ANTICONVULSANT ACTIVITY OF SOME MEDICINAL PLANTS: A REVIEW

Abstract

Epilepsy is a central nervous system (neurological) disorder characterized by a bizarre feelings, sensations, and behaviors. Muscle spasms, convulsions, and loss of consciousness occasionally from epileptic seizures. Neuronal dependent on neurotransmitters in the central nervous system. In this review, we discussed epilepsy and its therapies, placing particular emphasis on some medicinal plants and their mechanism of action. The majority of herbal remedies that are both tested for anticonvulsant activity and utilized in ethno medicine to treat epilepsy were reported. The findings demonstrate that active components extracted from medicinal plants can prevent and treat neuronal disorder.

Key Word: Transmitter, excitotoxic neuronal plasticity, seizure, neurosyphilis

Introduction

Epilepsy is a brain disorder that result from intense, improperly coordinated, confined, or broadly dispersed electrical discharges from neurons (Chauvel and McGonigal, 2014). An epileptic seizure is a period of aberrant neuronal discharge that manifests clinically as alterations in sensory perception, motor coordination, mood, or autonomic function (Rabiei, 2017). Numerous factors, including congenital, developmental, or inherited ones, can result in epileptic seizure disorders. Most seizures are spontaneous, without prior warning, short-lived (a few minutes or even seconds), and terminate on their own (Weinstein, 2016). In various human communities, epileptic seizures are regarded as the most prevalent neurologic symptoms, and they continue to be the most prevalent neurological disorder affecting people of all ages. About fifty million people worldwide suffer from epilepsy, a chronic noninfectious brain disorder (Lozano et al., 2020; (Suleiman et al., 2022). According to reports, epilepsy affects 1/125 of the population in Nigeria, which indicates that it is a significant burden (Owolabi et al., 2019). Periodic seizures, which are defined by fleeting episodes of uncontrollable movement involving either a section of the body or the full body, are what make this medical disorder distinct. Sometimes they accompany loss of awareness and control of the bowels or the bladder (WHO, 2019). There are two primary categories of seizures: focused or partial seizures and generalized seizures. One area of the brain, referred to as the seizure's "focus," is the only one affected by focal seizures. Focal seizures can affect a large portion of one hemisphere or just a small portion of a lobe, but generalized seizures happen when seizure activity is widespread in both the left and right hemispheres of the brain, and the affected person falls unconscious, albeit briefly except in myoclonic seizures (Sinke et al., 2016). High-frequency action potential bursts and excessive synchronization of a neuronal population are two concurrent characteristics that mark the beginning of seizures (Jiruska et al., 2010). Extracellular Ca++ causes an inflow of Na+, the opening of voltage-dependent Na+ channels, the formation of recurrent action potentials, and the bursting activity that arises from the neuronal membrane's comparatively protracted depolarization. Depending on the type of cell, the gamma-aminobutyric acid (GABA) receptors and Cl influx or K+ efflux mediate the hyperpolarizing potential (Nawafleh et al., 2022). GABA is a specific kind of inhibitory neurotransmitter in the brain that effectively stops the brain from delivering messages (Rabiei, 2017). In some cases, GABA interneurons may paradoxically

promote particular types of epileptic discharges. Effective anticonvulsants are those that boost synaptic GABA by inhibiting its breakdown or reuptake. These include benzodiazepines, which enhance GABA binding to the GABA receptor and increase the frequency of chloride channel openings (Greenfield, 2013), (Rabiei, 2017), (Janković et al., 2021). Seizures can be brought on by several GABA production inhibitors, such as thiosemicarbazide, 4-deoxypyridoxine, isoniazid, and L-allyglycine (Akyuz et al., 2021). The two main kinds of receptors, $GABA_A$ and $GABA_B$, are involved in the interactions between GABA, the main inhibitory neurotransmitter. While $GABA_B$ receptors are located presynaptically and can consequently influence synaptic release, $GABA_A$ receptors are positioned postsynaptically. In the adult brain, $GABA_A$ receptors are permeable to Cl-ions; Cl-influx activation hyperpolarizes the membrane and suppresses action potentials. Barbiturates and benzodiazepines are $GABA_A$ receptor agonists, and as a result, they reduce seizure activity. Because of their presynaptic position, $GABA_B$ receptors are associated to second messenger systems but not Cl^- channels, and thus attenuate transmitter release (Alten et al., 2022). A kind of amino acid called glutamate serves as the brain's main excitatory neurotransmitter. Under normal circumstances, glutamate produced from synapses is taken up by astrocytes and quickly transformed by glutamine synthetase into the non-excitotoxic amino acid glutamine (Vasilev et al., 2018). Epileptic seizures are mediated by the metabotropic glutamate receptor and the ionotropic N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid / kainate, and others (Rabiei, 2017). In chronic epilepsy models, excitatory glutamatergic pathways have a role in both long-term adaptive neuronal plasticity associated to epileptogenesis and acute, transitory, provoked seizures. The excitatory effects of glutamate increase sodium and calcium conductance via activating ligand-gated ion channels (NMDA and non-NMDA receptors) (Rabiei, 2017). Glutamate and aspartate are more easily reabsorbed after synaptic release, these effect is enhanced by the neuronal excitatory amino acid carrier 1 (EAAC1) and glial glutamate transporters. Reduced glutamate transporter activity may be consistent with increased excitatory activity (Srivastava et al., 2020).

Etiology of Epilepsy

Despite the fact that the frequency of symptomatic epilepsy gradually increases with age, idiopathic epilepsy continues to be the most prevalent in all age groups (Sen et al., 2020). In Nigeria, between 55 and 60 percent of epilepsy cases are considered to be idiopathic (Olubunmi, 2009). In other regions of the world, approximately 30% of seizure patients have a diagnosable neurological or systemic illness, with the remaining patients having either idiopathic or cryptogenic epilepsy.

Genetics: Recent research from several studies revealed that 20% of epilepsy sufferers, especially in adolescents, have genetic variants of the condition (Laxer et al., 2014). There is little data on the genetic epidemiology of epilepsy among Nigerians, but there have been instances of tuberous sclerosis in Nigerians who have the condition (Ogunrin et al., 2013).

Infections

Central nervous system infections, such as bacterial and viral meningitis, encephalitis, neurosyphilis, brain abscesses, and tuberculosis, continue to be the most common cause of symptomatic epilepsy. These infections were the cause of 10% to 20% of the epilepsy cases that were documented in Africa (Olubunmi, 2009). In the tropics, where there are little medical facilities, especially in rural and suburban areas, CNS infections are the primary cause of acute seizures. There is scant evidence that local parasites frequently cause epilepsy despite the high incidence of parasitic diseases in Nigeria. Nevertheless, there are several studies from other parts of the world, particularly other developing nations, implicating parasites in the development of epilepsy (Gourama, 2020). In some regions of the world, cysticercosis is the most frequent cause of epilepsy because computed tomography (CT), which was developed in the 1970s and early 1980s, made it possible to diagnose it. The most prevalent manifestation of neuro cysticercosis is epilepsy, which frequently manifests as a single clinical symptom. As a result, prevalence estimates for idiopathic epilepsies in endemic locations cannot be trusted unless participants have undergone a CT scan. In contrast to her neighbors Cameroun and Togo, where cysticercosis was the leading cause of epilepsy cases, Nigeria has only seldom recorded occurrences of this infection (Siewe et al., 2020), (Ogunrin et al., 2013). It is through cardiac embolization of the brain that Trypanosoma Cruzi, the causative agent of Chaga's disease, and epilepsy are indirectly linked. Seizures are a possibility in the late stages of the African Trypanosoma infection, sleeping sickness, as well as perhaps as a follow-up in survivors (Kennedy and Rodgers, 2019). One of the distinguishing features of cerebral malaria caused by Plasmodium falciparum is seizures. The most prevalent infection linked to febrile seizures in this region may be P. Vivax, the more prevalent cause of malaria in Latin America, however this is not confirmed (Recht et al., 2017).

Trauma

In Nigeria, two of the most frequent causes of epilepsy are trauma and hypoxia. Due to subpar obstetric care, these risks may act singly or in concert during pregnancy, or throughout life in instances of domestic violence, workplace violence, and auto accidents. Birth trauma can result in epilepsy after severe scalp molding and hypoxia, which then have a negative impact on the hippocampus and amygdala and induce incisura sclerosis. In Africa, it accounts for 1–2% of cases of symptomatic epilepsies (Ba-Diop et al., 2014). The world's greatest rate of car accidents per million vehicle miles occurs in Nigeria and the East African nations, and as a result, post traumatic epilepsy is more prevalent. The occurrence of a seizure in the first week following a head injury suggests an increased likelihood of another seizure.

Tumors

In Africa, 3–10% of symptomatic epilepsies are caused by cerebral tumors (Balogun et al., 2022). More occurrences of epilepsy owing to cerebral tumors are becoming visible with the

introduction and installation of CT in various tertiary institutions in several African countries (Ogunrin et al., 2013)

Vascular

Only 5% of patients with cerebral infarction have chronic seizures, which happen in 15% of individuals. Seizures can be caused by arteriovenous malformation, intracerebral hemorrhage, subdural hematoma, and inflammatory vasculitis (such as polyarteritis nodosa and lupus erythematosus) (Abdel et al., 2014).

Metabolic

Seizures may be caused by metabolic abnormalities, such as pyridoxine insufficiency, which is connected to elevated glutamic acid and decreased gamma aminobutyric acid (GABA) levels in the brain (Wilson et al., 2019). Alkalosis, water intoxication, hypoglycemia, hypocalcemia, hypomagnesemia, uraemia, and aminoaciduria are additional metabolic conditions that can cause epilepsy (Steinman and Goilav, 2020). Rarely, an insulinoma that causes hypoglycemia may also cause epilepsy (Louda et al., 2013).

Pathophysiology of Epilepsy

An overly synchronized and prolonged discharge of a set of neurons is the cause of epileptic seizures. A continuous rise in neuronal excitability is the defining characteristic of all epileptic disorders. There are many different causes of abnormal cellular discharges, including trauma, oxygen deprivation, malignancies, infections, and metabolic disturbances. However, in roughly 50% of epilepsy patients, there are no definite causes established. Some types of epilepsy, such as those brought on by neuronal migratory abnormalities and monogenic epilepsies, have underlying causes and pathophysiological mechanisms that are (partially) characterized (Lesca et al., 2019), (Engelborghs et al., 2000). There is currently little information available about a number of other kinds of epilepsy. The main neuronal migratory problems that can have hereditary or intrauterine origins are those that lead to epilepsy (Stouffer et al., 2016). Different types of agyria and pachygyria are caused by abnormal neuronal migration patterns, whereas neuronal heterotopia in the subcortical white matter is caused by milder levels of neuronal migration failure (Verrotti et al., 2010). Studies have shown that the microgyric cortex has higher levels of postsynaptic glutamate receptors and lower levels of gamma-aminobutyric acid ($GABA_A$) receptors, which may encourage the development of epileptogenesis (Sarnat and Flores-Sarnat, 2021). Epilepsy and abnormal neural migration are two features that are frequently observed in people with tuberous sclerosis, a developmental condition inherited in an autosomal dominant manner. An X-linked dominant disease of cerebral cortical development is called periventricular heterotopia. It is known that periventricular heterotopia is caused by

mutations in the filamin 1 gene, which block the movement of cerebral cortical neurons (Ferland et al., 2009), (Sarkisian et al., 2008). Females with the condition exhibit seizures, whilst males with the condition experience embryonic death. However, a male patient who had bilateral periventricular and subcortical heterotopia was recently reported, raising the possibility of a new gene involved in brain development (Leventer et al., 2022), (Meuwissen and Mancini, 2012). Another abnormality of neuronal migration is the double cortex syndrome and X-linked lissencephaly. In contrast to more severe lissencephaly, which is prevalent in affected males, double cortex or subcortical band heterotopia frequently affects females (D'Agostino et al., 2002), (Liu, 2011). Recently, a causative mutation in the doublecortin gene was found. It has been hypothesized that doublecortin serves as an essential intracellular signaling molecule for the migration of growing neurons (Wu et al., 2014).

Anticonvulsant drugs

Anticonvulsants in particular are used in pharmacological therapy to manage the majority of epileptic seizures. Anticonvulsant medications are used as the mainstay of treatment for seizures, despite the fact that there are several anticonvulsant therapeutic options for distinct seizure types and epileptic disorders (Perucca & Tomson, 2011). The conventional anticonvulsants carbamazepine, valproic acid/valproate semisodium, phenytoin, and phenobarbital, as well as more recently gabapentin, oxcarbazepine, lamotrigine, or topiramate, can be used to treat newly diagnosed epilepsy patients who require treatment (Rabiei, 2017). The intensity and frequency of the seizures, as well as the patient's age, general health, and medical history, all affect the recommended treatment. To select the most effective treatment, an accurate identification of the epilepsy type is necessary (N.J. et al., 2022), (An et al., 2020). Traditional antiepileptic medications may inhibit sodium channels or enhance GABA activity. Various antiepileptic medications have a variety of possibly ambiguous methods of action (Kobayashi et al., 2020). Their targets include $GABA_A$ receptors, GABA transporter 1, GABA transaminase, and voltage-gated calcium channels in addition to voltage-gated sodium channels and parts of the GABA system (Rogawski et al., 2016). Antiepileptic medications reduce the release of excitatory glutamate, which rises in epilepsy, as well as GABA, by blocking sodium or calcium channels (Lasoń et al., 2013). Given that GABA can either directly or indirectly act pro convulsively, this may be a side effect of several antiepileptic medications or perhaps their real mode of action (Wang and Chen, 2019). Due to the prolonged therapy given to patients with epileptic conditions, the majority of these anticonvulsants currently in use have unpredictable pharmacological actions and undesirable side effects, such as chronic toxicity and birth defects, and yet patients continue to experience health problems (Perucca and Gilliam, 2012), (Charalambous et al., 2016). To treat epilepsy, which is a long-term procedure, it is vital to find novel medications with minimal or no adverse effects and predictable pharmacological action. These medications are also usually tapered off gradually over a period of around six months (Vicens et al., 2014). Biochemical and biological diversity are abundant in nature. Before any

other contemporary therapeutic strategy was used to treat epilepsy, numerous phytochemicals from plants have been known about and used traditionally. In effect, the present interest in traditional medicine has sped up the development and research of numerous treatments used by different ethnic groups worldwide. Table 1 summarizes the information on the types of extracts, as well as the mechanisms of action, techniques, and references pertaining to the plants that have been studied or reported to have anticonvulsant effects in animal models.

Table 1: Medicinal plants with anticonvulsant effect

S/N	Name of Plant	Family	Mechanism of Action	References
1	Abruss precatorius. Ethanolic extract in PTZ, MES, Picrotoxin	Fabaceae	GABAergic mechanisms, deteriorated autoregulation of glutamate release	(Amtul, 2018)
2..	Acorus calamus Linn leaves, roots (rhizomes) Aqueous Extract	Acoraceae	Block NMDA receptors	(Imam et al., 2013)
3.	Afzelia Africana leaves. Aqueous extract in PTZ	Caesalpinioideceae		(Chipiti et al., 2021)
4.	Anacyclus pyrethrum roots Methanol, petroleum ether, hydro alcoholic extract	Asteraceae	Increase in GSH levels of brain, decreased MDA levels of brain, increased AChE and BChE activity in brain	(Manouze et al., 2019)**,** (Pahuja et al., 2012)
5.	Angelica archangelica Linn. roots	Apiaceae	Block glutamatergic excitation	(A. U. Khan et al., 2020),

6.	Anisomeles malabarica	Lamiaceae	Decreased tonic hindlimb extension phase and extensor/flexion ratio in MES model	(Choudhary et al., 2011), (Ramalingam et al., 2013)
7.	Bunium persicum methanolic extract	**Apiaceae**	GABAergic mechanisms	(Mandegary et al., 2012), (Bansal et al., 2021)
8.	Centella asiatica. Leaves, methanol, hexane, chloroform, ethyl acetate, butanol	**Apiaceae**	Increased AChE activity, elevated levels of Ach	(Visweswari et al., 2010)
9.	Curcumin	Zingiberaceae	Increased brain norepinephrine level, reduced total nitrite levels of brain, reduced AChE activity	(Kaur et al., 2014), (Noor et al., 2012)
10.	Curcumol (from Rhizoma Curcumae)	Zingiberaceae	Facilitation of $GABA_A$ Rs by curcumol in hippocampal neurons, facilitation of recombinant $GABA_A$ Rs, enhancement of phasic GABAergic	(Hashem et al., 2021), (Ding et al., 2014)

			inhibition by curcumol in hippocampal slices, enhancement of tonic GABAergic inhibition by curcumol in hippocampal slices	
11.	Cymbopogon winterianus Jowitt	Poaceae	GABAergic mechanisms, deteriorated autoregulation of glutamate release	(Haerussana & Chairunnisa, 2022)**,** (Quintans-Júnior et al., 2008)
12.	Cyperus rotundus Linn.	Cyperaceae	Inhibit voltage-dependant Na+ channels, block glutamatergic excitation mediated by the NMDA receptor	(Peerzada et al., 2015)**,** (Al-Snafi, 2016)
13.	Feretia apodanthera Del lyophilized aqueous extract	Rubiaceae	Decreased brain MDA levels, increased brain GSH levels, increase of AChE and BChE activity in brain	(Taiwe et al., 2015)**,** (Hassanzadeh et al., 2021)

14.	Ficus platyphylla methanol extract	Moracea	Affinity for undifferentiated glutamate receptors, affinity for the 3H-GABA binding assay, decrease the K+-stimulated glutamate release from rat hippocampal slices	(Chindo et al., 2015)
15.	Harungana madagascariensis. Methanol extract in isoniazide induced siesure	Hypericaceae	GABAergic mechanisms	(Obiora et al., 2022)
16.	Lavandula angustifolia	Lamiaceae	Modulate glutamate activation expression, reduction of the ACh-evoked release, direct interaction with the NMDA receptor complex	(Patil et al., 2022)
17.	Mentha spicata	Lamiaceae	GABAergic mechanisms	(Mahboubi, 2021)**,** (Koutroumanidou et al., 2013)

18.	Nigella sativa	Ranunculaceae	Attenuate the increased NO levels resulting from pilocarpine, attenuate the decrease in hippocampal Na+, K+ ATPase activity, increase the AchE enzyme	(Noor et al., 2012)**,** (Aboul Ezz et al., 2011)**,**
19.	Ocimum basilicum	Lamiaceae	Modulate glutamate activation expression, reduction of the ACh-evoked release, direct interaction with the NMDA receptor complex	(Koutroumanidou et al., 2013)
20.	Origanum dictamnus	Rutaceae	GABAergic mechanisms	(da Fonsêca et al., 2019)
21.	Origanum vulgare	Rutaceae	GABAergic mechanisms	(Martins et al., 2014)**,** (Bahr et al., 2019)
22.	Panax ginseng root butanol extract	Araliaceae	T2 relaxation time in rat hippocampus, entorhinal cortex,	(Suleymanova et al., 2014)**,** (Mohd Sairazi et al., 2015)

			piriform cortex, amygdala, thalamus	
23.	Pimpinella anisum	Apiaceae	Inhibited production of dark neurons, inhibited induction of long-term potentiation in hippocampal slices	(Shojaii & Abdollahi Fard, 2012), (Karimzadeh et al., 2012)
24.	Piper guineen. Seeds	Piperaceae	Activity against NMDA	(Guine & Goncalves, 2015)
25.	Psidium guajava (guava) leaves ethanolic extract	Myrtaceae	Selectively inhibit NMDA receptor	(Nurhussen, 2017)
26.	Rosmarinus officinalis	Lamiaceae	Elevate GABA levels in the midbrain Region	(Bahr et al., 2019), (Capatina et al., 2020)
27.	Soy extract	legumiaceae	Phytoestrogens of soy affect seizure Severity	(Goudarzi et al., 2020)
28.	Trachyspermum ammi (L.) methanol extract	Apiaceae	Excite GABA responses mainly by stimulating human GABAA receptors and increasing the chloride ion	(S. Khan et al., 2016), (Asif et al., 2014)

			channel opening	
29.	Trichosanthes dioica Roxb fruits aqueous extract	Cucurbitaceae	Activity against generalized tonic-clonic and cortical focal seizures	(Arora & Gill, 2020)**,** (Rabiei, 2017)
30.	Turmeric methanolic extract	Zingiberaceae	Higher lipophilicity and easily cross the blood–brain barrier, suppress oxidative DNA damage and lipid peroxidation	(Orellana-Paucar et al., 2012)**,** (Dixit, 2018)
31.	Valeriana officinalis root aqueous Extract	Caprifoliaceae	Existence of adenosine ligand(s) in the valerian aqueous extract and activation of A1 adenosine system, binding to GABA Receptors	(Nouri & Abad, 2011)**,** (Rezvani et al., 2010)
32.	Withania somnifera methanolic extract	Solanaceae	Ameliorated spatial memory deficit in Ymaze	(Khattak et al., 2021)
33.	Zhumeria majdae essential oil and	Lamiaceae	Inhibit voltage-dependent Na+ channels,	(Khattak et al., 2021)**,** (da Fonsêca et al., 2019)

	methanolic extract		block glutamatergic excitation mediated by the NMDA receptor	
34.	Zingiber officinale (ginger) rhizomes hydroethanolic extract	Lamiaceae	Antioxidant activity, inhibit NO production, reduce inducible nitric oxide synthase	(Hosseini & Mirazi, 2014), (Gawel et al., 2021)
35.	Zizyphus jujuba hydroalcoholic Extract	Rhamnaceae	Increase in brain GSH, decreased brain MDA levels, increased brain AChE and BChE activity	(Al-humaidhi et al., 2021), (Pahuja et al., 2011)

Discussion

Epilepsy is the most common neurological disorder, after stroke affecting at least 50 million people globally (Feigin et al., 2017), (Siuly & Zhang, 2016). Medicinal plants have a wider range of pharmacological effects on neurological disorders when compared to conventional synthetic antiepileptic drugs. According to ethnobotanical reports, several herbal medications have positive effects on those who are seizure prone (Rabiei, 2017), (Devinsky et al., 2016). One popular screening methodology for evaluating anticonvulsive drugs is the PTZ kindling model. It primarily affects the $GABA_A$ receptor's t-butyl-bicyclo-phosphorothionate/picrotoxin site. The preferred $GABA_A$ receptor chloride ionophore complex blocker is PTZ (Rabiei, 2017). It affects numerous neurotransmitter systems, including the adenosinergic, GABAergic, and glutamatergic systems, causes convulsant effects following repeated or single intake. Significant changes in the levels of GSH, cysteine, glutathione disulfide, and protein thiols as well as protein disulfides and

protein carbonyl were seen in the mouse cerebral cortex following PTZ-induced convulsions (Pieróg et al., 2021). The efficacy of an anticonvulsant medicine against generalized tonic-clonic seizures is thought to be predicted by the MES seizure test, which induces tonic hind limb seizures through bilateral corneal or transauricular electrical stimulation. Some side effects from epilepsy medications are possible. The likelihood of adverse effects depends on the dosage, length of therapy, and type of medication used (Perucca & Gilliam, 2012). Higher medicine doses make side effects more likely to occur, but as the body gets used to the treatment, they usually lessen with time. Over 50% of all medications used in clinical settings globally are natural compounds and their derivatives (Thomford et al., 2018). When compared to conventional synthetic antiepileptic medicines, medicinal plants have a wider range of pharmacological effects and structural diversity.

Conclusion

From ethnobotanical reports, plant-based extracts are crucial to identifying chemical compounds for novel anticonvulsant therapy with minimal side effects and accessibility.

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