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OVERVIEW OF HERBAL TREATMENTS USED FOR EPILEPSY: A SYSTEMIZED REVIEW

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ABSTRACT
Traditional medicine occupies an important place in the healthcare systems of developing countries. The people in developing countries depend on traditional medicine because it is cheaper and more accessible than orthodox medicine. Herbal medicine is currently enjoying a revival in popularity in the West and is the primary form of medicine in many parts of the world. Epilepsy is a progressive disorder comprising many seizure types and syndromes. Even with the advent of numerous new antiepileptic medications (AEDs), a sizable portion of epileptic patients still have seizures. Therefore, there is still a therapeutic need for anti-epileptic medications that are less harmful and more effective. As a result, herbal remedies are utilized extensively worldwide because of their broad application, therapeutic effectiveness, and few side effects. This has sped up research on natural therapy. We have compiled a list of herbal anti-epileptics in this review.

KEYWORDS: Epilepsy, Epidemiology, Pathogenesis, Herbal plants.

1. INTRODUCTION
Epilepsy is one of the most frequent major neurological disorders, accounting for significant morbidity and death due to seizures and available medicines. Around 50 million individuals worldwide have epilepsy, and roughly 5% of the general population has had at least one seizure, excluding febrile seizures, at some point in their lives. Currently, existing antiepileptic medications (AEDs) have limited efficacy and their unfavorable features limit their usage and complicate patient treatment. It is worthwhile to research novel AEDs with low side effects and efficacy against drug-resistant epilepsy. Herbal medication is also used for primary healthcare by around 75-80% of the world's population, primarily in underdeveloped nations, due to its greater cultural tolerance, compatibility with the human body, and lower risk of complications. Given the widespread reliance on traditional medicinal plants for illness treatment and the possibility of drug development, it becomes important to look for potent, effective, and reasonably safe plant medicines. Several medicinal plants have been utilized in traditional medicine to treat epilepsy.[1]

1.1 Epidemiology and Burden of epilepsy
Even though epilepsy is a worldwide condition, its prevalence varies by area based on population demographics, treatment accessibility, and the local distribution of risk factors. According to a recent meta-analysis, the overall lifetime prevalence of epilepsy was 7.60 per 1000 people (95% CI 6.17– 9.38); in low and middle-income countries (LMICs), this prevalence was greater (8.75 per 1000; 95% CI 7.23–10.59) than in high-income countries (5.18 per 1000; 95% CI 3.75–7.15). The incidence of epilepsy showed a similar pattern, with 139.0 cases per 100,000 person-years (95% CI 69.4–278.2) against 48.9 cases per 100,000 person-years (95% CI 39.0–61.1) in LMICs as opposed to high-income nations. The incidence of epilepsy showed a similar pattern, with 139.0 cases per 100,000 person-years (95% CI 69.4–278.2) against 48.9 cases per 100,000 person-years (95% CI 39.0–61.1) in LMICs as opposed to high-income nations. These figures show that populations in LMICs are more likely to suffer from epilepsy than those in developed nations. Indeed, residents in LMICs account for almost 80% of the global epilepsy burden. Particularly in sub-Saharan Africa, the median prevalence of epilepsy was found to be 14.2 per 1000 (IQR 8·0–33·2), with more than 90% of cases occurring in people under the age of 20. Annual epilepsy incidence was also high, at 81.7 per 100,000. Mortality was highest in the 18-24 age group, indicating a significantly poor life expectancy among people with epilepsy (PWE) in Africa. Epilepsy risk factors commonly observed in resource-limited settings, such as neonatal brain injuries, traumatic head injuries, and central nervous system infections, have been proposed as explanations for this trend. A varying genetic susceptibility to show seizures in different groups may also explain the reported regional inequalities in the occurrence of epilepsy around

the world, as people of diverse ethnic origins within a particular population have distinct incidence rates for epilepsy. According to the 2016 Global Burden of Disease Collaborators, epilepsy was responsible for 0.5% of the overall disease burden in 2016 and caused over 13 million Disability Adjusted living Years (DALYs), which are a measure of the number of years of healthy living lost to epilepsy within a particular population. Once more, significant regional variations were seen, with epilepsy ranking among the top five neurological conditions in low-income areas. Significant decreases in PWE mortality and DALY were also observed in that study between 1990 and 2016, indicating some advancements in epilepsy care and treatment.[2]

1.2 Classification of epileptic seizures

The International League against Epilepsy (ILAE) Commission on Categorization and Terminology suggested and adopted a categorization system for epileptic episodes in September 1981. The clinical manifestation of the seizure and the electroencephalogram readings during and in between seizures serve as the basis for this classification. This classification is primarily separated into two categories: generalized seizures and partial seizures.[2]

1.2.1 Partial seizure

Partial seizures are first classified into two types: those with intact consciousness and those with impaired consciousness. Both of these types can develop into generalized seizures, which create the third group.[2]

1.2.2 Simple partial seizures

The patient does not lose consciousness and consequently can relate to what happened, but the experience may be so odd that he may not be able to express himself adequately. When motor seizures occur, the primary motor cortex is the main focus. The face or the distal portion of the extremities is where the twitches begin. The spreading is referred to as a Jacksonian march, after Huglings Jackson, who lived from 1835 to 1911. The primary sensory cortex, or postcentral gyrus, is the focal point of sensory seizures. Feelings of tingling, pins and needles, heat or cold, or limb numbness are possible. There may occasionally be odd sensations accompanied by visual indicators, sounds, or smells. There are temporal lobe foci linked to autonomic seizures. Autonomic seizures have been linked to temporal lobe foci. There could be a sensation ascending from the epigastrium to the throat, palpitations, perspiration, or flushing. Psychic symptoms can include changes in mood, memory, or thinking. There could be erroneous views (of time, space, or people) or language issues. Structured hallucinations may arise (Music, scenery). These simple partial seizures are typically only diagnosed as epileptic seizures when they progress to generalized seizures.[3]

1.2.3 Complex partial seizures

Here the patient has compromised consciousness, there is no full loss of consciousness, he is partly aware of what is going on, but he cannot respond to anything, and neither can he change his conduct during an attack. There is an aura, a peculiar feeling in the stomach rising to the throat and head, or a sensation of light, smell, sound, or taste. The seizure may be associated with alterations in perception, such as time (time appears to pass too slowly or too quickly), light or sound, or space. There is a slow recovery after a complex partial seizure, with a period of confusion. After the attack, there is complete amnesia about it. These seizures were previously called 'psychomotor seizures', and as the localization of the abnormal discharge is often in the temporal lobe, the epilepsy is often called 'temporal lobe epilepsy (the focus might occur in the frontal lobe too).[3]

Partial seizures secondary to generalized

Both the simple partial seizures and the complex partial seizures may become generalized tonic-clonic seizures.

1.2.4 Generalized seizures

Complete unconsciousness and the lack of an aura are hallmarks of primary generalized seizures. They appear quickly and without warning, and patients run the risk of becoming hurt if they fall. The primary generalized tonic-clonic seizure (GTCS) is the most prevalent of the six seizure types that make up generalized seizures.[2]

Absence seizures

These are brief episodes of unconsciousness that last no more than a few seconds or less than 30 seconds. They typically have no motor symptoms or very few, and they start suddenly. A stoppage of continuous activity occurs, along with a momentary upward rotation of the eyes and a blank gaze. When spoken to, the child does not respond. The toddler resumes his previous activity after the abrupt end of the seizure. These convulsions are not recalled by the child. Due to their high frequency, these seizures were dubbed pyknolepsy or petit mal seizures. Because it is so vague, the phrase "petit mal" (small disease) needs to be dropped.[3]

Myoclonic seizures

These seizures consist of sudden, brief, shock-like muscle contractions, either occurring in one limb or more widespread and bilateral. They may be single jerks or jerks repeated over longer periods.[2]

Clonic seizures

These seizures are generalized seizures, where the tonic component is not present, only repetitive clonic jerks (clonic jerks are repetitive rhythmic flexing and stretching of limbs).[2]

Tonic seizures

Tonic seizures are sudden sustained muscle contractions, fixing the limbs in some strained position. There is an immediate loss of consciousness. Often there is a

deviation of the eyes and head towards one side, sometimes rotation of the whole body. Tonic-clonic seizures (GTCS) The patient loses consciousness, falls, sometimes with a scream, and develops a generalized stiffness (the tonic phase). Breathing stops, as all the muscles of the trunk are in spasm, and the patient becomes cyanotic, the head is retracted, the arms flexed and the legs extended.[3]

1.3 Pathogenesis of epilepsy

1.3.1 Neurotransmission signaling pathway

The two neurotransmitters that have been thoroughly investigated in epilepsy are glutamate and γ-aminobutyric acid (GABA). In epileptic events, both the glutamatergic and GABAergic systems are important. It has been proposed that an imbalance between glutamate-mediated excitation and GABA-mediated inhibition causes the neuronal hyperexcitability associated with epilepsy. The primary excitatory neurotransmitter in the brain, glutamate, depolarizes neurons to produce excitatory postsynaptic potentials. Glutamate receptors are generally divided into two categories: metabotropic (G protein-coupled) receptors and ionotropic (ligand-gated cation channels) receptors, which include α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA), N-methyl-D-aspartic acid (NMDA), and kainite Upregulation of glutamate receptors, an increase in extracellular glutamate concentration, anomalies in glutamatergic transporters, and autoimmune processes are some of the glutamatergic molecular mechanisms that contribute to the development and progression of epilepsy. These processes lead to increased glutamatergic activity, which is a major factor in epilepsy and hyperexcitability. On the other hand, GABA is known to be the primary inhibitory neurotransmitter that hyperpolarizes neurons to produce inhibitory presynaptic potentials. To counterbalance neuronal excitation and hence inhibit epileptiform discharges, the GABAergic system plays a crucial role. The mechanisms behind epilepsy also involve other neurotransmitters like dopamine, serotonin, and noradrenaline. There are several serotonin receptor subtypes expressed in the central nervous system, such as 5- HT1A, 5-HT2C, and 5-HT7. Receptors are present on cortical and/ or hippocampal neurons. Experimental data from animal models and humans reveal that serotonergic neurotransmission is significantly involved in the pathogenesis of epilepsy. The variety of serotonin receptor subtypes has complicated the role of the serotonergic system in regulating neuronal excitability. Neuronal excitability is often decreased when 5-HT1A receptors hyperpolarize glutamatergic neurons, 5-HT2C receptors depolarize GABAergic neurons, and 5-HT3 and 5-HT7 receptors are inhibited. Endogenous noradrenaline has been shown in numerous investigations to have an anticonvulsant effect on epilepsy. These include noradrenaline loss leading to greater neuronal injury in several limbic regions of rats following seizure induction, and noradrenaline depletion increasing vulnerability to seizure induction. Dopamine, another catecholamine neurotransmitter, plays a complex and unclear role in the etiology of epilepsy. Researchers discovered that the dopaminergic pathway is linked to the pathophysiology of two idiopathic epilepsies: autosomal dominant nocturnal frontal lobe epilepsy, which has a significant reduction in dopamine D1 receptor binding, and juvenile myoclonic epilepsy, which has a decrease in dopamine transporter binding.[4]

1.3.2 Molecular and Genetic mechanisms

Ion receptors and channels Recent developments in molecular biology and genetics have shown that mutations in genes encoding ion channel proteins, which cause neurons to become hyperexcitable, are responsible for several epileptic syndromes. Ion channel malfunction or deficiency is referred to as "channelopathy." Idiopathic epilepsy has been linked to mutations in genes that express acetylcholine and GABA receptors as well as channels for potassium, sodium, chloride, and calcium. Furthermore, subsequent alterations in ion channels through transcriptional and posttranslational pathways can cause channelopathies, which can also be the etiology of acquired epilepsy.[4]

1.3.3 Neurogenesis and Rewiring pathway

Structural, neurochemical, and cellular modifications Aberrant hippocampus neurogenesis, the process of creating new neurons and circuits, has been proposed as another significant etiology in epilepsy. Structural, neurochemical, and cellular alterations may occur after acute seizures in patients with brain injuries. Multiple anatomical abnormalities in the hippocampus may develop following acute seizures, including degeneration. of dentate hilar neurons and CA1 - CA3 pyramidal neurons, abnormal sprouting, mossy fiber synaptogenesis, and the loss of inhibitory GABAergic interneurons.[4]

1.3.4 Immunological and Inflammatory pathway

Inflammatory responses and immune system activation are linked to cytokines, which are polypeptide mediators. Inflammatory cytokines have been implicated in the pathophysiology of epilepsy in recent research using animal models. Brain areas associated with the generation and propagation of epileptic activity exhibit overexpression and up-regulation of inflammatory cytokines, including interleukin (IL)-1β, IL-6, and tumor necrosis factor-α. The inflammatory cytokines in the tissues of epileptics are known to originate from glial cells, the nonneuronal cell components of the central nervous system, especially microglia and astrocytes. As a result, during epileptogenesis, glial cells regulate inflammatory or immunological responses. The role that the activated inflammatory pathway plays in the pathophysiology of epilepsy, however, is a matter of concern. These inflammatory cytokines have been shown to cause neuronal excitability changes, the production of toxic mediators, and increased blood-brain barrier (BBB) impermeability (91,94). IL-1β can activate the NMDA receptor, which increases NMDA-mediated ion calcium

influx into neurons and ultimately promotes neuronal hyperexcitability; similarly, tumor necrosis factor-α can cause neuronal excitability by up-regulating AMPA receptors, which favor ion calcium influx into neurons, and down-regulating GABA receptors, which results in a decrease in inhibitory synapse strength. In addition to excitotoxic effects, inflammatory cytokines may also cause apoptotic neuronal death, which is probably caused by the production of neurotoxic mediators and NMDA- and AMPA-mediated glutamatergic excitotoxicity.[4]

1.3.5 Apoptotic pathway

Experimental and clinical data have demonstrated that significant neuronal cell loss occurs following brain insults, and apoptotic pathways may be involved in this cell loss in addition to other mechanisms like excitatory glutamate-mediated toxicity. Apoptosis is a programmed cell death process during normal growth and development in multicellular organisms for maintaining cell homeostasis.[4]

2. Herbal medicinal plant used in convulsion

2.1 Abelmoschus manihot

Abelmoschus Manihot is commonly known as Hibiscus Manihot. It belongs to the family Malvaceae. It is native to China. J. Guo et al. evaluated anticonvulsants and the effects of Abelmoschus Manihot ethanol extract (AMEE) in mice against PTZ-induced clonic convulsions and mortality. The PTZ-induced convulsion paradigm was selected to assess AMEE's activity. The onset of convulsions and death caused by pentylenetetrazole (PTZ) was significantly postponed by pretreatment of the AMEE. PTZ is known to cause convulsions by blocking GABA's function in the central nervous system. Thus, it's probable that AMEE's agonistic effect on the GABA/benzodiazepine receptor prevented the convulsion.[5]

2.2 Abrus precatorius L.

Abrus precatorius L. is commonly known as jequirity. It belongs to the family Fabaceae.it is native to Asia and Africa. Ogbuehi et al evaluated the anticonvulsant activity of ethanol extract of A. precatorius leaves was investigated using pentylenetetrazole, strychnine, and picrotoxin-induced convulsion in murine models. MEAP may have an antiepileptic effect, which is most likely mediated by the chloride channel of the GABA/benzodiazepine receptor complex rather than the chloride channel of glycine receptors. PTZ causes convulsions by inhibiting GABAergic neurotransmissions and interacting with GABAA receptors. The augmentation and inhibition of GABA neurotransmission will reduce and intensify convulsions, respectively.[6]

2.3 Benincasa hispida

Benincasa Hispida is commonly known as Kushmanda in Sanskrit/ Hindi, Kumora in Assamese, and Ash Gourd in English. It belongs to the family Cucurbitaceae. It is native to South and Southeast Asia. Kaushik et al evaluated the anticonvulsant activity of Ethanolic extract of Benincasahispida (EEBH) by Maximal Electroshock seizure (MES) and Pentylenetetrazol induced seizure models on Albino (Wistar strain) rats. The anticonvulsant action of the MES The model is defined by the drug's effect on the tonic hind-limb extensor phase of the convulsion, which is either entirely abolished or reduced in duration. In the current investigation, it was discovered that the duration of the extensor phase was reduced in the test groups. The extensor phase was completely abolished in the Phenytoin standard group.[7]

2.4 Butea monosperma

Butea monosperma is commonly known as Bastard Teak. It belongs to the family Fabaceae.it is native to Meerut, Uttar Pradesh, India. Dr. K.S Lakshmi & Dr. K. Ilango evaluated the anticonvulsant activity of the Methanolic Extract of Butea monosperma leaves (MEBM) using the Maximal electroshock induced convulsion (MES) model, Pentylenetetrazole (PTZ) and strychnine induced seizure model. Butea monosperma extract delayed the occurrence of PTZ-induced convulsion, it may probably be by interfering with the GABA aminergic mechanism and Ca2+ channels. Thus, the methanolic extract of Butea monosperma leaves possesses anticonvulsant properties against MES and PTZ-induced seizures which could be by interfering with GABA, glutaminergic mechanism, and Na+, Ca2+ channels.[8]

2.5 Clerodendron infortunatum

Clerodendron infortunatum is commonly known as Bhat or hill glory bower. It belongs to the family Verbenaceae.it is native to India. S. Das et al. evaluated the anticonvulsant effect of methanolic extract of Clerodendron infortunatum Linn. (MECI) leaves in Swiss albino mice. Against pentylenetetrazole and strychnine-induced convulsion. Both PTZ-induced and STZ-induced convulsions were suppressed by MECI at both dosages (250 and 500 mg/kg b.w. i.p). These findings suggest that the chloride channels of the glycine receptor and the GABA/benzodiazepine receptor complex may be involved in the anticonvulsant effects of MECI. In the etiopathology of epilepsy, GABA is essential. GABAergic systems have been linked to defense against a range of seizures brought on by chemotherapy and electroshock. PTZ-induced seizure convulsion can be effectively prevented by MECI at both dosages. Since PTZ interferes with GABA transmission, this data implies that the GABAergic system may be involved in the action of MECI.[9]

2.6 Delphinium denudatum

Delphinium denudatum is commonly known as ‘Jadwar’. It belongs to the family Ranunculaceae. It is native to the Himalayas region from Pakistan to Kashmir and northwest India. M. Raza et al. evaluated the anticonvulsant activity of the ethanolic extract (EE) and aqueous fraction (AF) of this plant utilizing the maximal electroshock (MEST) and subcutaneous

pentylenetetrazole (scPTZ), bicuculline (scBIC), picrotoxin (scPTX) and strychnine (scSTN) tests for anticonvulsant activity in mice. The testing material's capacity to suppress or stop seizure discharge within the brainstem is further demonstrated by an anticonvulsant effect in the MEST model. At 600 and 800 mg/kg, AF had a much stronger effect and effectively inhibited HLTE, whereas EE had a modest dose-dependent effect. This reveals the presence of anticonvulsant chemicals in AF that can be useful in inhibiting MES-induced HLTE and suggests that compounds in the AF effectively treat generalized tonic-clonic and partial seizures. In the scPTZ test, EE showed mild dose-dependent anticonvulsant efficacy. The presence of anticonvulsant chemicals was demonstrated by the gradual development in its anticonvulsant properties, which at 600 mg/kg protected against tonic fore and hind limb seizures by 40%. These inflammatory cytokines have been shown to harm neurons by altering neuronal excitability, producing toxic mediators, and increasing BBB impermeability (91,94). IL-1β activates the NMDA receptor, increasing calcium input into neurons and causing hyperexcitability. Tumor necrosis factor-α, like IL-1β, can increase neuronal excitability by up-regulating AMPA receptors, which promote calcium input, and down-regulating GABA receptors, which weaken inhibitory synapse strength. Aside from excitotoxic effects, inflammatory cytokines may contribute to apoptotic neuronal death, most likely through the generation of neurotoxic mediators and NMDA- and AMPA-mediated glutamatergic excitotoxicity.[10]

2.7 Elettaria cardamomum

Elettaria cardamomum is commonly known as the queen of spices. It belongs to the family Zingiberaceae.it is native to humid Asian areas. Masoumi-Ardakani Y et al. evaluated the anticonvulsant activity of the essential oil and methanolic extract of E. cardamomum against chemically (pentylenetetrazole)- and electrically (maximal electroshock)-induced seizures in mice. At 0.75 mL/kg, cardamom essential oil might considerably block and extend HLTE. The beginning of tonic seizures occurs at 0.25 mL/kg. It also enhanced the latency time for clonic seizures by 1 mL/kg. Because their anticonvulsant effects fall between neurotoxic and deadly, they are ineffective for therapeutic uses. The only significant anticonvulsant activity observed in the PTZ model was an increase in HLTE time.[11]

2.8 Glycyrrhiza glabra

Glycyrrhiza glabra is commonly known as licorice. It belongs to the family Leguminosae. It is native to Eurasia, central and southwestern Asia, and the Mediterranean region. S.D. AMBAWADE et al evaluated the anticonvulsant activity of ethanolic extract of roots and rhizomes of Glycyrrhiza glabra (10, 30, 100, and 500 mg/kg, i.p.) in mice was assessed using maximum electroshock seizure (MES) test and pentylenetetrazol (PTZ) using albino mice. EE had no fatal impact at doses up to 1 g/kg and showed dose-dependent anticonvulsant efficacy against seizures caused by PTZ and lithium pilocarpine. However, it did not work against MES-induced seizures. Since inhibition of the MES test predicts activity against generalized tonic-clonic and cortical focal seizures, a lack of activity against MES-induced seizures implies that the EE is ineffective in suppressing generalized tonic-clonic seizures. Phenobarbitone, sodium valproate, diazepam, and trimethadione all prevent pilocarpine-induced limbic seizures in rats, although phenytoin and carbamazepine do not. Blocking post-synaptic 5-HT receptors and inhibiting serotonergic transmission have been demonstrated to decrease lithium-pilocarpine-induced seizures as well as PTZ-induced seizures.[12]

2.9 Hyoscyamus niger

Hyoscyamus niger is commonly known as henbane, black henbane, and stinking nightshade. It belongs to the family Solanaceae. as it is native to Iran. Heidari Mahmoud Reza et al. evaluated the anticonvulsant activity of methanolic extract of H. niger L. on seizures induced by picrotoxin in mice. H. niger methanolic extract only partially and weakly antagonized PIC-induced seizures and was much less effective compared with Phenobarbital. H. niger methanolic extract only partially and poorly inhibited PIC-induced seizures and was much less efficacious than Phenobarbital. H. niger inhibits GABAergic neurotransmission, but most likely not through GABA-A receptor sites. H. Niger has been reported. It includes several alkaloids such as hyoscyamine, hyoscine (scopolamine), and atropine, which have been shown to have anticholinergic (parasympatholytic) properties. Although anticholinergic medications are beneficial against nerve gas-induced seizures. Anticholinergic medications worsened epileptic episodes. The anticonvulsant action of H. niger methanolic extract is most likely due to enhanced GABAergic neurotransmission. The plant extract's apparent anticonvulsant efficacy could be attributed, at least in part, to its ability to depress the central nervous system (CNS) via one or more of the recognized anticonvulsant pathways.[13]

2.10Hypericum perforatum

Hypericum perforatum is commonly known as St. John wort. It belongs to the family Hypericaceae.it is native to the North of Iran. H. Hosseinzadeh et al evaluated the anticonvulsant activity of the aqueous and ethanolic extracts of Hypericum perforatum aerial parts in mice. Both the ethanolic and aqueous extracts increased the latency of convulsions induced by PTZ dose-dependently. Both ethanolic and aqueous extracts increased the delay of PTZ-induced convulsions in a dose-dependent manner. Thus, Hypericum perforatum may have a favorable effect on this type of seizure in clinical studies. In the MES test, neither the aqueous nor the ethanolic extracts showed anticonvulsant efficacy. L-NAME (1, 5, and 10 mg/kg) prolonged the latency of PTZ-induced convulsions, although the impact was not

significant. LNAME lowered the extracts' anticonvulsant activity in the PTZ test. L-NAME decreased the antiseizure effect of the extracts. In mice, nitric oxide was generated in response to NMDA receptor activation, increasing cGMP and seizure activity termination. The anticonvulsant activity of this plant might be partially mediated by the nitric oxide pathway.[14]

2.11Ichnocarpus frutescens

Ichnocarpus frutescens black paper. It belongs to the family Apocynaceae.it is native to India. Anticonvulsant activity and probable mechanism of action of the methanol root extract from I. frutescens (MEIF) was evaluated in maximal electroshock- (MES-), pentylenetetrazole-(PTZ), and isoniazid- (INH-) induced convulsions models in rats. In the mammalian brain, GABA T is the main catabolic enzyme that catalyzes the conversion of amino groups from GABA to α-ketoglutarate, which lowers the amount of GABA. GABA-T activity in the rat brain was markedly elevated by PTZ. Vigabatrin (50 mg/kg, i.p.) and MEIF (200–400 mg/kg, p.o.) administration dramatically reduced the enzyme activity, suggesting a strong GABA-T inhibitory action. It is well known that convulsions produce free radicals, which throw off the brain's GABA-glutamate activity balance. In convulsive rats, MEIF (200 and 400 mg/kg, p.o.) has strong antioxidant action.[15]

2.12Lavandula stoechas

Lavandula stoechas are commonly known as Ustu khuddoos. It belongs to the family Lamiaceae. It is native to Arabic and Mediterranean Coasts to Asia Minor. A.H. Gilani et al. evaluated anticonvulsant activity. The aqueous-methanolic extract of L. stoechas flowers (LS) in mice, LS (600 mg/kg) induced by pentylenetetrazole (PTZ). L. stoechas has been used traditionally in epilepsy. Anticonvulsive activities are mediated through calcium channel blockade. Some recent studies revealed that calcium antagonists were also found useful in convulsive disorders.[16]

2.13Mimosa pudica

Mimosa pudica is commonly known as a shame plant. It belongs to the family Mimosaceae.it is native to It is native from Middle America and now widely distributed in all tropical areas. E. Ngo Bum et al. evaluated the anticonvulsant activity of the decoction of Mimosa pudica leaves given intraperitoneally at a dose of 1000–4000 mg kg protected mice against pentylenetetrazol and strychnine-induced seizures. Antagonism of PTZ-induced seizures suggests that M. pudica extract may affect GABA-ergic neurotransmission, as PTZ has been found to interact with the GABA neurotransmitter w10,11,13x. M. pudica inhibits STR-induced seizures and NMDA-induced turning behavior, implying that other processes may be involved. Inhibition of STR-induced seizures indicates interaction via glycine. Receptors w14x, whereas inhibition of NMDA-induced turning behavior indicates interaction via NMDA receptors w7,8x. M. pudica's diverse method of action and a broad spectrum of anticonvulsant efficacy could be attributed to the presence of many active components interacting at the same time.[17]

2.14Murraya koenigii

Murraya koenigii is commonly known as Meethi neem and karry tree. It belongs to the family Rutaceae. It is native to India. The aqueous extract of the leaves of M. koenigii (200 and 300 mg/kg) was studied for its antiepileptic effect on maximal electroshock-induced seizures and pentylenetetrazole-induced seizures in mice. The MES is likely the best-validated approach for evaluating antiepileptic medications in generalized tonic-clonic seizures. At the highest tested dose (300 mg/kg), the aqueous extract was observed to considerably reduce the duration of the hind limb tonic extensor phase, whereas the lower dose (200 mg/kg) had a lesser effect on seizures. M. koenigii leaf extracts demonstrated anticonvulsant efficacy by delaying the onset of PTZ-induced seizures and shielding treated mice against seizure-related death. Drugs that prevent tonic-clonic seizures caused by PTZ are thought to be effective in regulating myoclonic and absence seizures in humans.[18]

2.15Nigella sativa

Nigella sativa is commonly known as black seeds or black cumin. It belongs to the family Ranunculaceae. It is native to Pakistan, India, and Iran. H. Hosseinzadeh and S. Parvardeh evaluated the anticonvulsant activity of thymoquinone, the major constituent of Nigella sativa seeds, against pentylenetetrazole (PTZ)- and maximal electroshock (MES)-induced seizure models. The findings from the PTZ-induced seizure model in mice that had received flumazenil beforehand imply that thymoquinone may help the GABAergic system's inhibitory activity, most likely by acting as a competitive agonist in the GABA receptors' BZD region. Thymoquinone has been demonstrated to have antinociceptive effects by indirectly activating opioid receptors. Thymoquinone activates the κ-opioid receptor subtypes to generate antinociceptive effects. This study shows that κ-opioid receptor stimulation has an anticonvulsive effect. It is commonly known that the κ-opioid receptor. Agonists primarily restrict Ca2+ entrance by affecting Ca2+ channels. By lowering Ca2+ entry, postsynaptically localized κ-opioid receptors may help to reduce excitability brought on by postsynaptic blockage of GABAA receptors. These documents significantly support the hypothesis that κ-opioid receptors may contribute to the anticonvulsant activity of thymoquinone. Agonists generally inhibit Ca2+ admission by altering Ca2+ channels. Postsynaptically localized κ-opioid receptors can reduce excitability caused by GABAA receptor blockage by decreasing Ca2+ entry. These documents strongly support the concept that κ-opioid receptors contribute to thymoquinone's anticonvulsant effect.[19]

2.16Pimpinella anisum

Pimpinella anisum is commonly known as anise seed. It belongs to the family Apiaceae. It is native to the eastern Mediterranean region and southwest Asia. Karimzadeh et al evaluated the anticonvulsant activity of anise oil was tested on seizure attacks induced by pentylenetetrazol (PTZ) injection and neuronal hypoxia induced by oxygen withdrawal on models of rat brains. The anticonvulsant effects of anise oil may be due to the activation of GABAA receptors. It has been shown that anise oil exerts its effect on opioid receptors via activation of GABAA receptors in mice. In addition, it has been revealed that anise oil enhances the activity of the Na+ -K+ ATPase. The Na+ -K+ pumps play an important role in the regulation of neuronal excitability. Disruption of the pump activity is suggested as a mechanism in the development of epileptiform burst discharges. Na+ -K+ pump inhibition altered both GABAA and GABAB components of inhibitory postsynaptic potentials.[20]

2.17Plectranthus barbatus

Plectranthus barbatus is commonly known as Plectranthus forskohlii Briq, Plectranthus forskalaei Willd., and Plectranthus kilimandschari (Gurke).it belongs to the family Lamiaceae. It is native to Africa. Anticonvulsant activity of a hydroalcoholic extract of P. barbatus leaves on seizures induced by strychnine sulfate and pilocarpine in mice. Plectranthus barbatus has anticonvulsant properties that prevent seizures brought on by pilocarpine and strychnines. Diterpenoids such as forskolin, plectranthone J, plectrin, (16S)-coleon E, coleon F, (16R)-plectrinone A, plectrinone B, cyclobarbatusin, barbatusin, and 7β-acetyl-12-desacetoxicyclobarbatusin have been identified through phytochemical research on P. barbatus. Since forskolin has been demonstrated to inhibit seizures brought on by pentylenetetrazol, it is a promising candidate for P. barbatus's anticonvulsant function. Adenylate cyclase is activated by forskolin. And raises cAMP levels inside cells. Mediated via cAMP activation of inward rectifier K+ currents, forskolin has been shown to induce membrane depolarization in medium spiny neurons of the mouse nucleus accumbens. In isolated rat substantia gelatinosa neurons, forskolin enhances the amplitude of glycinergic small inhibitory postsynaptic currents even when there is little extracellular glycine present.[21]

2.18Piper methysticum

Piper methysticum is commonly known as kava. It belongs to the family Piperaceae. It is native to the South Pacific islands. The anti-convulsive potential of aqueous extracts prepared from specific tissues of Kava (Piper methysticum) stems in zebrafish was evaluated by using the PTZ-induced seizure model. Extracts from kava roots increase the binding of GABA type A receptors and ligands, which results in an anticonvulsant action. Kavalactones such as kavain, desmethoxyyangonin (DMY), and 7,8-dihydromethysticin (DHM) are thought to be responsible for these effects. After 45 minutes of pretreatment, the 50 mg/L aqueous Kava extract from the stems without peel (SNPA) showed anti-convulsive potential. Following treatment with the aqueous Kava extracts, there was a considerable decrease in BDNF expression, which may be one of the reasons for its anti-convulsive effects.[22]

2.19Pentas schimperiana

Pentas schimperiana (A. Rich.) Vatke is commonly known as Woinagrefet, also known as Dibexxo (Gideo) and Moonyeer or Dasie (Afaan Oromo). It belongs to the family Rubiaceae.it is native to Ethiopia, while subspecies occidental is occurring in Cameroon. To evaluate the anticonvulsant activity of 80% methanol root bark extract and solvent fractions of Pentas schimperiana (A. Rich.) Vatke used the pentylenetetrazole and maximal electroshock-induced seizure test in mice. The ME400 dose of the crude extract demonstrated strong anticonvulsant effectiveness against PTZ-induced clonic seizures in the PTZ-induced seizure model investigation. This may be because the ME400 dose markedly shortened the mean duration of THLE. Compared to the aqueous and chloroform fractions, the butanol fraction exhibited a greater effect on THLE duration reduction. The anticonvulsant properties of the higher dose crude extract and butanol fraction may be attributed to the broadspectrum phytoconstituents included in both extracts. Anticonvulsant action against generalized tonic-clonic seizures, such as inhibiting the Na+ channel and/or improving GABAergic neurotransmission.[22]

2.20Rubus brasiliensis

Rubus brasiliensis is commonly known as amora Branca. It belongs to the family Rosaceae. It is native to Brazil. E. Nogueira, V.S. Vassilieff evaluated the anticonvulsant activity of the alcoholic extract of Rubus brasiliensis by using Pentylenetetrazol-induced seizures in Male Swiss mice. Observations demonstrate that the hexanic fraction profile is similar to the agonist of the benzodiazepine receptor.

To determine if the benzodiazepine receptor participates in the hexanic fraction-induced hypnotic, anticonvulsant, and muscle relaxant effects. It can be strongly suggested that the hexanic fraction obtained from R. brasiliensis contains an agonist benzodiazepine-like principle.[23]

2.21Rauvolfia vomitoria

Rauvolfia Vomitoria is commonly known as “Asofeyeje” and “Akanta”.it belongs to the family Apocynaceae. It is native to Asia and West African countries. The anticonvulsant activity of the aqueous leaf extract of Rauvolfia vomitoria (Afzel) was investigated by testing the effects of the extract on strychnine-, picrotoxin, and pentylenetetrazole-induced seizures in mice. GABA is the major inhibitory neurotransmitter in the brain and its inhibition is thought to be an underlying factor in epilepsy. It is, therefore, probable that the anticonvulsant effect of the extract might involve both GABAergic and glycinergic inhibitory mechanisms. The aqueous leaf

extract of R. vomitoria demonstrated potential anticonvulsant properties and less toxicity in the experimental animals at the doses used.[24]

2.22Solanum nigrum

Solanum nigrum is commonly known as jimson weed, Datura, or sacred datura. It belongs to the family Solanaceae.it is native to Eurasia, Australia, and South Africa. Anticonvulsant activity of aqueous leaf extract of Solanum nigrum evaluated by a pentylenetetrazole-induced seizure in mice and rats and picrotoxin-induced seizure in mice and rats. Aqueous extract of S. nigrum increases the release of GABA. It has been observed that an increase in catecholamines, will enhance anticonvulsant activity. Enhancement of central dopaminergic transmission is responsible for anticonvulsant activity. Higher doses of the extract (30-60 mg/kg) gave complete protection against seizures. The administration of amphetamine enhanced the anticonvulsant activity of the extract in rats and mice while co-administration of the extract with chlorpromazine increased the seizure threshold in rats but offered no protection against seizures.[25]

2.23Solanum tuberosum

Solanum tuberosum is commonly known as potato. It belongs to the family Solanaceae. It is native to Peruvian -the Bolivian Andes. Anticonvulsant activity of potato juice evaluated by bicuculline-induced seizure threshold test in mice. The anticonvulsant effect of the potato juice after both i. c. as well as per os administration was significant which allows us to suggest penetration of GABA receptor active compounds via the brain-blood barrier. The amount of pharmacologically active benzodiazepines that can be ingested on a daily diet containing potatoes or by drinking potato juice seems to be below the pharmacologically used doses. The therapeutic dose of diazepam ranges from 5 – 20 mg per day. However, the results of our study suggest that potato juice might contain other GABA pathway-modulating substances in addition to benzodiazepine.[26]

2.24Trigonella foenum-Graecum L

Trigonella foenum-Graecum L is commonly known as Fenugreek. It belongs to the family Fabaceae. Dr. Muhammad Mohtashim evaluated the anticonvulsant action of methanolic extract Trigonella foenum graecum L in rats by strychnine-induced convulsions. Administration of TFGS-ME for 14 days to rats indicated a significant delay in the onset of convulsion at 50 and 100 mg/kg while very significant delay at 200mg/kg comparable to diazepam. Additionally, the frequency of convulsions was greatly reduced at 100 and 200 mg/kg, which were equivalent to diazepam. All three doses resulted in a considerable reduction in convulsion duration when compared to control animals. It presumably works by binding to the benzodiazepine site of the GABAA receptor complex, extending the length of seizure onset in mice with PTZ-induced seizures. Quercetin had anticonvulsant properties as well. It is proposed that it inhibits N-methyl D and modifies GABAA receptors. receptors for aspartate (NMDA). By reducing oxidative stress, rutin demonstrated an anticonvulsant effect in seizures caused by kainic acid. Additionally, via positively allosterically modulating the GABAA receptor, rutin functions as a ligand for benzodiazepine receptors. The inclusion of several flavonoids in TFGS-ME is responsible for its anticonvulsant properties.[27]

2.25Valeriana edulis

Valeriana edulis is commonly known as tobacco root. It belongs to the family Caprifoliaceae.it is native to western and central North America. M.E. Gonzalez-Trujano et al. evaluated the anticonvulsant activity of ethanol extract of V. edulis against pentylenetetrazole-induced seizures in rats. The anticonvulsant activity of V. edulis was preliminarily investigated in a neuropharmacological profile in mice, where it was demonstrated a dose-dependent and significant delay in the PTZ-induced tonic-clonic seizures. A dose-effective produced a significant reduction in seizure severity and the percentage of generalized seizures in implanted rats. Additionally, the occurrence of SWDs was changed. These changes may be associated with enhanced GABAergic transmission; it has been reported that valerenic acid and V. officinalis delay the latency of generalized seizures, and this protective effect is more prominent when V. Officinalis is combined with antiepileptic drugs such as clonazepam. The parietal cortex is known to be a driver of SWD generation and alters corticothalamic loop excitability; the enhancement is due to a synergistic effect with GABA; some antiepileptic medications exacerbate the symptoms of absence epilepsy. One noteworthy finding was the increase in SWDs in the P15 and P30 groups, though only the increase in the P30 group was significant.[28]

2.26Withania somnifera

Withania somnifera is commonly known as Ashwagandha. It belongs to the family Solanaceae.it is native to India, the Middle East, and parts of Africa. S. K. Kulkarni and B. George evaluated the anticonvulsant activity of methanolic extract of Withania somnifera root extract against PTZ-induced seizure in mice It has been found that a methanolic extract of W somnifera root prevented the specific binding of ['SIGABA and ['S] TBPS; increased the binding of [3H] flunitrazepam to GABAreceptor-mediated anticonvulsant properties. Their potential receptor locations and elevated 36Cl-influx in mammalian spinal cord neurons when GABA is not present. According to these biochemical investigations, there is a component in the W somnifera extract that possesses GABA-mimetic properties. W somnifera exhibited a protective effect against PTZ-induced kindling that was similar to that of the well-known GABAergic anticonvulsant drug diazepam.[29][30]

3. CONCLUSION

The limited efficacy of AEDs is still a matter of concern. Since the beginning of time, animal models have been used to test novel medications, and as science and technology advance, they get increasingly complex. Some of the possible herbal treatments that have been tried and shown effective in animal models have been highlighted in this review. How many of these possible treatments advance to clinical trials and end up on the AED list is still unknown. To ascertain which is most effective, more study in this field is desperately needed. Strict research methodology with consistent herbal combinations and clinical investigations using chosen standardized botanical extracts are also required.

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