

## Review Article

### ANTICONVULSANT ACTIVITY OF NIGERIAN MEDICINAL PLANTS. A REVIEW

**Comment [H1]:** Please, rephrase as "Anticonvulsant activity of some Medicinal Plants: A Review"

#### Abstract

Epilepsy is a brain disorder characterized by groups of nerve cells, or neurons that occasionally signal incorrectly and result in bizarre feelings, sensations, and behaviors. Muscle spasms, convulsions, and loss of consciousness can also occasionally result occur from the epileptic seizure. Neuronal excitations is excitability is significantly influenced by and dependent on neurotransmitters in the central nervous system. In this review, we discussed epilepsy and its therapies, placing particular emphasis on medicinal plants and their mechanism of actions. The majority of herbal remedies that are either tested for anticonvulsant action or that are 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. or treat the signs of epileptic seizure.

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#### 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). (Lozano et al., 2020). (Suleiman et al., 2022). According to reports, it 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<sup>++</sup> causes an inflow of Na<sup>+</sup>, the opening of voltage-dependent Na<sup>+</sup> channels, the formation of

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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<sup>-</sup> influx or K<sup>+</sup> 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<sub>A</sub> and GABA<sub>B</sub>, are involved in the interactions between GABA, the main inhibitory neurotransmitter. While GABA<sub>B</sub> receptors are located presynaptically and can consequently influence synaptic release, GABA<sub>A</sub> receptors are positioned postsynaptically. In the adult brain, GABA<sub>A</sub> receptors are permeable to Cl<sup>-</sup> ions; Cl<sup>-</sup> influx activation hyperpolarizes the membrane and suppresses action potentials. Barbiturates and benzodiazepines are GABA<sub>A</sub> receptor agonists, and as a result, they reduce seizure activity. Because of their presynaptic position, GABA<sub>B</sub> receptors are associated to second messenger systems but not Cl<sup>-</sup> 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**

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

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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).

## **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<sub>A</sub> 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 extract, essential oils, and active ingredients, as well as the mechanisms of action, techniques, and references pertaining to the plants that have been studied or reported to have anticonvulsant effects.

Table 1: Some medicinal plants with potentials anticonvulsant effect

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S/N	Name of Plant	Family	Mechanism of Action	References
1	Abruss preicatorius. Ethanollic 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	Asteraceae	Increase in GSH levels of brain,	(Manouze et al., 2019), (Pahuja et

	roots Methanol, petroleum ether, hydro alcoholic extract		decreased MDA levels of brain, increased AChE and BChE activity in brain	al., 2012)
5.	Angelica archangelica Linn. roots essential oil	Apiaceae	Block glutamatergic excitation	(A. U. Khan et al., 2020),
6.	Anisomeles malabarica (flavonoids fraction from the leaves)	Lamiaceae	Decreased tonic hindlimb extension phase and extensor/flexion ratio in MES model	(Choudhary et al., 2011), (Ramalingam et al., 2013)
7.	Bunium persicum essential oil and methanolic extract	<b>Apiaceae</b>	GABAergic mechanisms	(Mandegary et al., 2012), (Bansal et al., 2021)
8.	Centella asiatica. Leaves, methanol, hexane, chloroform, ethyl acetate, butanol	<b>Apiaceae</b>	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 <sub>A</sub> Rs by curcumol in  hippocampal neurons, facilitation of  recombinant GABA <sub>A</sub> Rs, enhancement of  phasic GABAergic inhibition by curcumol  in hippocampal slices, enhancement of  tonic GABAergic inhibition by curcumol in  hippocampal slices	(Hashem et al., 2021), (Ding et al., 2014)
11.	Cymbopogon winterianus Jowitt essential oils	Poaceae	GABAergic mechanisms, deteriorated  autoregulation of glutamate release	(Haerussana & Chairunnisa, 2022), (Quintans-Júnior et al., 2008)
12.	Cyperus rotundus Linn. essential oil	Cyperaceae	Inhibit voltage- dependant Na <sup>+</sup> channels,  block glutamatergic excitation mediated by  the NMDA	(Peerzada et al., 2015), (Al-Snafi, 2016)

			receptor	
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 <sup>+</sup> - 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  essential  Oils	Lamiaceae	Modulate glutamate activation expression,  reduction of the ACh-evoked	(Patil et al., 2022)

			release, direct interaction with the NMDA receptor complex	
17.	Mentha spicata essential oils	Lamiaceae	GABAergic mechanisms	(Mahboubi, 2021), (Koutroumanidou et al., 2013)
18.	Nigella sativa oil	Ranunculaceae	Attenuate the increased NO levels resulting from pilocarpine, attenuate the decrease in hippocampal Na <sup>+</sup> , K <sup>+</sup> ATPase activity, increase the AchE enzyme	(Noor et al., 2012), (Aboul Ezz et al., 2011),
19.	Ocimum basilicum essential oils	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	(da Fonsêca et al.,

	essential oils		mechanisms	2019)
21.	Origanum vulgare essential oils	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, piriform cortex, amygdala, thalamus	(Suleymanova et al., 2014), (Mohd Sairazi et al., 2015)
23.	Pimpinella anisum essential oil	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 essential oils	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 channel opening	(S. Khan et al., 2016), (Asif et al., 2014)
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 methanolic extract	Lamiaceae	Inhibit voltage- dependent Na <sup>+</sup> channels,  block glutamatergic excitation mediated by  the NMDA receptor	(Khattak et al., 2021), (da Fonsêca et al., 2019)
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 condition, after stroke affecting at least 50 million people globally (Feigin et al., 2017), (Siuly & Zhang, 2016). One popular screening methodology for evaluating anticonvulsive drugs is the PTZ kindling model. It primarily affects

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the GABA<sub>A</sub> receptor's t-butyl-bicyclo-phosphorothionate/picrotoxin site. The preferred GABA<sub>A</sub> receptor chloride ionophore complex blocker is PTZ (Rabiei, 2017). It affects numerous neurotransmitter systems, including the adenosinergic, GABAergic, and glutamatergic systems, and 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 hindlimb 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. According to the research available, several herbal medications could have negative effects on those who are seizure prone (Rabiei, 2017), (Devinsky et al., 2016).

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## Conclusion

We can draw the conclusion that research on the bioactive components in plant-based extracts may be crucial to identifying chemical compounds for the eventual creation of anticonvulsant therapies.

**Comment [H19]:** Please, rephrase as "From ethnobotanical reports, plant-based extracts are crucial to identifying chemical compounds for novel anticonvulsant therapy with minimal effects".

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