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Review Article

MEDICINAL PLANTS USED IN THE TREATMENT OF EPILEPSY

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ABSTRACT
Epilepsy may be defined as a neuropsychological disorder, which occurs due to over discharge of neurotransmitter substance. Epilepsy differs from seizure; a seizure is the paroxysmal events due to abnormal excessive hyper synchronous discharge from an aggregate of central nervous system (CNS) neurons. There are number of drugs available for treatment of epilepsy in modern therapy. But the major disadvantage being faced is their chronic side effects. One patient out of three is resistant to antiepileptic drug. , thus there is a need of new drugs which have least side effect and minimum interaction and provide more effectiveness. From times immemorial plants have been used by mankind for their relieving and therapeutic abilities and still we rely on their healing properties. Plants with number of active constituent have a direct pharmacological action on our body including various organs. One such major complex organ is brain, so complex that still only few drugs are approved by drug authorities for ailments like epilepsy. The Indian system of medicine "Ayurveda" classified the plants affecting central nervous system. Treatment of epilepsy with herbal drugs as adjuvant seems to be more beneficial and is gaining more popularity due to their fewer side effects. Herbal drugs are acting at target site having same mechanism of action as that of synthetic drugs. There are number of drugs being used in the traditional medicine for treatment of epilepsy and presently many of these drugs are being explored scientifically to ascertain their anticonvulsant activity.

KEY WORDS: Anticonvulsant herbs, Antiepileptic plants, Epilepsy, Herbal medicine, Ayurveda

INTRODUCTION
Epilepsy is a common chronic neurological condition that is characterized by recurrent unprovoked epileptic seizures. These seizures are transient signs or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. It affects approximately 50 million people worldwide.[1] it is characterized by recurrence of seizures, defined as manifestation of paroxysmal and disordered neuronal discharges in the brain. Seizures can vary widely in their clinical presentation, depending on site, extent and mode of propagation of the paroxysmal discharge and hence now looked at as spectrum of clinically different varieties rather than a single disease.[2] Many different types of seizures can be identified on the basis of their clinical phenomenon.[3] Conventional medical treatments for epilepsy are not uniformly effective.[4] A large number of agents called antiepileptic drugs are available to treat various types of seizures with the objective to reduce seizure frequency and severity within a framework of an acceptable level of side effects. The ideal anti-seizure drug would suppress all seizures without causing any unwanted effect. Unfortunately the drugs used currently not only fail to control seizure activity in some patients, but they frequently cause side effects.[2]
Traditional herbs are very useful and indispensable in the struggle for seizure management and future AED development.[5] Therefore alternative therapy including herbal drugs and complementary medicine is becoming increasingly popular.[6]

MATERIAL AND METHOD

A literature survey was carried out to assess the published literature for the appraisal of information available on the biological effect of drug. As per the guideline for the use of electronic and internet media, a high quality and reliable medical information from the internet was retrieved. Some of the literature was retrieved from the books like Materia medica and Wealth of India etc.

ANTIEPILEPTIC HERBS

Brahmi Ghrita: A polyherbal formulation

Brahmi ghrita belongs to family Scrophulariaceae (Figure1) a polyherbal formulation containing Bocopa monneria (4%), Evolvulus alsinoids (4%), Acorus calamus (4%), Sassurea leppa (4%), these are uniformly mixed & blended with cow's ghee (84%), prepared as a suspension with 1% acacia. It is used on the Swiss albino mice (25g). These formulation exhibits reduced alertness, spontaneous locomotory activity. It also antagonizes the behavioral effect of d-amphetamine. It protects the mice from electroshock and pentylene tetrazole induced convulsion.[7]

Cissus Sicyoides: Aerial part

The Cissus plant (Figure 2) is used as an anticonvulsant. Hydroalcoholic extract obtained from the aerial parts of Cissus sicyoides L. (Vitaceae) and experimented on male and female mice using several behavioral assays. Groups of males and females were treated via intraperitoneal (i.p.) with doses of 300, 600, and 1000 mg/kg of the extract showed significant action in the elevated plus-maze, time spent in the open arms and number of entries in the open arms. The board hole test also showed a significant increase in the time spent in head dipping and in marble burying test of the number of marbles buried. The same treatment increased the duration of sleeping time induced by sodium pentobarbital and also showed a significant increase in protection against pentylenotetrazole-induced convulsions. These results indicated an anxiolytic and anticonvulsant activity of C. sicyoides L. extracts on mice, probably due to the action of flavonoid, linalool, and α-tocopherol present in the C. sicyoides leaves.[8]

Passion Flower: Leaves and flower

Passion flower (Figure 3) belongs to family Passifloraceae . It is used as a traditional anticonvulsant drug in Europe and South America. Its hydro-alcoholic extract is given to PTZ induced model on mice. Pasipay (0.4mg/kg), diazepam (0.5-1mg/kg) & normal saline (10ml/kg) are introduced 30 min. before PTZ. Time taken before onset of clonic convulsion, duration and percentage of seizure and mortality protection were recorded. Result found that Pasipay prolonged the onset time of seizure and decreased the duration of seizure as compared to saline. Traditionally, it is used to treat the absence seizure.[9]

Rosa Domescana: Flower

The activity of Rosa domescana (Figure 1) belongs to family Rosaceae. Its Essence was studied on the PTZ induced seizure in rats. PTZ was injected to 40 male wistar rats to produce different grade of seizure. Essential oil was given to all groups before PTZ and during the experimental period the epileptiform behavior of all rate of different group was evaluated before and after essential injection. The flavonoides of Rosa domescana shows the anticonvulsant effect may be acting via $GABA_A$ receptor.[10]

Argyreia Speciosa: Leaves

Argyreia speciosa (Figure 2) belongs to family Convolvulaceae. Argyreia speciosa extract was given to mice in 100, 200, 400 mg/kg for 10 days and then subjected to PTZ or maximum electroshock seizure treatment. The hydroalcoholic extract Argyreia speciosa at the dose of 200 and 400 mg/kg significantly delayed and latency to the onset of first clonus as well as onset of the death in unprotected mice and exhibited protection in 16.66% and 33.33% of PTZ treated mice respectively, In case of maximal electroshock seizure, the dose of 200 and 400 mg significantly reduced the duration of hind limb extension and both dose were statistically found to be equipotent compared to reference standard, clonazepam (0.1mg/kg) and phenytoin (20mg/kg) which provided complete protection.[11]

Drosera Burmannii: Whole plant

Drosera burmannii (Figure 3) belongs to family droseraceae. The antiepileptic activity of the alcoholic and aqueous extracts of Drosera burmannii was examined against pentylenetetrazole (PTZ) induced seizures in mice. Acute toxicity studies were carried out to evaluate the drug's toxicity and to determine the minimum lethal dose of the drug extracts, using swiss albino mice. It was found that alcoholic and aqueous extracts up to a dose of 3000 mg/kg body weight, did not show any toxic manifestations or death.

In PTZ induced seizures, the administration of Drosera burmannii alcoholic extract at a dose of 500 mg/kg 1 h prior to the injection of PTZ, significantly delayed the onset of convulsions. Neither alcoholic nor aqueous extracts at the dose of 300 mg/kg body weight could exert any significant protective effect on PTZ induced convulsions. Alcoholic extract at the dose level of 500 mg/kg body weight showed significant antiepileptic activity.[12]

Glycerrhiza Glabra: Root

Glycerrhiza glabra (Figure 4) belongs to family Fabaceae. Aqueous Extract of Glycerrhiza glabra root possesses anticonvulsant activity which may be effective in petitmal seizure. Experimental animal was taken as mice that were divided in nine group, six were given intraperitonoal inj. of extract at increasing dose of 50, 60, 80, 100, 200, 300 mg/kg, 30 minute before administration of PTZ (90 mg/kg, i.p.) other group were given saline & diazepam (0.5-1mg/kg. It was found that liquorice extract at the dose of 300 mg/kg could significantly delay the onset of seizure and reduced the duration of seizure compared to control. Results of investigation shows that aq. extract of glycerrhiza has anticonvulsant effect in PTZ model.[13]

Oscimum Sanctum: Leaves

Ethanolic extract of Oscimum sanctum (OS) (Figure 5) is used to treat the haloperidol (1.0mg/kg, intraperitonoal) induced catalepsy. It belongs to family Lamiaceae. Albino mice were allocated to several groups. Each group containing 6 animals. The effect of test drug OS (at 1.75, 4.25 and 8.5mg/kg) and the standard drugs scopolamine (1.0 mg/kg) & ondansetron (0.5 and 1.0mg/kg) were assessed after single and repeat dose administration for seven days, 30 minute prior to the haloperidol. The results suggest that ethanolic extract of OS have the protective effect against haloperidol induced catalepsy.[14]

Pongamia Pinnata: Leaves

Pongamia pinnata (Figure 6) is an indigenous plant belonging to the family Fabaceae (Papilionaceae) commonly known as Karanj. Freshly powdered leaves were evenly packed in soxhlet apparatus and extraction was done with 70% ethanol. The electric shock applied (150 mA for 0.2 s) through corneal electrodes to wistar albino mice produced convulsion and those showing response were divided into three groups of six animals each. The Ethanolic extract (250 mg/kg) showed significant anticonvulsant activity by lowering the duration of extension phase (4.12 ± 0.67) when compared to control group (9.64 ± 0.41). These significant results indicate that the anticonvulsant action of Pongamia pinnata leaf extract on mice, probably due to the presence of flavonoids.[15]

Berberis Vulgeris

Berberis vulgeris (Berberidaceae) (Figure 7) is useful in treatment of convulsion. It contains a Berberin isoquinoline alkaloid which shows the Anticonvulsant property. These results were observed against maximum electroshock (MES) and kainic (KA) acid induced convulsion in mice. The result revealed that in MES induced seizure model, Berberin (10,20mg/kg ip) decrease the duration of tonic hind limb extension & percentage mortality.[16]

Clerodendrum Infortunatum: Leaves

Clerodendrum Infortunatum (Figure 8) belongs to family Verbenaceae. Saponin (SN1) isolated from the leaves of the clerodendrum infortunatum, and converted to SN2 (more effective & pure compound) via TLC method. For this the experimental animal is taken as adult swiss albino mice of either sex (22±2 gm). SN1 was administered i.p. in mice (Leptazol-induced seizure) in varying dose (20-100mg/kg), 30 minutes prior to the administration of leptazol (80 mg/kg i.p.). Result found that it significantly decreases the onset & incidence of convulsion against leptazol induced seizure. Protection produced against the leptazol induced convulsion was dose dependent and ED_{50} & therapeutic index of SN1 was determined to be 45(30.2-65.0) mg/kg, i.p. and 8.3 respectively.[17]

Echium Amoenum: flower

The effect of methanolic extract of Echium amoenum (Boraginaceae) (Figure 9) against picrotoxin induced seizure in mice was studied. The extract with dose of 3.125, 6.25, 12.5 and 25 mg/kg were injected intraperitonially to mice, 20 minutes before picrotoxin 10 mg/kg. Latency of seizure, death time & percentage of mortality were measured in animals. Result revealed good anticonvulsant effect of methanolic extract of E.amoenum.[18]

Boerhaavia Diffusa: Roots

The methanol soluble fraction of Boerhaavia diffusa (Nyctaginaceae) (Figure 10) was successively extracted to obtain liriodendrin rich fraction and two side fractions, i.e. chloroform fraction and phenolic compound fraction. Anti-convulsant activity of methanolic extract [1000, 1500 and 2000 mg/kg, intraperitoneally (i.p.)] and its different fractions, i.e. liriodendrin-rich fraction (10, 20 and 40 mg/kg, i.p., chloroform fraction (20mg/kg, i.p.) and phenolic compound fraction (1 mg/kg, i.p.) were studied in pentylenetetrazole (PTZ) induced seizures (75 mg/kg−1, i.p.). The crude methanolic extract of B.diffusa and only its liriodendrin rich fraction showed a dose-dependent protection against PTZ induced convulsions. The liriodendrin rich fraction also showed significant protection against seizures induced by BAY k-8644. These findings reiterated the anti-convulsant activity of methanolic extract of B. diffusa roots. Furthermore, it can be concluded that the observed anti-convulsant activity was due to its calcium channel antagonistic action as this activity was retained only in the liriodendrin-rich fraction, which has additionally been confirmed by significant anti-convulsant activity of liriodendrin-rich fraction in BAY k-8644-induced seizures.[19]

Butea Monosperma: flower

The bioassay-guided fractionation of dried flowers of Butea monosperma (Fabaceae) (Figure 11) was carried out to isolate the active principle responsible for its anticonvulsant activity. The petroleum ether extract was fractionated by column chromatography using solvents of varying polarity such as n-hexane, n-hexane: ethyl acetate, ethyl acetate, and methanol. The anticonvulsive principle of *B. monosperma* was found to be a triterpene (TBM) present in the n-hexane: ethyl acetate (1:1) fraction of the petroleum ether extract. TBM exhibited anticonvulsant activity against seizures induced by maximum electroshock (MES) and its PD (50) was found to be 34.2+/-18.1 mg/kg. TBM also inhibited seizures induced by pentylenetetrazol (PTZ), electrical kindling, and the combination of lithium sulfate and pilocarpine nitrate.[20]

Valeriana Officinalis: Roots

Valeriana officinalis L. (Valerianaceae) (Figure 12) Root extract has been used as an antiepileptic herbal medicine in Iran. The effect of valerian extracts were observed on an experimental model of temporal lobe epilepsy (TLE). Bipolar stimulating and monopolar recording electrodes were implanted stereotaxically in the right basolateral amygdala of male Sprague Dawley rats. After kindling, the effect of aqueous (200, 500 and 800 mg/kg; intraperitoneal) and petroleum ether (PE; 50 and 100mg/kg; i.p.) extracts of valerian on after discharge duration of stage 5 seizure and latency to the onset of bilateral forelimb clonuses were measured. The results showed that aqueous extract of valerian had anticonvulsant effect.[21]

Saussurea Lappa: Roots

Roots of Saussurea lappa (Asteraceae) (Figure 13) are traditionally used in the Ayurvedic system of medicine for the treatment of epilepsy. Anticonvulsant activity of S. lappa petroleum ether extract (SLP), alcoholic extract (SLA), and water extract (SLW) was evaluated against pentylenetetrazole and picrotoxin induced convulsions, and maximal electroshock (MES) test in mice. The pharmacological screening reveals that the SLP (100mg/kg i.p.) and SLA (300mg/kg i.p.) significantly increased latency to clonic convulsions and reduced mortality in pentylenetetrazole and picrotoxin treated mice. SLW (300mg/kg i.p.) significantly increased latency to clonic convulsions, reduced convulsion episodes and mortality. SLP (100 and 300mg/kg i.p.), SLA (100 and 1000mg/kg i.p.) and SLW (100 and 1000mg/kg i.p.) reduced mortality of mice in electroshock experiment.[22]

Cymbopogon Winterianus: Leaves

Cymbopogon winterianus (Poaceae) (Figure 17) is used for its analgesic, anxiolytic and anticonvulsant properties in Brazilian folk medicine. This report aimed to perform phythochemical screening and to investigate the possible anticonvulsant effects of the essential oil (EO) from fresh leaves of C. winterianus in different models of epilepsy. The phytochemical analysis of EO showed presence of geraniol (40.06%), citronellal (27.44%) and citronellol (10.45%) as the main compounds. A behavioral screening demonstrated that EO (100, 200 and 400 mg/kg; ip) caused depressant activity on CNS. When administered concurrently, EO (200 and 400 mg/kg, ip) significantly reduced the number of animals that exhibited PTZ- and PIC-induced seizures in 50% of the experimental animals (po0.05). Additionally, EO (100, 200 and 400 mg/kg, ip) significantly increased (po0.05) the latencies of clonic seizures induced by STR. Our results demonstrated a possible activity anticonvulsant of the EO.[23]

Taxus Wallichiana

Taxus wallichiana (Figure 18) belongs to family Taxaceae. Its extract controls the pentylenetetrazole induced convulsions in mice. 100 and 200 mg/kg i.p doses of the extract significantly ($P < 0.05$) inhibited the mioclonus and clonus while inhibition of tonus and hind limb tonic extension (HLTE) was highly significant ($P < 0.01$). The anticonvulsant activity of this plant has been reported for the first time throughout the whole genus. The observed pharmacological activities provide the scientific basis for the folkloric use of the plant in treating epilepsy.[24]

Nardostachys Jatamansi: Root

Ethanol extract of the roots of Nardostachys jatamansi (Valerianaceae) (Figure 19) was studied for its anticonvulsant activity. Maximal electroshock seizure model was used in the present study to evaluate the anticonvulsant activity of the extract. Seizures were induced in rats by delivering electroshock of 150mA for 0.2 s by means of a convulsiometer through a pair of ear clip electrodes. The test animals (n = 6–9/group) received 50, 100, 200 and 400 mg/kg BW, i.p. and on second experiment 125, 250 and 500 mg/kg BW, p.o., of the extract and tested 1 h after for MES seizure response. Further, the extract (125 and 250 mg/kg bw) was administered orally to rats (6–10/group) for 15 days and tested for anticonvulsant activity 1 h after the last dose.[25]

Dorstenia Arifolia: Rhizome

Dorstenia arifolia (Moraceae) (Figure 20) rhizome methanolic extract (ME) of Dorstenia arifolia act on the central nervous system (CNS). ME was tested for anticonvulsant effects using locomotor activity evaluation, pentylenetetrazol (PTZ) induced convulsion. Intraperitoneal administration of ME (50 mg/kg) significantly decreased locomotor activity from 205.2±25.6 movements/min (DMSO) to 114.9±16.9 ($P < 0.05$). The latencies to seizures after intraperitoneal injection of PTZ was recorded and compared between groups. ME promoted a significant protection of PTZ-induced seizures and mortality in a dose-dependent manner. These findings indicate that ME of Dorstenia arifolia rhizome has pronounced central effects, and anticonvulsant activities may be related to a facilitation of the GABAergic transmission.[26]

Scutellaria Lateriflora: Arial part

Arial part of Scutellaria lateriflora (Lamiaceae) has been traditionally used in Native American for its anticonvulsant property. Aqueous plant extract were used in 200-250 gm (n=59) Sprague Dawley rats. Temperature was maintained at 22±1° c and humidity at 50±5%. Pilocarpine (300mg/kg ip), methylescopolamine (1mg/kg sc) and PTZ (50mg/kg ip) were used to induce the seizure. This plant has flavonoid, which is responsible for anticonvulsant activity.[27]

Sutherlandia Frutescens: Shoot

Sutherlandia frutescens (fabaceae) used in the childhood convulsion in South African region. Shoot aq. Extract (25-400mg/kg ip) used against Pentylene tetrazole (PTZ), picrotoxin (PCT) and Bicculin (BCL) induced seizure in mice. It is found that *S.frutescens* shoot aq. extract significantly delayed the onset of, and antagonized the PTZ and PCT induced seizure, but weakly antagonize the BCL induced seizure. It shows the anticonvulsant activity directly by acting like GABA or indirectly by enhancing GABAergic neurotransmitter in brain.[28]

GENERAL MODELS USED IN EPILEPSY

The search for therapeutic approaches to epilepsy has been based on animal seizure models.[29]

***IN VITRO* MODELS**:-

1. ^{3}H GABA receptor binding.
2. $GABA_A$ Receptor binding.
3. $GABA_B$ Receptor binding.
4. ^{3}H GABA uptake in Rat cerebral cortex syneptosomes.
5. GABA uptake and Release in Rat hippocampal slices.

***IN VIVO* MODELS**:-

1. Maximum electroshock in mice.
2. Pentylenetetrazol induced convulsion in mice and rat.
3. Strychnine-induced convulsion in mice.
4. Picrotoxin-induced convulsion in mice.
5. Isoniazid-induced convulsion in mice.
6. Bicuculline induced convulsion in rat.

7. Lithium pilocarpine induced status epilepticus in rat.
8. Pilocarpine induced convulsion in rat.
9. Continuous ventral hippocampal stimulation followed by low dose pilocarpine in Rat.
10. Electric kindling seizure by amygdale stimulation (temporal lobe epilepsy).
11. BAY K- 8644 induced seizure in Rat.

RESULT

The present review clearly revealed the anticonvulsant potential of some herbs that are now documented scientifically. These herbal remedies can make the anticonvulsant treatment more rationale and patient friendly. The review also found that certain herbal drugs mentioned in various traditional systems of medicines across the globe have not been exploited up to the desired level.

DISCUSSION

Present review revealed the anticonvulsant potential of various herbs. There is a growing interest in correlating phytochemical constituents of plant with its pharmacological activities. Proper utilization of technological advances helped in logical interpretation of traditional medicine which has become a necessity in order to promote the research in phytopharmacological field.

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Figure 1: Brahmi ghrita



Figure 2: Cissuss Sicyoides



Figure 3: Passon Flower



Figure 4: Rosa Domescana



Figure 5: Argyreia Speciosa



Figure 6: Drosera Burmannii


Figure 7: Glycerrhiza Glabra


Figure 14: Oscimum Sanctum


Figure 9: Pongamia Pinnata


Figure 10: Berberis Vulgeris


Figure 11: Clerodendrum Infortunatum


Figure 15: Echium Amoenum


Figure 16: Boerhaavia Diffusa


Figure 17: Butea Monosperma


Figure 15: Valeriana Officinalis


Figure 18: Saussurea Lappa


Figure 19: Cymbopogon Winterianus


Figure 20: Taxus Wallichiana


Figure 21: Nardostachys Jatamansi


Figure 20: Dorstenia Arifolia