is collectively designated for a group of chronic central nervous system disorders characterized by spontaneous occurrence of seizures generally associated with the loss of consciousness and body movements (convulsions). The disease has its origin from an early age. Anticonvulsant drugs are used to control the convulsions by inhibiting the neuronal discharge and then producing hypnosis. Various synthetic drugs, viz. sodium diphenyl hydantoin, barbiturates, pyrimidon, succinamides, diazepines etc. are used for the treatment. Synthetic drugs and even surgical techniques are found to have side effects and toxicity. This work contributes a literature review on medicinal plants and plant components, which might have anticonvulsant or antiepileptic activity. The aspect of the research will be on medicinal plants, their extraction and pharmacological activity using animal models. The discovery of novel antiepileptic drugs relies upon the preclinical employment of animal models to establish efficacy and safety prior to the introduction of the antiepileptic drugs (AEDs) in human volunteers.

## INTRODUCTION

Epilepsy is a serious neural disease that affects around 50 million people all over the world. Although for the majority patients with epilepsy, seizures are well controlled by currently available antiepileptic drugs (AEDs), there are still >30% of patients suffering from medically refractory epilepsy and approximately 30–40% of all epileptic patients affected by numerous side effects and seizure resistance to the current AEDs. Therefore, we as researchers try to develop novel approaches to treat epilepsy. In last 15 years, a new generation antiepileptic drugs has been introduced for the management of seizures[1]. It is estimated that there are more than 10 million people with epilepsy in our country[2]. AEDs are widely used not only for the treatment of epilepsy, but also for additional indications such as bipolar disorder, migraine, and chronic pain. Because these drugs are commonly prescribed for

long periods, many patients will require treatment with other agents for the management of concomitant or intercurrent conditions. In this setting, the potential for drug interactions is considerable. The increasing use of over- the- counter medication creates a further source of potential clinically significant interactions[3].

However as nature is a rich source of biological and chemical diversity and a number of plants in the world have been used in traditional medicine remedies, i.e., anticonvulsant, anxiolytic, analgesic, antidepressant. This work constitutes a literature review on medicinal plants showing anticonvulsant properties. The aspect of the research will be on medicinal plants, their extraction and pharmacological activity using animal models.

The discovery of novel antiepileptic drugs relies upon the preclinical employment of animal models to establish efficacy and safety prior to the introduction of the antiepileptic drugs (AEDs) in human volunteers[4] .

## TYPES OF EPILEPSY:

Seizure can be differentiated in focal and generalized seizure epilepsy[5].

Generalized seizures - Convulsive (bilateral motor manifestations with or without loss of consciousness; “Grand mal” seizures), Tonic- clonic, Tonic, Clonic, Myoclonic, Nonconvulsive (consciousness impaired; “Petit mal” or absence seizures).

Partial seizures- Simple partial (with no loss of consciousness; “Focal motor” seizures,

Complex partial (with unusual behaviour stereotypes; usually impaired consciousness; “Psychomotor” seizures), Partial seizures with secondary generalization (can occur with either simple partial or complex partial seizures) [6].

## DIAGNOSIS AND TREATMENT:

Recent studies suggest that many neurochemical pathways play an important role in seizure initiation, maintenance, and arrest[7]. The visual content of seizures is capable of being recorded, coupled with simultaneously linked electroencephalographic (EEG). Radiological diagnosis has evolved from pneumoencephalograms (PEG) to computed axial tomography (CT scan), superseded by magnetic resonance imaging (MRI). Magnetic resonance angiogram (MRA) may be used in the investigation of stroke which may be associated with seizures. Positron emission tomography (PET) has also been developed. Single photon emission tomography (SPECT), has gained acceptance worldwide as an additional test, for localization of sites of origin of seizures.

## OLDER GENERATION DRUGS:

Carbamazepine-It blocks voltage- dependent sodium channels, thereby limiting rapid, repetitive neuronal firing. It is a first- line treatment for partial epilepsy, but is ineffective against, and may exacerbate, absence and myoclonic seizures[8].

Phenytoin-It blocks voltage- dependent neuronal sodium channels and is a first- line treatment for partial onset and primary generalized tonic- clonic seizures. It is ineffective against myoclonic, atonic, and absence seizures[9].

Sodium valproate -It blocks voltage- dependent sodium channels, facilitates the effects of the inhibitory neurotransmitter gamma- aminobutyric acid (GABA), and reduces low threshold (T- type) calcium ion channel[10]. It is effective for virtually all seizure types[11].

Ethosuximide-It reduces T- type calcium ion channel in thalamic neurons. It is a first- line treatment for patients with absence seizures, but ineffective against myoclonic, primary generalized tonic- clonic, and partial onset seizures.

Primidone- It is effective against partial onset and primary generalized tonic- clonic seizures.

## NEWER ANTIEPILEPTICS:

Gabapentin-It binds to the neuronal voltage- gated calcium channels, inhibiting calcium flow. It is effective against partial onset seizures, but may exacerbate myoclonic and absence seizures

Lamotrigine-It is a sodium channel blocker that is effective against partial onset seizures and generalized seizure subtypes, though it has been reported to exacerbate myoclonic seizures[12].

Felbamate-It potentiates GABA- mediated inhibition, and blocks voltage- dependent sodium channels as well as the ionic channel at the *N*- methyl- d- aspartate receptor. It is effective against partial onset seizures as well as generalized seizures.

Levetiracetam-It binds to synaptic vesicle protein and has actions on neuronal GABA- .and glycine- gated currents, as well as voltage- dependent potassium currents. It is used though generalized seizure types, including myoclonic and absence seizures[13].

Oxcarbazepine- It blocks voltage- dependent sodium channels, and modulates calcium and potassium currents. It is the 10, 11 keto analogue of Carbamazepine, and has a similar spectrum of efficacy against partial onset[13] and primary generalized tonic- clonic seizures.

Pregabalin-It binds with high affinity to the voltage- gated calcium channels and inhibits calcium flow, an action similar to Gabapentin[14] . It is effective against partial onset seizures and is six to eight times more potent than Gabapentin[15] .

Tiagabine- It inhibits neuronal and glial reuptake of GABA, which increases the availability of GABA to inhibit postsynaptic neurons. It is effective against partial- onset seizures[16] .

Topiramate-It blocks sodium channels and high voltage activated calcium channels, attenuates the effects of excitatory neurotransmitters, enhances GABAergic neurotransmission and inhibits carbonic anhydrase. Topiramate is used for partial- onset, primary generalized tonic- clonic and myoclonic seizures.

Zonisamide-It blocks voltage- dependent sodium channels as well as T- type calcium channels, and inhibits carbonic anhydrase. It is effective against

partial- onset seizures and generalized seizure subtypes, tonic- clonic, tonic, atonic, atypical absence, and myoclonic seizures[17,18].

**Common side effects of antiepileptic drugs:** Nausea, vomiting, diarrhoea, hyponatremia, rash, pruritus, fluid retention, drowsiness, dizziness, blurred or double vision, lethargy, headache, agranulocytosis, Stevens- Johnson syndrome, aplastic anemia, hepatic failure, dermatitis, serum sickness, pancreatitis, vertigo, somnolence, hypersensitivity syndrome, anorexia, weight loss, insomnia, headache, ataxia, hepatic failure, toxic epidermal necrolysis, weight gain, tremors[19].

## OBJECTIVE:

Because of the overall medication costs idiosyncratic reactions, teratogenic effects, and side effects, herbal drugs are preferred in the treatment of epilepsy. Traditional systems of medicine are popular in developing countries and up to 80% of the population relies on traditional medicines for their primary healthcare needs. Several plants used for the treatment of epilepsy in different systems of traditional medicine have shown activity when tested on modern bioassays for the detection of anticonvulsant activity and many such plants remain to be scientifically investigated[20].

## HERBAL DRUGS USED IN THE TREATMENT OF EPILEPSY:

Herbal medicine is an area of complementary and alternative medicines (CAMs), is readily amenable to empirical research. Some herbal drugs have effects in the central nervous system, and thus have at least the theoretical potential for affecting seizures in patients with epilepsy and interacting with some antiepileptic medications[21] .

**Nardostachys jatamansi (Jatamanasi)-**The roots and the rhizomes of *N. jatamansi* DC. (Valerianaceae) have been used to treat epilepsy, hysteria, syncope, and mental weakness. The ethanolic extract of *N. jatamansi* considerably increased the seizure threshold in the experimental model of generalized tonic- clonic seizures with very low neurotoxic effect[22].

**Cotyledon orbiculata (seredile, plakkie, imphewula)-***C. orbiculata* L. (Crassulaceae) is reported that the juice has been used to treat epilepsy. The leaves of *C. orbiculata* contain saponins, which may be of triterpenoid type, and the triterpene steroid present in *Cotyledon orbiculata* might contribute to the anticonvulsant activity of the plant[23] .

**Laurus nobilis-** *L. nobilis* Linn. (Lauraceae) the leaves of this plant have been used to treat epilepsy, neuralgia, and parkinsonism. Furthermore, some analogs of a pinene prevent the audiogenic seizures in susceptible rats[24].

**Bacopa monnieri (Bramhi)-***B. monnieri*, an Indian herbal drug, reputed nootropic plant. Commonly used to treat asthma, epilepsy, insanity, and hoarseness. *B. monniera* to epilepticrat prevents the occurrence of seizures, thereby reducing the impairment on peripheral nervous system[25] .

**Rhizoma Pinelliae-**It is tuber of *Rhizoma ternate* (Thumb, Family: Araceae). The study showed

ethanolic fraction from Rhizoma Pinelliae Praeparatum (EFRP) could reduce the rate of Nikethamide (NKTM) induced convulsion death and prolong the latency, but not affect the convulsion latency which suggested that EFRP had the potential to modify the course of convulsive episodes and interfere in seizure threshold and/or block seizure propagation[26].

**Taxus wallichiana (Himalayan Yew)-** *T. wallichiana* Zucc. (Himalayan Yew) is often used in epilepsy. Leaves of the plant are used to make herbal tea for indigestion and epilepsy. Anticonvulsant effect of *T. wallichiana* was compared with that produced by the GABA- A agonist diazepam, a potent antiepileptic drug, highly effective to prevent convulsions induced by Pentylenetetrazole (PTZ)[27].

**Sutherlandia frutescens (umwele, cancerbush)-** Aerial parts of *S. frutescens* R. BR. (Fabaceae) are extensively used in childhood convulsions and epilepsy *S. frutescens* shoot aqueous extract (SFE, 50-400 mg/kg intraperitoneally (i.p.) significantly delayed the onset of and antagonized PTZ induced seizures. The plant's shoot aqueous extract (SFE, 50-400 mg/kg i.p.) also profoundly antagonized Picrotoxin (PCT) induced seizures[28].

**Ficus platyphylla (Dell- holl)-***F. platyphylla* (Moraceae) is Nigerian traditional medicine to treat psychoses, depression, epilepsy, pain, and inflammation for many years; Since saponins, which form the major components of the crude extract are believed to have profound central nervous system activities[29].

**Scutellaria baicalensis (Skullcaps)-***S. baicalensis* (Lamiaceae) is one of the most important medicinal herbs in traditional Korean medicine. Flavonoids from *S. baicalensis* may show anxiolysis, anticonvulsion, myorelaxation, and sedation; because they have high affinity for the benzodiazepine binding site of GABA- A receptors[30].

**Harpagophytum procumbens (Devil's claw)-***H. procumbens* DC (Pedaliaceae) is widely used in South African traditional medicine. Aqueous root extract of *H. procumbens* possesses anticonvulsant activity in the experimental animal model used. The plant's extract appears to be relatively more effective in PTZ and PCT induced convulsions[31].

**Delphinium denudatum (Jadwar)-** *D. denudatum* Wall. (Ranunculaceae) is used for the treatment of epilepsy. Aqueous fraction (AF) exhibited dose dependent activity against hind limb tonic extension phase (HLTE) of maximal electroshock (MES) and comparatively stronger anticonvulsant activity against seizures induced by PTZ[7].

**Withania somnifera (Ashwagandha)-** When *W. somnifera* was combined with the standard antiepileptic drugs, the combination was able to reduce significantly the effective dose of diazepam and clonazepam to offer full protection with no mortality[32].

**Leonotis leonurus (lion's tail)-**Water extract of *L. leonurus* was tested for anticonvulsant activity against seizures produced in mice by PTZ, PCT, bicuculline, and N- methyl- DL aspartic acid (i.p. injections). L. leonurus extract protected 37.5 and

50% of animals used and significantly ($P < 0.05$) delayed PTZ (90 mg/kg) induced tonic seizures[33].

**Magnolia grandiflora (Him- champa)-**The di ethyl ether and hydroalcoholic extract of *M. grandiflora* L. (Magnoliaceae) seeds orally administered in a single dose of 250 and 200 mg/kg, exhibited abolition of the extensor reflex of maximal electric induced seizure test in 50 and 40% of the experimental animals, respectively[35] .

## PERSPECTIVES FOR THE FUTURE:

In the US, herbal medicines have been regulated by the 1994 Dietary Supplement and Health Education Act, which did not require manufacturers to use good manufacturing practice (GMP) standards, which is the case for pharmaceuticals. However, in 2007 the FDA issued "current good manufacturing practice in manufacturing, packaging, labelling, or holding operations for dietary supplements"[35]. This new regulation prevents significant variation from lot to lot, bottle to bottle, or pill to pill for any dietary supplement[36].

In developing countries, natural products is more accessible, culturally acceptable and affordable than "western" medicines. In the case of epilepsy therapies, evaluation of products in animal models of epilepsy for clinical studies is needed. Some studies report *in vivo* effects and others on mechanisms of action. Another interesting approach is to screen plants for potential activity in models of epileptogenesis[37] . Another approach, is to: (1) identify herbal therapies and compounds isolated from them that have promising activity in animal epilepsy models and / or relevant *in vitro* assays; (2) conduct the pre-clinical studies necessary to proceed with early stage clinical studies; and (3) plan and initiate these clinical studies. Extracts and mixtures of extracts of herbal therapies, as well as pure compounds isolated from them, are first identified based on clinical recommendations of herbal experts around the world, review of original text references, and published results of laboratory or clinical studies.

## SUMMARY:

Anticonvulsant drugs have an increased potential for interactions and side effects due to enzyme induction and / or inhibition. AEDs are often associated with adverse effects and toxicity. Ayurvedic treatment which are having lesser side effects in comparison to synthetic drugs can be an option for the control and treatment of epilepsy[38].

Based on the present review we need to check if, AEDs in therapeutic doses have any cognitive effects at all [39]. Indeed, preclinical work at Harvard and elsewhere based on this approach suggests that the study of herbal therapies and herbal- derived compounds may yield promising results for further clinical development. Herbal therapies may, therefore, potentially yield new treatment options for patients whose seizures are uncontrolled despite available AEDs, and may also represent inexpensive, culturally acceptable treatments for the millions of people around the world with untreated epilepsy[40].

## CONFLICTS OF INTEREST:

All authors have none to declare.

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