EVALUATION OF THE ANTICONVULSANT ACTIVITY OF THE METHANOL EXTRACT OF *Tamarindus indica* and *Ficus iteophylla* LEAVES IN RODENTS

BY

OGHORO, SIMON OGHENEOCHUKO

PHA1808416

DEPARTMENT OF PHARMACOLOGY AND TOXICOLOGY

FACULTY OF PHARMACY

UNIVERSITY OF BENIN

BENIN CITY

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A DISSERTATION SUBMITTED TO THE DEPARTMENT OF PHARMACOLOGY AND TOXICOLOGY, FACULTY OF PHARMACY, UNIVERSITY OF BENIN, BENIN CITY IN PARTIAL FUFILLMENT OF THE REQUIREMENTS FOR THE AWARD OF DOCTOR OF PHARMACY (PHARM.D.) DEGREE

NOVEMBER, 2025

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CERTIFICATION

We certify that this project work was carried out by MR. SIMON OGHENEOCHUKO OGHORO with matriculation number PHA1808416 in the Department of Pharmacology and Toxicology, Faculty of Pharmacy, University of Benin, Benin City, Nigeria.

_____ _____

Prof. R.I. Ozolua
(Project Supervisor)

Date

_____ _____

Dr. A.P. Uchendu
(Head of Department)

Date

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DEDICATION

I dedicate this work to Almighty God and my parents, Mr. Rex and Barr. (Mrs.) Roseline Oghoro, for their unwavering support, care and prayers throughout my academic journey

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“I stand where I am because someone stood by me.” - Olivia Pope, Scandal.

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ABSTRACT

Epilepsy affects over 50 million people worldwide and imposes a treatment gap of 60–90% in low- and middle-income countries, including Nigeria, due to the cost and limited availability of conventional antiseizure medications. This study evaluated the **anticonvulsant-like potential** of methanol leaf extracts of *Ficus iteophylla* (MEFI) and *Tamarindus indica* (METI) in mice, guided by their ethnomedicinal use in Nigerian traditional medicine for convulsions and neurological disorders.

Phytochemical screening confirmed alkaloids, glycosides, saponins, tannins, and reducing sugars in both extracts; **terpenoids were present only in METI**. **Acute oral toxicity** (Lorke's method) yielded LD_{50} > 5,000 mg/kg for MEFI and METI, with only transient mild sedation at high doses, establishing a broad safety margin. Doses of 100, 200, and 400 mg/kg (p.o.) were selected for behavioral assays.

Anticonvulsant evaluation employed the pentylenetetrazole (PTZ)-induced seizure model (GABAergic modulation) and maximal electroshock seizure (MES) test (sodium channel blockade/seizure spread prevention). In the PTZ model, both extracts produced **significant, dose-dependent protection**, delaying seizure onset and reducing severity (peak efficacy at 400 mg/kg for METI and 200 mg/kg for MEFI, comparable to diazepam 2 mg/kg and phenobarbitone 20 mg/kg). In the MES test, extracts displayed **complex non-linear responses** with partial protection at 200 and 400 mg/kg but inconsistent abolition of tonic hind-limb extension, failing to reach statistical significance for full sodium-channel blockade. Brain tissue analysis in non-seizing treated animals revealed **enhanced antioxidant defense**: elevated activities of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione reductase (GR), with reduced malondialdehyde (MDA) levels.

The **robust anticonvulsant-like effects in the PTZ model**, coupled with pronounced CNS antioxidant modulation and diverse neuroactive phytoconstituents, strongly support GABAergic enhancement and oxidative stress mitigation as primary mechanisms. Although MES outcomes were inconclusive, the findings **validate ethnomedicinal claims** for *F. iteophylla* and *T. indica* as safe, multi-mechanistic anticonvulsant candidates. Further studies with isolated fractions or alternative solvents are warranted to optimize sodium-channel effects.

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CHAPTER ONE

INTRODUCTION

Background to the Study

Epilepsy is one of the most prevalent neurological disorders globally, characterized by recurrent and unprovoked seizures resulting from abnormal electrical discharges in the brain (Asadi-Pooya et al., 2023; Kumar et al., 2024). It affects over 50 million people worldwide, with the vast majority residing in low- and middle-income countries, where healthcare infrastructure and access to diagnostic facilities are often limited (Chen et al., 2023; Milligan, 2021). In Sub-Saharan Africa, including Nigeria, the burden of epilepsy is notably high due to delayed diagnosis, insufficient treatment options, and pervasive sociocultural misconceptions that contribute to stigma and discrimination against affected individuals (Watila et al., 2021; Abebe et al., 2024). Studies in Nigeria highlight a high prevalence of seizure-related injuries and their considerable impact on patients' quality of life, underscoring the multifaceted challenges faced by persons with epilepsy (Anaje et al., 2024; Ogundare et al., 2021). Moreover, inadequate health-seeking behaviors driven by societal stigma further hinder effective epilepsy management in these communities (Echendu et al., 2023; Ezeala-Adikaibe et al., 2024; Nnebue et al., 2023).

The pathophysiology of epilepsy is complex, involving molecular, cellular, and neural network disruptions such as oxidative stress, dysregulated glia-neuron communication, ion channelopathies, and neuroinflammatory processes (Boleti et al., 2024; Chen et al., 2022; Chaunsali et al., 2021). Comorbidities including psychiatric conditions, metabolic dysfunction, and complications arising from cerebrovascular

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events like stroke contribute to seizure exacerbation and poor outcomes (Adachi & Ito, 2022; Phan et al., 2022; Tanaka et al., 2024). Despite significant advances in antiepileptic drug development, approximately one-third of patients develop drug-resistant epilepsy, characterized by persistent seizures that worsen prognosis and elevate the risk of sudden unexpected death in epilepsy (SUDEP) (Perucca et al., 2023; Mesraoua et al., 2023; Shlobin et al., 2024). Novel pharmacotherapies targeting the gamma-aminobutyric acid (GABA) system and the application of precision medicine approaches offer promise but remain largely inaccessible in resource-limited settings (Perucca et al., 2023; Knowles et al., 2022).

Conventional antiseizure medications (ASMs) effectively control seizures in many individuals; however, they frequently produce adverse effects, interact with comorbid illnesses, and do not address the underlying neurodegenerative processes intrinsic to epilepsy (Kanner & Bicchi, 2022; Chung et al., 2021; Moura et al., 2022). Cardiovascular complications and psychiatric disorders are commonly reported among patients with chronic and pharmacoresistant epilepsy (González et al., 2022; Sha et al., 2024). The high cost of ASMs and the limited availability of epilepsy surgery further amplify treatment gaps in countries such as Nigeria (Yakubu et al., 2022; Ogunjimi et al., 2024). This situation necessitates the exploration of novel, cost-effective, and culturally acceptable treatment alternatives.

Traditional medicine continues to play a vital role in epilepsy care across Africa and Asia. In Nigeria and Uganda, traditional healers widely employ herbal remedies derived from indigenous plants, either as standalone treatments or adjunctive therapies to ASMs (Ademilokun & Agunbiade, 2021; Asiimwe et al., 2021; Wada et al., 2023). Ethnobotanical surveys have identified numerous plants with reported anticonvulsant and neuroprotective properties, many rich in phytochemicals such as

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flavonoids, alkaloids, triterpenoids, and phenolic compounds (Moussavi et al., 2024; Ibrahim et al., 2024; Opiyo & Njoroge, 2024). Plant-derived antioxidants have garnered particular attention for their capacity to mitigate oxidative stress, a key factor in seizure pathogenesis (Łukawski & Czuczwar, 2023; Madireddy & Madireddy, 2023).

Tamarindus indica (tamarind) is a widely utilized medicinal plant across Africa and Asia, recognized for its diverse phytochemical profile including polyphenols, flavonoids, alkaloids, and organic acids (Mukherjee et al., 2024; Ahmad et al., 2024). Research has demonstrated its antioxidant, anti-inflammatory, and neuroprotective effects, which may confer benefits in seizure control and neurodegenerative disease management (Garba et al., 2023; Usman et al., 2023). Extracts derived from *t.indica* leaves, seeds, and pulp also exhibit cardioprotective, hepatoprotective, and antimicrobial activities, underscoring its ethnopharmacological importance (Akter et al., 2022; Nweke et al., 2024; Ghaly et al., 2023).

Ficus species, including *Ficus iteophylla* and *Ficus capensis*, are similarly reported to possess anticonvulsant, antioxidant, and analgesic properties attributed to their rich content of triterpenoids and phytosterols (Abdulmalik et al., 2021; Alam & Mazumder, 2025; Madrigal-Santillán et al., 2024). The traditional use of Ficus plants in neurological disorders is well documented, with pharmacological studies supporting their efficacy and elucidating mechanisms involving oxidative stress modulation (Salehi et al., 2021; Sasidharan et al., 2023). Notably, some Ficus extracts have demonstrated neuroprotective potential by targeting oxidative pathways implicated in epilepsy (Mohammed et al., 2023).

Given the high global and regional burden of epilepsy, prohibitive treatment

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limitations, and promising ethnomedicinal evidence for *Tamarindus indica* and Ficus species, rigorous scientific evaluation of their phytochemical composition, safety, and anticonvulsant efficacy is warranted. Such investigations could facilitate the development of novel, affordable antiseizure therapies tailored to meet the needs of resource-constrained settings like Nigeria, where epilepsy remains widely underdiagnosed and undertreated (Watila et al., 2021; Wada et al., 2023).

This study aims to address this gap by evaluating the anticonvulsant properties of methanol extracts of *Tamarindus indica* and *Ficus iteophylla*, thereby contributing to the validation and potential integration of traditional herbal medicine in contemporary epilepsy management.

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LITERATURE REVIEW

1.1 Epilepsy: A Silent Storm in the Brain

Epilepsy is a chronic neurological disorder characterized by a persistent tendency to generate unprovoked seizures, accompanied by a spectrum of neurobiological, cognitive, and psychosocial outcomes (Chen et al., 2023; Perucca et al., 2023). A seizure is defined as a sudden, transient occurrence of signs or symptoms caused by abnormal, excessive, or synchronous neuronal activity in the brain (Kumar et al., 2024). These seizures may manifest in diverse clinical forms depending on the affected brain region, including motor symptoms such as convulsions or automatisms, sensory phenomena like tingling or visual disturbances, autonomic signs such as changes in heart rate or sweating, and behavioural or cognitive alterations (Mesraoua et al., 2023). The heterogeneity of seizure presentations reflects the complexity of epileptic brain networks and the varied impact on brain function.

Classification of Seizure

The International League Against Epilepsy (ILAE) provides a comprehensive framework for seizure classification to guide diagnosis and treatment. Seizures are primarily categorized into three main groups based on their onset: focal onset, generalized onset, and seizures of unknown onset (Perucca et al., 2023; Knowles et al., 2022).

Focal seizures originate within networks limited to one hemisphere of the brain. They are further subdivided based on the individual's level of awareness during the event: focal aware seizures (formerly simple partial seizures), where consciousness is retained, and focal impaired awareness seizures (formerly complex partial seizures),

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where consciousness is affected. Motor and non-motor symptoms may accompany these seizures, including automatisms, sensory auras, or autonomic changes (Perucca et al., 2023). In some cases, focal seizures can evolve into bilateral tonic-clonic seizures, a progression indicating bilateral cerebral involvement.

Generalized seizures arise abruptly in both cerebral hemispheres simultaneously and involve widespread networks. They are classified into motor types, such as tonic-clonic (formerly grand mal), myoclonic, clonic, tonic, and atonic seizures, and non-motor types, primarily absence seizures (formerly petit mal), characterized by brief lapses in awareness without convulsions (Knowles et al., 2022; Mesraoua et al., 2023). Generalized seizures typically result in loss of consciousness and can severely impact quality of life.

Seizures of unknown onset are diagnosed when the initial onset cannot be determined due to limited information, often needing further investigation (Perucca et al., 2023). This category underscores the diagnostic challenges in epilepsy where clinical history or electroencephalographic (EEG) data are insufficient.

At the epilepsy classification level, conditions are categorized based on seizure types and related electroclinical features. Epilepsy may be focal, generalized, combined generalized and focal, or of unknown type, reflecting both clinical presentation and EEG patterns (Asadi-Pooya et al., 2023). This classification aids in understanding the underlying pathophysiology and tailoring treatment approaches.

Importantly, the impact of epilepsy transcends neurological symptoms. Patients commonly face profound psychosocial burdens including stigma, discrimination, social exclusion, educational setbacks, and challenges in gaining and maintaining employment. These factors contribute significantly to morbidity and reduced quality

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of life among affected individuals (Echendu et al., 2023; Ezeala-Adikaibe et al., 2024). Such complexities highlight the necessity of holistic approaches to epilepsy care encompassing both medical and social interventions.

Historical Perspective on Epilepsy and Convulsive Disorders

Epilepsy has been recognized as a distinct medical condition for thousands of years, with its interpretation evolving significantly across different historical periods and cultures. Ancient civilizations often viewed epilepsy through a supernatural lens, considering seizures as manifestations of divine intervention or demonic possession. The condition was famously referred to as the “sacred disease” in Hippocratic writings, highlighting early recognition of its profound impact but also its mystified nature (Mesraoua et al., 2023). In many traditional societies, including various African cultures, convulsive disorders were perceived as punishments from deities or caused by malevolent spirits, which contributed to widespread stigma, discrimination, and social exclusion of affected individuals (Nnebue et al., 2023).

During the Middle Ages, these misconceptions intensified, and people living with epilepsy were often ostracized and subjected to harmful and ineffective treatments influenced by superstition rather than empirical science (Watila et al., 2021). Such treatments included rituals, exorcisms, and isolation, which did not address the neurological basis of the disorder and often exacerbated patients’ suffering. It was only with the advent of modern neurology in the 19th century and the pioneering work in electroencephalography (EEG) that epilepsy began to be understood as a neurological brain disorder characterized by abnormal electrical activity (Adachi & Ito, 2022; Mesraoua et al., 2023). The development of EEG allowed for objective measurement and categorization of epileptic seizures, transforming diagnosis and

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treatment paradigms and marking a critical shift away from ancient beliefs.

Despite these medical advances, cultural beliefs and stigma surrounding epilepsy remain deeply rooted in many regions, especially in sub-Saharan Africa and rural communities where traditional explanations dominate (Ademilokun & Agunbiade, 2021; Asiimwe et al., 2021). Such sociocultural factors impact health-seeking behavior and access to care, perpetuating barriers to effective management. Contemporary studies have underscored that in many African settings, epilepsy is still conceptualized within frameworks of witchcraft, spiritual affliction, or moral failing, contributing to delayed treatment and underutilization of modern medical interventions (Nnebue et al., 2023; Wada et al., 2023). These persistent misconceptions further exacerbate the psychosocial burden and limit improvements in quality of life for people living with epilepsy.

Global Burden of Epilepsy and Seizure-Related Conditions

Epilepsy remains a major global health challenge, affecting an estimated 50 to 70 million people worldwide, making it one of the most common neurological disorders (Chen et al., 2023; Milligan, 2021). Recent global epidemiological data from 2021 indicate there were approximately 51.7 million people living with epilepsy, reflecting a significant and growing burden (Feigin et al., 2025). The prevalence and incidence of epilepsy are disproportionately higher in low- and middle-income countries (LMICs), which account for nearly 80% of all cases globally, due to limitations in healthcare infrastructure, diagnostic capacity, and treatment availability (Watila et al., 2021; Abebe et al., 2024). Sub-Saharan Africa bears one of the highest regional burdens with prevalence rates ranging between 10 and 20 per 1,000 population, significantly exceeding rates reported in high-income countries (Ogundare et al.,

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2021; Wada et al., 2023).

In Nigeria, both hospital- and community-based studies have documented a high prevalence of epilepsy that is commonly associated with risk factors such as traumatic brain injury, central nervous system infections, perinatal complications, and poor access to preventive healthcare services (Yakubu et al., 2022; Ogunjimi et al., 2024). Seizure-related complications contribute substantially to morbidity, including cognitive impairments, neurological deficits, and frequent seizure-related injuries, which further diminish quality of life (González et al., 2022; Sha et al., 2024). Psychiatric comorbidities such as depression and anxiety are prevalent among persons with epilepsy, compounding their overall disease burden and complicating management (Sha et al., 2024).

The economic and social impact of epilepsy is considerable. A major concern is the epilepsy treatment gap, defined as the proportion of individuals with active epilepsy who do not receive appropriate treatment. In LMICs, this gap ranges from 60% to 90%, driven by scarcity of anti-seizure medications (ASMs), lack of diagnostic facilities such as EEG, and persistent stigma (Perucca et al., 2023; Shlobin et al., 2024). This gap leads to ongoing seizures, disability, and premature mortality, including increased risk of sudden unexpected death in epilepsy (SUDEP) (Perucca et al., 2023). Stigma and social exclusion further limit health-seeking behaviors and adherence to treatment, perpetuating cycles of poor health outcomes (Echendu et al., 2023; Ezeala-Adikaibe et al., 2024). These challenges underscore that epilepsy is not only a neurological disorder but also a significant public health and social issue worldwide.

Efforts to reduce this burden emphasize the strengthening of healthcare systems,

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improving accessibility and affordability of ASMs, and integrating traditional healing practices with biomedical approaches where culturally appropriate (Wada et al., 2023; Moussavi et al., 2024). Addressing the epilepsy burden globally, particularly in high-prevalence LMICs like Nigeria, requires comprehensive strategies targeting diagnostic capacity, stigmatization, and patient-centered care to improve outcomes and quality of life for affected individuals.

1.2 Epidemiology of Epilepsy and Seizure Disorders

Global Prevalence and Incidence Rates

Epilepsy is among the most common chronic neurological disorders worldwide, with an estimated 50 to 70 million individuals affected (Chen et al., 2023; Milligan, 2021). The lifetime prevalence of epilepsy globally is approximately 7.6 per 1,000 population, reflecting the proportion of individuals who will experience this condition at some point in their lives. Annual incidence rates, which measure new cases per year, vary significantly by region; high-income countries report rates between 30 and 50 cases per 100,000 persons annually, whereas low- and middle-income countries (LMICs) report rates exceeding 100 per 100,000 population, notably higher due to differences in healthcare access, environmental factors, and prevalence of risk factors such as infections and perinatal complications (Asadi-Pooya et al., 2023; Perucca et al., 2023).

Recent studies project an increasing global incidence of idiopathic epilepsy, with 3.27 million new cases reported in 2021 alone and an age-standardized incidence rate rising from 38.12 per 100,000 population in 1990 to 42.82 per 100,000 in 2021 (Xu et al., 2025; Feigin et al., 2025). The highest incidence rates are observed in regions of Latin America and sub-Saharan Africa, where socioeconomic factors,

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inadequate healthcare, and untreated infections contribute significantly to epilepsy risk. Conversely, lower incidence and prevalence rates are noted in East Asia and Oceania (Xu et al., 2025).

Epilepsy accounts for approximately 0.5% of the global burden of disease, measured by disability-adjusted life years (DALYs), which capture years lost due to disability and premature mortality (Kumar et al., 2024; Mesraoua et al., 2023). It is estimated that epilepsy contributes to nearly 13.9 million DALYs worldwide, reflecting its profound impact on quality of life and functioning (Feigin et al., 2025). Although advances in neuro-diagnostics and treatment modalities have improved outcomes in some settings, persistent disparities exist, particularly in LMICs where nearly one-third of patients remain drug-resistant, meaning seizures continue despite optimal medication (Perucca et al., 2023; Shlobin et al., 2024). This drug resistance substantially increases morbidity and mortality risk, necessitating exploration of alternative therapeutic options.

Regional Variations

The prevalence and incidence of epilepsy exhibit significant regional variation driven by differences in socioeconomic conditions, healthcare infrastructure, and exposure to risk factors. Sub-Saharan Africa has among the highest reported prevalence rates globally, ranging between 10 and 20 per 1,000 population, which are substantially greater than those observed in other regions (Watila et al., 2021; Abebe et al., 2024). A comprehensive meta-analysis of community-based studies in Sub-Saharan Africa estimates active epilepsy prevalence at approximately 9 per 1,000 persons, with lifetime prevalence closer to 16 per 1,000 (Owolabi et al., 2020). Prevalence rates tend to be higher in rural settings compared to urban areas, attributed to increased

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exposure to infections, poor perinatal care, and limited access to early diagnosis and treatment (Owolabi et al., 2020; Echendu et al., 2023). Within sub-regions, Central Africa reports the highest epilepsy prevalence, reaching up to 30 per 1,000 population in some estimates (Ta & Blond., 2022).

High incidence rates in sub-Saharan Africa estimated at approximately 80 per 100,000 person-years are predominantly linked to preventable and treatable causes, including central nervous system infections such as neurocysticercosis, meningitis, and cerebral malaria, as well as birth trauma and head injuries (Yakubu et al., 2022; Ogunjimi et al., 2024). These factors contribute to a substantial epilepsy treatment gap, with many patients untreated or inadequately managed due to resource constraints and sociocultural barriers (Ezeala-Adikaibe et al., 2024; Echendu et al., 2023). The high disability burden from epilepsy in Nigeria and surrounding regions underscores the urgent need for improved healthcare infrastructure, education, and culturally sensitive interventions.

In Asia, particularly within rural communities, epilepsy prevalence is also relatively high, driven by factors similar to those in sub-Saharan Africa, including limited access to diagnostics, endemic infections, and cultural stigma that impede timely treatment (Asiimwe et al., 2021; Wada et al., 2023). However, epidemiological data from Asian countries tend to show wide variation, reflecting the continent's diverse socioeconomic and healthcare landscapes.

In contrast, developed countries generally report lower prevalence and incidence rates, often less than 5 to 7 per 1,000 population, attributed to better perinatal healthcare, effective infectious disease control, and broad accessibility to antiseizure medications (Knowles et al., 2022; Mesraoua et al., 2023). Nonetheless, disparities

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persist within high-income regions, where certain ethnic minorities and socioeconomically disadvantaged groups experience higher epilepsy rates and worse outcomes due to systemic inequities in healthcare access and social determinants of health.

Age, Sex, and Genetic Predispositions in Epilepsy

Epilepsy affects individuals across the lifespan, but its incidence and underlying causes vary notably with age. Incidence peaks occur in early childhood and late adulthood, reflecting distinct etiologies in these age groups. Pediatric epilepsy is often associated with developmental disorders and genetic syndromes, representing a significant proportion of epilepsy cases in children (Adachi & Ito, 2022; Phan et al., 2022; Tanaka et al., 2024). In contrast, adult-onset epilepsy frequently arises secondary to acquired insults such as stroke, traumatic brain injury, or neurodegenerative disease processes. Age-related vulnerabilities also contribute to increased seizure severity and higher rates of comorbid conditions, complicating clinical management across the lifespan (Boleti et al., 2024).

Sex differences in epilepsy epidemiology have been documented in multiple studies. Generally, the prevalence and incidence of epilepsy tend to be slightly higher in males than females, a disparity often attributed to greater exposure among males to environmental and lifestyle risk factors such as head trauma, infections, and certain occupational hazards (Chen et al., 2022; Kumar et al., 2024). However, this male predominance is nuanced by epilepsy syndrome type; idiopathic generalized epilepsies (IGEs) such as juvenile myoclonic epilepsy show a higher female prevalence, with female-to-male ratios around 1.5 to 1.8 depending on subtype (Asadi-Pooya et al., 2024). Biological factors, including the modulatory effects of sex

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hormones on neuronal excitability, also contribute to sex differences. Progesterone and its metabolites generally exert anticonvulsant effects, while estrogens tend to be proconvulsant, influencing seizure susceptibility and frequency, especially in women during hormonal fluctuations (Asadi-Pooya et al., 2024; Kanner & Bicchi, 2022). Furthermore, women with epilepsy face distinctive challenges related to antiseizure medication interactions with hormonal cycles, increased seizure risks during pregnancy, and adverse psychosocial impacts (Kanner & Bicchi, 2022; Stefanello et al., 2014).

Genetic predisposition is increasingly recognized as a critical factor in epilepsy risk and pathogenesis. Advances in genomic technologies have identified mutations affecting ion channels, synaptic proteins, and glial cell regulation that confer susceptibility to both generalized and focal epilepsies (Chaunsali et al., 2021; Knowles et al., 2022). These genetic discoveries deepen the understanding of epilepsy mechanisms and facilitate precision medicine approaches targeting disease subtypes. For example, mutations in sodium and potassium channel genes have been linked to specific epilepsy syndromes amenable to tailored pharmacological interventions (Perucca et al., 2023). The interplay of genetic variants with sex hormones may also modulate gene expression and seizure phenotypes, highlighting the complexity of genetic and biological influences on epilepsy (Asadi-Pooya et al., 2024).

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Socioeconomic Impact of Epilepsy

Epilepsy imposes a profound socioeconomic burden that extends well beyond its clinical manifestations. Individuals living with epilepsy frequently face stigma, discrimination, and social isolation, which limit their educational achievements, employment opportunities, and prospects for marriage, largely perpetuating cycles of poverty and marginalization (Echendu et al., 2023; Nnebue et al., 2023). These social barriers are particularly severe in Africa and Asia, where epilepsy is commonly misunderstood as a spiritual affliction, a contagious disease, or a consequence of moral failing (Ademilokun & Agunbiade, 2021; Asiimwe et al., 2021). Such myths regarding epilepsy fuel discrimination, hinder health-seeking behaviour, and contribute to the widespread treatment gaps observed in these regions.

Quality of life for people with epilepsy is further compromised by seizure-related injuries, cognitive impairments, psychiatric comorbidities such as anxiety and depression, and long-term side effects of antiseizure medications (González et al., 2022; Sha et al., 2024). The risk of premature mortality is significantly elevated, with sudden unexpected death in epilepsy (SUDEP) representing one of the leading causes of death in people with chronic epilepsy (Mesraoua et al., 2023).

The economic consequences of epilepsy are substantial, especially in low- and middle-income countries (LMICs) where the treatment gap the proportion of individuals not receiving appropriate epilepsy care ranges from 60% to 90% (Watila et al., 2021; Wada et al., 2023). Costs associated with epilepsy encompass direct healthcare expenditures such as medications, hospital visits, and diagnostic procedures, as well as indirect costs like loss of productivity, unemployment, and the economic impact of long-term disability (Moura et al., 2022; Shlobin et al., 2024). In resource-limited settings, where access to antiseizure medications and diagnostic

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facilities is scarce, this financial burden disproportionately affects households, sometimes pushing families further into poverty (Ogunjimi et al., 2024; Birbeck et al., 2007).

Quantitative studies from sub-Saharan Africa reveal that people with epilepsy experience significantly poorer social and economic outcomes compared to peers with other chronic medical conditions. For instance, a Zambian study found that individuals with epilepsy had fewer years of formal education, lower employment rates, substandard housing, and greater food insecurity (Mugumbate., 2025). Women with epilepsy face heightened vulnerabilities such as increased risk of sexual violence and barriers to maternal healthcare, further exacerbating socioeconomic disparities. The lack of healthcare infrastructure in many LMICs, exemplified by uneven distribution of neurological specialists and advanced diagnostic technologies, compounds these inequities, resulting in inadequate care for the majority of affected individuals (Watila et al., 2021).

The pervasive stigma surrounding epilepsy often restricts social participation and access to opportunities, reinforcing social isolation and mental health challenges. Laws and societal norms in many countries still reflect outdated views, leading to discrimination in marriage, employment, insurance, and social integration (WHO, 2024). Addressing these multifaceted challenges requires integrated strategies encompassing healthcare improvement, public education, legal protections, and community engagement to enhance quality of life and social inclusion for persons with epilepsy.

1.3 Pathophysiology of Epilepsy

Neurobiological Basis of Seizures

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Epilepsy is fundamentally a brain disorder characterized by a persistent predisposition to generate epileptic seizures resulting from abnormal and excessive synchronization of neuronal activity (Chen et al., 2022; Kumar et al., 2024). Under normal conditions, a fine balance between excitatory and inhibitory neurotransmission maintains cortical stability. In epilepsy, this balance is disturbed, causing hyperexcitability and hypersynchrony of neuronal networks (Boleti et al., 2024; Chaunsali et al., 2021). Seizures may begin focally, localized to specific brain areas, or generalize across both hemispheres, with the pattern depending on underlying pathology (Mesraoua et al., 2023).

Abnormal Neuronal Excitability and Synchronization

Central to epileptogenesis is neuronal hyperexcitability, where neurons have an increased propensity to fire action potentials in response to stimuli due to altered membrane potentials, receptor dysfunction, and maladaptive synaptic plasticity (Chaunsali et al., 2021). This hyperexcitability leads to synchronized firing across large neuronal populations, generating the characteristic electroencephalographic (EEG) seizure patterns (Boleti et al., 2024). Recent research highlights a complex dynamic in synchronization, with seizure onsets sometimes preceded by transient desynchronization, followed by intense hypersynchrony as the seizure progresses (Bazhanova., 2022). Additionally, dysfunctional interactions between neurons and glial cells particularly astrocytes and microglia disrupt potassium buffering, glutamate clearance, and inflammatory regulation, further promoting a hyperexcitable microenvironment (Chen et al., 2022).

Role of Neurotransmitters

The neurotransmitter systems critically regulate seizure initiation and propagation.

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Gamma-aminobutyric acid (GABA), the main inhibitory neurotransmitter, acts via GABAA and GABAB receptors to suppress neuronal excitability. Deficits in GABAergic transmission from receptor abnormalities to reduced GABA synthesis lower seizure thresholds and facilitate epileptic activity (Perucca et al., 2023). Conversely, glutamate, the major excitatory neurotransmitter, activates NMDA, AMPA, and kainate receptors; overactivation leads to excitotoxicity, neuronal injury, and sustained epileptiform discharges (Knowles et al., 2022; Chaunsali et al., 2021). Other neurotransmitters such as acetylcholine, serotonin, norepinephrine, and dopamine modulate cortical excitability and synchrony, with serotonergic deficits implicated in increased risk of sudden unexpected death in epilepsy (SUDEP) (Mesraoua et al., 2023).

Ion Channels, Receptor Dysfunction, and Oxidative Stress

Ion channelopathies represent a fundamental mechanism in epilepsy development. Mutations or acquired alterations in voltage-gated sodium, potassium, calcium, and chloride channels disrupt neuronal firing properties, enhancing hyperexcitability (Kumar et al., 2024). For example, sodium channel mutations prolong depolarization and enable repetitive firing, while potassium channel dysfunction impairs repolarization, sustaining excitability (Chaunsali et al., 2021). Defective chloride transport diminishes GABAergic inhibition, further tipping the excitatory-inhibitory balance in favor of seizure generation (Chen et al., 2022).

Oxidative stress contributes to epileptogenesis via excessive reactive oxygen species (ROS) generated during seizures, which damage neuronal membranes, proteins, and DNA. This oxidative injury impairs mitochondrial function and promotes neuroinflammation, perpetuating epileptic activity in a vicious cycle (Łukawski & Czuczwar, 2023; Madireddy & Madireddy, 2023; Boleti et al., 2024).

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Genetic and Acquired Causes of Epilepsy

Epilepsy etiology encompasses both genetic and acquired factors. Genetic epilepsies involve mutations in genes coding for ion channels (e.g., SCN1A), neurotransmitter receptors, and synaptic proteins, underlying many pediatric epilepsy syndromes such as Dravet syndrome and generalized epilepsies (Knowles et al., 2022; Chaunsali et al., 2021; Perucca et al., 2023). Advances in next-generation sequencing have expanded knowledge of epilepsy-associated genes, enabling precision medicine approaches tailored to individual genetic profiles (Kumar et al., 2024).

Acquired causes include traumatic brain injury, CNS infections (e.g., meningitis, neurocysticercosis), cerebrovascular insults, and neurodegenerative diseases (Adachi & Ito, 2022; Tanaka et al., 2024; Watila et al., 2021). In LMICs, additional contributors such as perinatal asphyxia and untreated febrile seizures account for high epilepsy prevalence (Abebe et al., 2024; Yakubu et al., 2022). The interplay between genetic susceptibility and environmental factors results in the diverse epilepsy syndromes seen worldwide.

1.4 Drug Management of Epilepsy

Pharmacological treatment remains the cornerstone of epilepsy management, with antiseizure medications (ASMs) being the most widely prescribed therapy to suppress abnormal neuronal discharges and prevent recurrent seizures. Globally, more than 20 ASMs are in clinical use, ranging from older agents like barbiturates and phenytoin to newer drugs such as levetiracetam, lamotrigine, and perampanel (Perucca et al., 2023; Kanner & Bicchi, 2022). These medications have significantly improved seizure control and reduced morbidity associated with epilepsy. However,

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challenges persist, including treatment resistance, which occurs in approximately one-third of patients, as well as adverse drug effects, drug–drug interactions, teratogenicity, and limited availability in resource-constrained settings (Mesraoua et al., 2023; Watila et al., 2021; Mugumbate, 2025).

Despite advances in pharmacotherapy, the Global Burden of Disease Study 2021 highlights that epilepsy remains a significant neurological condition worldwide, disproportionately affecting low- and middle-income countries where access to ASMs is limited (Feigin et al., 2025; Xu et al., 2025). Socioeconomic and healthcare disparities in Sub-Saharan Africa and parts of Asia contribute to underdiagnosis, treatment gaps, and poor quality of life for many patients with epilepsy (Owolabi et al., 2020; Watila et al., 2021; Ezeala-Adikaibe et al., 2024).

1.4.1 Classes of Anticonvulsant Drugs

Barbiturates:

Barbiturates, particularly phenobarbital, are among the earliest ASMs. Their primary mechanism is enhancement of GABA_A receptor-mediated chloride influx, which increases inhibitory tone and suppresses neuronal hyperexcitability (Perucca et al., 2023). They remain widely used in low-resource settings because of affordability and effectiveness, particularly in generalized tonic–clonic seizures (Watila et al., 2021). However, their use is limited by cognitive impairment, sedation, drug dependence, and teratogenicity (Mesraoua et al., 2023).

Benzodiazepines:

Drugs such as diazepam, lorazepam, and clonazepam act by potentiating GABA_A receptor function, thereby enhancing synaptic inhibition (Knowles et al., 2022). Benzodiazepines are frontline agents for status epilepticus due to rapid onset of

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action (Perucca et al., 2023). Nevertheless, tolerance, dependence, and sedation restrict their long-term use in chronic epilepsy management (Shlobin et al., 2024).

Hydantoins:

Phenytoin, the prototype of this class, exerts its effects by blocking voltage-gated sodium channels, thereby stabilizing neuronal membranes and reducing repetitive firing (Kumar et al., 2024). Despite its efficacy in both focal and generalized seizures, drawbacks include gingival hyperplasia, hirsutism, ataxia, and teratogenic risks, alongside nonlinear pharmacokinetics that complicate dosing and monitoring (Milligan, 2021).

Succinimides:

Ethosuximide is the primary agent in this class and is particularly effective for absence seizures. Its mechanism is selective inhibition of T-type calcium channels in thalamic neurons, which are central to absence seizure pathophysiology (Chaunsali et al., 2021). Adverse effects include gastrointestinal irritation, drowsiness, and rare blood dyscrasias (Perucca et al., 2023).

Valproates:

Valproic acid and derivatives are broad-spectrum ASMs effective against multiple seizure types. They act via enhancing GABAergic activity, inhibiting sodium channels, and reducing T-type calcium currents (Mesraoua et al., 2023). However, their use is limited by hepatotoxicity, teratogenicity, and metabolic side effects such as weight gain, making them less suitable for women of reproductive age (Kanner & Bicchi, 2022; Sha et al., 2024).

Newer Antiepileptic Drugs (AEDs):

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Recent decades have seen the development of second- and third-generation ASMs with more targeted mechanisms and improved tolerability. For example:

- **Gabapentin** enhances GABA release and modulates calcium channels.
- **Lamotrigine** stabilizes neuronal membranes by inhibiting sodium channels and suppressing glutamate release.
- **Levetiracetam** acts on synaptic vesicle protein 2A (SV2A), modulating neurotransmitter release and offering broad-spectrum efficacy (Knowles et al., 2022; Perucca et al., 2023).

While newer ASMs generally offer better safety profiles and reduced drug–drug interactions, high cost and limited accessibility remain barriers in low- and middle-income countries (Watila et al., 2021; Mugumbate, 2025). Moreover, even with newer agents, drug-resistant epilepsy (DRE) remains a major clinical challenge, necessitating adjunctive therapies such as ketogenic diets, neurostimulation, or surgery (Mesraoua et al., 2023; Yakubu et al., 2022).

1.4.2 Mechanisms of Action of Anticonvulsants

The pathophysiology of epilepsy involves an imbalance between excitatory and inhibitory neurotransmission, leading to neuronal hyperexcitability and synchronized firing (Chen et al., 2022; Boleti et al., 2024). Antiseizure medications (ASMs) restore this balance through diverse molecular mechanisms targeting ion channels, neurotransmitter systems, and synaptic proteins.

Sodium Channel Modulation:

Several ASMs, including phenytoin, carbamazepine, lamotrigine, and newer agents

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such as lacosamide, stabilize voltage-gated sodium channels in the inactivated state, thereby reducing high-frequency neuronal firing (Kumar et al., 2024; Perucca et al., 2023). By preventing rapid depolarizations, these drugs limit seizure propagation in focal epilepsies. Lacosamide uniquely enhances the slow inactivation of sodium channels, offering an alternative for drug-resistant epilepsy (Mesraoua et al., 2023). Despite efficacy, long-term sodium channel blockade may cause adverse effects such as ataxia, dizziness, and teratogenic risks (Kanner & Bicchi, 2022).

Calcium Channel Effects:

T-type calcium channels in thalamic neurons play a key role in absence seizures. Drugs such as ethosuximide and valproate inhibit these channels, preventing abnormal thalamocortical oscillations that generate spike-and-wave discharges (Chaunsali et al., 2021). Gabapentinoids (gabapentin and pregabalin) act on the α2δ subunit of voltage-gated calcium channels, reducing presynaptic excitatory neurotransmitter release (Knowles et al., 2022). More recent findings indicate that calcium channel modulation also contributes to neuroprotection by reducing excitotoxic calcium overload, which is critical in chronic epilepsy and seizure-induced neuronal injury (Łukawski & Czuczwar, 2023; de Melo et al., 2023).

GABAergic Enhancement:

GABA (gamma-aminobutyric acid) is the primary inhibitory neurotransmitter in the CNS, and enhancing GABAergic tone remains a central strategy in ASM development. Benzodiazepines and barbiturates increase GABAA_AA receptor activity by prolonging chloride channel opening, thereby enhancing neuronal hyperpolarization (Perucca et al., 2023). Valproate, in addition to sodium and calcium channel effects, increases synaptic GABA levels by inhibiting GABA transaminase and stimulating

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glutamic acid decarboxylase (Mesraoua et al., 2023). Tiagabine (a GABA reuptake inhibitor) and vigabatrin (an irreversible GABA transaminase inhibitor) further extend the range of GABAergic strategies (Kanner & Bicchi, 2022). However, long-term GABAergic potentiation may cause sedation, tolerance, and dependence (Shlobin et al., 2024).

Glutamate Receptor Inhibition:

Excessive glutamatergic neurotransmission drives excitotoxicity and seizure propagation. Drugs such as lamotrigine and topiramate inhibit AMPA/kainate receptor-mediated responses and reduce glutamate release, thereby counteracting hyperexcitability (Chaunsali et al., 2021; Knowles et al., 2022). Perampanel, a selective noncompetitive AMPA receptor antagonist, has emerged as an effective adjunctive therapy for partial and generalized seizures, especially in drug-resistant cases (Perucca et al., 2023). Novel therapies targeting NMDA receptor signaling and metabotropic glutamate receptors are under investigation, offering future avenues for drug development (Zhang et al., 2024).

Novel and Adjunctive Mechanisms:

Recent therapeutic strategies extend beyond classical targets. Levetiracetam, for instance, acts on synaptic vesicle protein 2A (SV2A), modulating neurotransmitter release and synaptic plasticity (Ignacio-Mejía et al., 2023). Other agents regulate oxidative stress, mitochondrial function, and neuroinflammation, mechanisms increasingly implicated in epileptogenesis (Madireddy & Madireddy, 2023; Ismy et al., 2024). Antioxidant-based therapies are gaining traction, with evidence showing reduced oxidative damage and improved seizure outcomes (Łukawski & Czuczwar, 2023; Yilgor & Demir, 2024). Moreover, precision medicine approaches seek to align

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ASM selection with genetic and molecular profiles of epilepsy syndromes, heralding a shift toward individualized therapy (Knowles et al., 2022; Zhang et al., 2024).

1.4.3 Challenges in Conventional Drug Therapy

Despite the significant progress in epilepsy pharmacotherapy, the management of the disease remains far from optimal. Several challenges limit the effectiveness of conventional antiseizure medications (ASMs), contributing to a high burden of morbidity and mortality globally (Asadi-Pooya et al., 2023; Feigin et al., 2025). These challenges include adverse effects, pharmacoresistance, accessibility issues, and social barriers to treatment.

Side Effects and Toxicity:

Most ASMs exert their effects through modulation of neuronal ion channels or neurotransmitter systems, but these mechanisms are not selective to epileptogenic neurons, leading to a wide range of adverse effects. Common side effects include sedation, dizziness, cognitive impairment, weight gain, and cosmetic issues such as gingival hyperplasia or hirsutism (Mesraoua et al., 2023). More severe toxicities, including hepatotoxicity, hematological abnormalities, and teratogenicity, are well documented, particularly with drugs such as valproate and phenytoin (Kanner & Bicchi, 2022). In women of childbearing age, valproate is associated with neural tube defects and impaired neurodevelopment in offspring, raising significant concerns for its continued use in this population (Sha et al., 2024). Similarly, long-term use of older ASMs may negatively impact bone health, fertility, and cardiovascular outcomes (González et al., 2022). These complications impair adherence and significantly reduce quality of life for patients with epilepsy, particularly children, adolescents, and women (Ogundare et al., 2021; Echendu et al., 2023).

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Drug Resistance and Treatment Failure:

Around 30% of patients experience drug-resistant epilepsy (DRE), defined as the failure to achieve seizure freedom after adequate trials of two or more appropriately chosen and tolerated ASMs (Perucca et al., 2023; Mesraoua et al., 2023). Mechanisms proposed for pharmacoresistance include upregulation of efflux transporters at the blood–brain barrier, alterations in drug targets such as sodium or calcium channels, maladaptive synaptic plasticity, and genetic variability influencing drug metabolism (Boleti et al., 2024; Zhang et al., 2024). Patients with DRE are at increased risk of seizure-related injuries, psychiatric comorbidities, cognitive decline, and sudden unexpected death in epilepsy (SUDEP) (Shlobin et al., 2024; Anaje et al., 2024). Treatment options for this group remain limited, with surgical interventions, ketogenic diets, and neuromodulation available only in specialized centers, leaving most patients inadequately managed (Yakubu et al., 2022).

Cost and Accessibility in Low-Resource Settings:

In low- and middle-income countries (LMICs), where the prevalence of epilepsy is highest, the treatment gap remains alarmingly wide between 60–90% of individuals with epilepsy do not receive appropriate medical therapy (Watila et al., 2021; Feigin et al., 2025). Contributing factors include high drug costs, erratic supply chains, inadequate diagnostic facilities, and shortages of trained neurologists (Echendu et al., 2023). Social and cultural factors further exacerbate the problem: stigma, misconceptions about epilepsy being caused by supernatural forces, and reliance on traditional healers often delay or prevent biomedical treatment (Ademilokun & Agunbiade, 2021; Nnebue et al., 2023). These barriers not only worsen health outcomes but also perpetuate the socioeconomic burden of epilepsy on households

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and communities (Abebe et al., 2024; Mugumbate, 2025).

1.5 Experimental Animal Models of Epilepsy

Animal models remain indispensable in epilepsy research, providing controlled platforms to investigate the neurobiology of seizures, evaluate the efficacy and safety of novel therapeutic agents, and explore the mechanisms underlying epileptogenesis (Knowles et al., 2022; Kumar et al., 2024). Since epilepsy is a heterogeneous disorder with multiple etiologies and seizure types, no single model can reproduce all clinical features of the human condition. Instead, researchers rely on a spectrum of chemical, electrical, and genetic models, each with unique advantages and limitations. These models have been pivotal in the discovery and preclinical testing of most currently available antiseizure medications (Perucca et al., 2023).

Chemically Induced Models

Pentylenetetrazole (PTZ) model:

PTZ, a non-competitive GABA_A receptor antagonist, is one of the most widely used chemo-convulsants. By reducing inhibitory GABAergic neurotransmission, PTZ induces generalized clonic and tonic seizures in rodents (Łukawski & Czuczwar, 2023). This model is particularly useful for evaluating drugs effective against absence and myoclonic seizures and is commonly employed in the initial screening of plant extracts and synthetic compounds for anticonvulsant activity (Yakubu et al., 2022). The PTZ model also allows assessment of both anticonvulsant and proconvulsant properties, making it versatile in pharmacological testing. However, it poorly replicates focal seizures and does not model the process of epileptogenesis, limiting its translational value (Mesraoua et al., 2023).

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Pilocarpine model:

Pilocarpine, a muscarinic acetylcholine receptor agonist, induces status epilepticus (SE) when administered in high doses. Following SE, animals develop chronic epilepsy characterized by spontaneous recurrent seizures, closely mimicking human temporal lobe epilepsy (TLE) (Boleti et al., 2024). This model is widely used to study mechanisms of epileptogenesis, neuronal death, neuroinflammation, and drug resistance (Chen et al., 2022). Importantly, the pilocarpine model reproduces hippocampal sclerosis, a hallmark pathology in human TLE. However, its limitations include high mortality rates, variability in seizure susceptibility, and the need for supportive care such as anticonvulsant administration during SE to reduce lethality (Adachi & Ito, 2022).

Kainic acid (KA) model:

Kainic acid, an excitotoxin that activates AMPA/kainate receptors, produces limbic seizures and SE followed by hippocampal sclerosis resembling human TLE (Chaunsali et al., 2021). The KA model is valuable for studying excitotoxicity, neuroinflammation, oxidative stress, and seizure-induced neuronal injury (Boleti et al., 2024). It is particularly useful for investigating long-term neurodegenerative processes associated with epilepsy. However, the model is limited by inter-animal variability in seizure severity and the extent of regional neurodegeneration, which complicates reproducibility and interpretation.

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Electrically Induced Models

Maximal electroshock seizure (MES) test:

The MES model involves delivering an electrical stimulus via corneal or auricular electrodes to induce generalized tonic-clonic seizures in rodents (Perucca et al., 2023). It is considered the “gold standard” for screening drugs effective against generalized tonic-clonic and partial seizures, especially sodium channel blockers such as phenytoin and carbamazepine (Kumar et al., 2024). MES has been instrumental in identifying the efficacy of many classical antiseizure medications. However, its scope is restricted to acute seizure screening, as it does not replicate epileptogenesis, spontaneous recurrent seizures, or chronic epilepsy (Knowles et al., 2022).

Genetic Models

Genetic models exploit naturally occurring or engineered mutations that predispose animals to seizures. Transgenic and knockout mice with mutations in specific ion channels, neurotransmitter receptors, or synaptic proteins provide invaluable insights into the genetic basis of epilepsy. For instance, SCN1A knockout mice serve as models for Dravet syndrome, while mutations in GABA receptor subunits help to elucidate mechanisms of generalized epilepsies (Chaunsali et al., 2021).

In addition, spontaneous epilepsy models such as Genetic Absence Epilepsy Rats from Strasbourg (GAERS) and Wistar Albino Glaxo/Rijswijk (WAG/Rij) rats replicate absence seizures with characteristic spike-and-wave discharges on EEG, closely resembling human absence epilepsy (Perucca et al., 2023). While highly informative, genetic models are expensive to maintain, technically demanding, and often specific to inherited epilepsies, limiting their generalizability to acquired forms of epilepsy

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(Knowles et al., 2022).

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Advantages and Limitations of Each Model

Experimental animal models of epilepsy remain fundamental to preclinical research, but each carries inherent advantages and drawbacks that influence its translational value. The selection of an appropriate model is therefore guided by the specific research objectives, such as drug screening, mechanistic exploration, or the study of epileptogenesis (Knowles et al., 2022; Kumar et al., 2024).

Chemically Induced Models:

Models such as pentylenetetrazole (PTZ), pilocarpine, and kainic acid are widely used due to their simplicity, reproducibility, and cost-effectiveness. The PTZ model is particularly useful in assessing compounds with activity against absence and myoclonic seizures and is often the first-line method for evaluating plant extracts and novel agents (Łukawski & Czuczwar, 2023; Yakubu et al., 2022). Pilocarpine and kainic acid models, on the other hand, provide closer parallels to human temporal lobe epilepsy (TLE), replicating neuropathological hallmarks such as hippocampal sclerosis, neuroinflammation, and spontaneous recurrent seizures (Boleti et al., 2024; Chen et al., 2022). However, their predictive value comes at the cost of significant limitations: pilocarpine and kainic acid administration are associated with high mortality rates, dose variability, and complex animal care requirements (Adachi & Ito, 2022). Moreover, chemically induced models do not fully reproduce the multifactorial nature of epileptogenesis in humans.

Electrically Induced Models:

The maximal electroshock seizure (MES) test remains the “gold standard” for identifying anticonvulsants effective against generalized tonic-clonic and partial seizures (Perucca et al., 2023). It is straightforward, reproducible, and highly

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predictive for sodium channel-blocking drugs such as phenytoin and carbamazepine (Kumar et al., 2024). However, its utility is limited to acute seizure screening. MES does not provide insights into epileptogenesis, neurodegeneration, or chronic epilepsy, and therefore cannot be relied upon for testing disease-modifying or neuroprotective strategies (Knowles et al., 2022).

Genetic Models:

Genetic models, such as SCN1A knockout mice for Dravet syndrome or absence epilepsy rat strains (GAERS, WAG/Rij), provide precise insights into the molecular and genetic underpinnings of inherited epilepsies (Chaunsali et al., 2021; Perucca et al., 2023). They replicate electroclinical features closely resembling human conditions, including spike-and-wave discharges and pharmacological responses, thus enhancing their predictive validity. However, these models are resource-intensive, technically demanding, and costly to maintain (Kumar et al., 2024). Furthermore, their applicability is limited to rare genetic syndromes, and they may not capture the full clinical heterogeneity of acquired epilepsies, such as those resulting from trauma, infection, or neurodegenerative disease (Boleti et al., 2024).

Integrative Use of Multiple Models:

No single model can capture the complexity of human epilepsy. As such, a combination of models is often employed in preclinical research to maximize translational relevance. Acute seizure models (e.g., MES, PTZ) are typically used for initial screening of anticonvulsant efficacy, while chronic models (e.g., pilocarpine, kainic acid) provide insights into epileptogenesis, neurodegeneration, and long-term drug effects (Chen et al., 2022). Genetic models complement these approaches by offering mechanistic clarity on molecular pathways implicated in epileptic

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syndromes (Knowles et al., 2022). This integrative strategy enhances the reliability of preclinical findings, reduces false negatives in drug discovery, and bridges the translational gap between laboratory research and clinical practice (Boleti et al., 2024).

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1.6 Overview of Plants with Anticonvulsant Property

1.6.1 Tamarindus indica

1.6.2 Nomenclature and Taxonomy

Tamarindus indica L. belongs to the family **Fabaceae**, subfamily **Caesalpinioideae**. It is the sole recognized species in the genus *Tamarindus*, giving it a distinct taxonomic identity within the legume family (Kumar et al., 2024). The plant is widely known by different vernacular names that reflect its global cultural importance. In English, it is called “tamarind,” in Hindi “imli,” in Hausa “tsamiyu,” and in Yoruba “ajagbon.” These local designations highlight its dual role as both a food source and a medicinal resource in various traditional systems of medicine (Yakubu et al., 2022).

1.6.3 Geographical Distribution and Description

Although *T. indica* is native to tropical Africa, it has spread widely across the tropics and subtropics, particularly in South and Southeast Asia, the Middle East, the Caribbean, and Central America (Abebe et al., 2024). Its adaptability enables it to thrive in semi-arid, tropical, and subtropical environments, where it is often planted along roadsides, farm boundaries, and homesteads as a multipurpose tree.

Morphologically, *T. indica* is a large, long-lived, evergreen tree that can reach heights of 12–25 meters. It is characterized by a dense, spreading crown that provides ample shade. The leaves are pinnately compound with 10–20 pairs of small, oblong leaflets. The flowers are yellow with reddish or orange streaks, borne in racemes, while the fruits are brown, curved pods containing a sticky, acidic pulp that encloses 1–12 hard, glossy seeds. The pulp is used in culinary preparations such as soups, sauces, beverages, and confectionaries, while also serving as a base for traditional

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medicinal remedies (Kumar et al., 2024).

1.6.4 Ethnomedicinal Uses

Ethnomedical evidence underscores the broad therapeutic applications of *T. indica*. In African, Asian, and Caribbean traditional medicine, various parts of the plant (pulp, leaves, bark, and seeds) are used in the treatment of:

Fever and malaria, where its extracts are employed as febrifuges and supportive remedies (Yakubu et al., 2022).

Gastrointestinal ailments, including constipation, diarrhea, and dysentery, due to its laxative and antimicrobial properties.

Inflammatory conditions, wound infections, and skin diseases, leveraging its antimicrobial and healing effects (Madireddy & Madireddy, 2023).

Neurological disorders, where the pulp and leaf extracts are reputed in some communities to calm seizures and reduce epilepsy-associated symptoms, possibly due to sedative or anxiolytic actions (Watila et al., 2021).

Beyond neurological relevance, *T. indica* has been associated with antioxidant, hepatoprotective, hypoglycemic, antimicrobial, and wound-healing properties, reflecting its wide therapeutic scope (Adachi & Ito, 2022; Abebe et al., 2024).

1.6.5 Toxicological and Pharmacological Studies

Toxicological profile:

Toxicological investigations generally indicate that *T. indica* is safe when consumed as food or at moderate medicinal doses. Acute and sub-acute toxicity studies in rodents have demonstrated a wide safety margin, with no mortality at doses far

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exceeding normal consumption levels (Yakubu et al., 2022). Nonetheless, very high doses have occasionally been linked to mild gastrointestinal disturbances and rare hepatotoxic changes, emphasizing the need for cautious dose standardization.

Pharmacological studies:

Research into the pharmacological potential of *T. indica* has yielded a broad spectrum of activities:

Antioxidant activity: Extracts contain phenolic compounds, flavonoids, vitamin C, and tartaric acid, all of which contribute to robust free radical scavenging and reduction of oxidative stress (Madireddy & Madireddy, 2023). Since oxidative stress is strongly implicated in seizure generation and neuronal injury, this property enhances the plant's relevance in anticonvulsant research (Łukawski & Czuczwar, 2023).

CNS activity: Preclinical evidence suggests that *T. indica* extracts exert sedative, anxiolytic, and potential anticonvulsant effects, likely mediated through GABAergic facilitation and modulation of oxidative pathways (Watila et al., 2021; Kumar et al., 2024). These activities support its traditional use in epilepsy and related nervous disorders.

Other pharmacological actions: Studies also confirm hypoglycemic, hepatoprotective, anti-inflammatory, antimicrobial, and wound-healing effects, which broaden its therapeutic profile and underscore its role as a multipurpose medicinal plant (Adachi & Ito, 2022; Abebe et al., 2024).

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Figure 1.1: *Tamarindus indica*

Source: University of Benin, Faculty of Engineering..

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1.7 Ficus iteophylla

1.7.1 Nomenclature and Taxonomy

Ficus iteophylla Miq. belongs to the family **Moraceae**, which comprises more than 800 species of figs globally, many of which hold profound cultural, nutritional, and medicinal significance (Yakubu et al., 2022). Within this family, *F. iteophylla* is considered one of the lesser-studied species, yet it remains ethnobotanically important in several African regions.

Commonly referred to as a **"fig tree,"** the plant bears diverse vernacular names across Nigeria and West Africa, reflecting its widespread use in traditional healing practices. Like other *Ficus* species, it is often associated with **sacred or ritualistic value**, as well as medicinal relevance in community health (Watila et al., 2021).

1.7.2 Geographical Distribution and Description

Ficus iteophylla is predominantly distributed in tropical Africa, where it grows naturally in forest zones, savannah woodlands, and along riverbanks (Yakubu et al., 2022). It thrives in moist, fertile soils, particularly in West African countries such as Nigeria, Ghana, and Cameroon, where it is used both for medicine and as a wild edible species.

Morphologically, the plant is a medium-sized tree or shrub, characterized by:

- Smooth bark and the development of aerial roots, a hallmark of the genus.
- Simple, alternate leaves, oblong to lanceolate in shape, with a leathery texture.
- Small, globular figs (syconia) that transition from green to purple upon ripening, serving as both food and medicinal resources.

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The general vegetative and reproductive morphology is consistent with other *Ficus* species, many of which are well-documented for their ethnopharmacological relevance (Watila et al., 2021).

1.7.3 Ethnomedicinal Uses

In African traditional medicine, *F. iteophylla* has a strong reputation for treating neurological and convulsive disorders. Decoctions or infusions of the leaves, bark, or latex are administered orally to reduce seizure frequency, calm the nervous system, and manage epilepsy (Yakubu et al., 2022).

Beyond epilepsy, it has been widely applied in the management of:

- Fever and malaria
- Diarrhea and gastrointestinal disturbances
- Inflammatory and infectious conditions
- Wounds and skin diseases (Abebe et al., 2024)

Reports from ethnobotanical surveys also confirm that species within the *Ficus* genus generally exhibit sedative, anxiolytic, and anticonvulsant effects, supporting the traditional application of *F. iteophylla* for epilepsy (Watila et al., 2021).

1.7.4 Toxicological and Pharmacological Studies

Toxicological profile:

Although few modern toxicological evaluations have been conducted on *F. iteophylla*, its long-standing use in African ethnomedicine suggests a favorable safety profile at therapeutic doses. Animal model studies indicate no significant toxicity at moderate

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extract levels. However, ingestion of excessive doses of latex or concentrated extracts may cause gastrointestinal irritation, abdominal discomfort, or local inflammation, necessitating careful dosing (Yakubu et al., 2022). Further controlled toxicological investigations are essential to establish its long-term safety.

Pharmacological studies:

Emerging pharmacological evidence suggests that *F. iteophylla* exhibits multiple bioactivities:

Anticonvulsant potential: Experimental studies in rodent models suggest that F. iteophylla extracts may reduce seizure activity by enhancing GABAergic neurotransmission, modulating ion channels, and attenuating oxidative stress (Watila et al., 2021). These findings align with its traditional use in epilepsy management.

Antioxidant properties: Like other *Ficus* species, it is rich in polyphenols, flavonoids, and tannins, which exhibit significant free radical scavenging activity. This is particularly relevant to epilepsy, where oxidative damage contributes to neuronal hyperexcitability and progression of epileptogenesis (Madireddy & Madireddy, 2023).

Other pharmacological actions: In addition to CNS-related activity, extracts have shown anti-inflammatory, antimicrobial, and wound-healing effects in preliminary studies, supporting its diverse applications in traditional medicine (Abebe et al., 2024).

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Figure 1.2: *Ficus iteophylla*

Source: University of Benin, Faculty of Engineering.

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1.8 Antioxidants and Epilepsy

1.8.1 Oxidative Stress in Epilepsy

Oxidative stress, defined as an imbalance between the production of reactive oxygen species (ROS) and the capacity of endogenous antioxidant defense systems, is increasingly recognized as a central mechanism underlying seizure initiation, propagation, and epileptogenesis (Łukawski & Czuczwar, 2023; Madireddy & Madireddy, 2023).

During seizures, neurons experience intense metabolic demand due to sustained depolarization and excessive firing. To meet this demand, mitochondria increase oxidative phosphorylation, but the electron transport chain becomes "leaky," generating ROS such as superoxide ($O_2^{-}\cdot$), hydrogen peroxide (H_2O_2), and hydroxyl radicals (·OH) (Boleti et al., 2024). Excessive ROS overwhelm antioxidant defenses (e.g., glutathione, superoxide dismutase, catalase), causing structural and functional damage to cellular macromolecules.

Key mechanisms linking oxidative stress and epilepsy include:

Lipid peroxidation: ROS attack polyunsaturated fatty acids in neuronal membranes, producing reactive aldehydes such as malondialdehyde (MDA) that compromise membrane fluidity, disrupt ion-channel function, and alter receptor activity. These changes favor neuronal hyperexcitability and reduced seizure threshold (Madireddy & Madireddy, 2023; Chaunsali et al., 2021).

Protein oxidation and enzyme inactivation: Oxidative modification of ion channels (e.g., sodium, potassium, calcium channels) and neurotransmitter transporters alters gating kinetics and reuptake mechanisms, enhancing excitatory transmission while weakening inhibitory tone (Łukawski & Czuczwar, 2023). Critical enzymes such as

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Na^+/K^+-ATPase, which maintains ionic gradients, are also impaired, leading to neuronal depolarization and synchronous discharges (de Melo et al., 2023).

Mitochondrial dysfunction: Seizure-induced ROS damage mitochondrial DNA, proteins, and membranes, resulting in impaired ATP production and further ROS leakage. The resulting bioenergetic crisis exacerbates excitotoxicity and increases neuronal vulnerability to subsequent seizures (Boleti et al., 2024).

Neuroinflammation: ROS interact with redox-sensitive transcription factors (e.g., NF-κB, Nrf2) and activate glial cells, leading to the release of pro-inflammatory cytokines and nitric oxide (NO). This inflammatory milieu promotes neuronal excitability, perpetuating seizure activity and epileptogenesis (Chen et al., 2022; Boleti et al., 2024).

Clinical and preclinical evidence strongly supports these mechanistic pathways:

Human studies have reported elevated serum and brain levels of oxidative stress markers such as MDA, protein carbonyls, and 8-hydroxy-2'-deoxyguanosine in patients with epilepsy, particularly those with drug-resistant epilepsy, compared to healthy controls (Yilgor & Demir, 2024; Ignacio-Mejía et al., 2023).

Animal models demonstrate that seizure induction (e.g., with PTZ, kainic acid, or pilocarpine) consistently elevates ROS levels, reduces antioxidant enzyme activity, and worsens neuronal damage. Importantly, antioxidant interventions (e.g., N-acetylcysteine, vitamin E, or plant-derived flavonoids) attenuate both neuronal injury and seizure severity (de Melo et al., 2023; Łukawski & Czuczwar, 2023).

Some antiseizure drugs (ASMs) themselves influence oxidative stress pathways. For instance, levetiracetam has shown antioxidant and neuroprotective properties in temporal lobe epilepsy models, while others (e.g., valproate) may paradoxically

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exacerbate oxidative imbalance under certain conditions (Ignacio-Mejía et al., 2023).

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1.8.2 Antioxidant Defense Mechanisms

The brain possesses an elaborate but vulnerable antioxidant defense network to maintain redox homeostasis and counteract the continuous generation of reactive oxygen species (ROS). These systems operate through enzymatic and non-enzymatic pathways, acting synergistically to protect neurons from oxidative insults.

Enzymatic antioxidants are the primary defense against ROS:

- **Superoxide dismutases (SODs):** These enzymes catalyze the dismutation of superoxide radicals ($O_2^{-}\cdot$) into hydrogen peroxide (H_2O_2) and oxygen, representing the first line of defense against mitochondrial and cytosolic ROS.
- **Catalase (CAT):** Catalase further detoxifies H_2O_2 by converting it into water and oxygen, thereby preventing the generation of the highly reactive hydroxyl radical (·OH).
- **Glutathione peroxidases (GPx):** These selenium-containing enzymes reduce hydrogen peroxide and lipid hydroperoxides using reduced glutathione (GSH) as an electron donor, thereby protecting membranes from peroxidation (de Melo et al., 2023; Łukawski & Czuczwar, 2023).

Among non-enzymatic defenses, glutathione (GSH) is the most important redox buffer in neurons. Beyond serving as a cofactor for GPx, GSH directly scavenges free radicals and regenerates other antioxidants (e.g., vitamins C and E). Depletion of GSH has been consistently linked to increased seizure susceptibility, neuronal apoptosis, and progression of epileptogenesis (Madireddy & Madireddy, 2023).

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When seizures are prolonged or recurrent, endogenous defenses are overwhelmed. This leads to:

- Accumulation of oxidative damage to lipids, proteins, and DNA.
- Impaired energy metabolism due to mitochondrial dysfunction.
- Neuroinflammation, which exacerbates redox imbalance (Łukawski & Czuczwar, 2023; Boleti et al., 2024).

Experimental studies demonstrate that **augmenting antioxidant defenses** can mitigate seizure severity and protect neuronal integrity. Antioxidant therapy has been shown to:

- Reduce ROS burden,
- Preserve Na^+/K^+-ATPase activity,
- Prevent neuronal apoptosis and necrosis,
- Lower seizure frequency and duration (de Melo et al., 2023).

  Systematic reviews of preclinical studies further confirm that antioxidant interventions significantly improve biochemical markers (e.g., MDA reduction, SOD/CAT/GPx restoration) and histopathological outcomes in seizure models (de Melo et al., 2023).

Role of Diet and Plant-Derived Antioxidants in Seizure Control

Dietary antioxidants and plant-derived phytochemicals have attracted growing attention as accessible, safe, and multifunctional modulators of oxidative stress in epilepsy.

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- **Epidemiological and interventional evidence** suggests that diets rich in fruits, vegetables, and flavonoid-rich foods correlate with improved neurological outcomes and reduced seizure burden (Ismy et al., 2024; Zhang et al., 2024).
- **Plant polyphenols,** including flavonoids, tannins, proanthocyanidins, and phenolic acids, exert multiple neuroprotective effects:
    - Scavenging free radicals,
    - Chelating transition metals (e.g., Fe^{2+}, Cu^{2+}) that catalyze ROS formation,
    - Enhancing endogenous antioxidant enzyme expression,
    - Suppressing pro-inflammatory signaling pathways such as NF-κB (Zhang et al., 2024; Alyami et al., 2022).

Preclinical studies support these findings:

- Proanthocyanidins significantly reduced PTZ-induced seizures in mice, with effects attributed to improved antioxidant status (Alyami et al., 2022).
- Flavonoids have been widely reviewed as potential antiseizure agents, with evidence for antioxidant, anti-inflammatory, GABAergic modulatory, and glutamatergic inhibitory effects, making them strong candidates for drug discovery (Zhang et al., 2024).
- Antioxidant strategies may be particularly promising in drug-resistant epilepsy, where oxidative stress and mitochondrial dysfunction play key roles (de Melo et al., 2023; Madireddy & Madireddy, 2023).

Antioxidant Potential of *Tamarindus indica* and *Ficus iteophylla*

Specific to the plants under investigation:

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- **Tamarindus indica**: Methanolic and ethyl acetate extracts of *T. indica* leaves, fruit pulp, and seeds have shown potent free radical scavenging activity in DPPH, FRAP, and lipid peroxidation assays. In vivo, *T. indica* extracts lowered oxidative stress markers and preserved antioxidant enzyme levels, confirming strong redox-modulating effects (Garba et al., 2023; Dahiru et al., 2023; Fagbemi et al., 2022).
- **Ficus species (including F. iteophylla):** Several *Ficus* species are rich in polyphenols, flavonoids, and tannins, which exhibit both antioxidant and anti-inflammatory properties. These bioactivities can protect neuronal tissue from seizure-related oxidative damage and are consistent with traditional claims of anticonvulsant properties (Madrigal-Santillán et al., 2024; Salehi et al., 2021).

1.9 Control in Experimental Pharmacology

Importance of Controls in Seizure Studies

In experimental pharmacology, the concept of control groups is central to scientific rigor. Controls ensure that experimental outcomes are not confounded by extraneous biological, environmental, or methodological factors. In seizure research, this is especially critical because seizure susceptibility can be modulated by numerous variables, including animal strain, age, sex, circadian rhythms, stress, diet, and even subtle handling differences (Knowles et al., 2022; Kumar et al., 2024).

By providing a comparative baseline, controls enable researchers to determine whether observed anticonvulsant, pro-convulsant, or neuroprotective effects are causally linked to the intervention (e.g., plant extract) rather than chance fluctuations or procedural artifacts. Moreover, they improve reproducibility and translational reliability, key concerns in epilepsy research where reproducibility gaps often hinder

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clinical application (Perucca et al., 2023).

This is particularly important in phytomedicine research. Plant extracts are chemically complex, containing multiple secondary metabolites with diverse, sometimes opposing, pharmacological actions. Proper controls help distinguish genuine therapeutic effects from placebo responses, nonspecific physiological changes (e.g., sedation, motor impairment), or vehicle-related artifacts (Watila et al., 2021). Without them, any claims of anticonvulsant efficacy remain unsubstantiated.

Positive Controls (Standard Anticonvulsant Drugs)

Positive controls are well-characterized antiseizure medications (ASMs) with established efficacy in specific seizure models. Their inclusion serves multiple purposes:

1. **Validation of the experimental model** – A positive control confirms that the seizure-induction paradigm (e.g., PTZ, MES, pilocarpine) is sensitive to known treatments. If the positive control fails, the experimental conditions may be flawed.
2. **Benchmarking efficacy** – Test compounds (including plant extracts) can be compared to gold-standard drugs, helping to position them along the therapeutic spectrum.
3. **Mechanistic inference** – Since standard ASMs have defined molecular targets, their effects can provide insights into whether a test compound acts via similar or novel mechanisms (Perucca et al., 2023; Mesraoua et al., 2023).

Commonly used positive controls in seizure studies include:

- **Diazepam (benzodiazepine class):** Widely employed in chemically induced

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seizure models such as PTZ or isoniazid. Its action via positive allosteric modulation of GABAA_AA receptors enhances inhibitory neurotransmission, delaying seizure onset and reducing severity (Knowles et al., 2022).

- **Phenytoin (hydantoin class):** Standard in MES-induced seizure models. By blocking voltage-gated sodium channels, it prevents seizure propagation and tonic extension, validating sodium channel–dependent seizure paradigms (Kumar et al., 2024).
- **Valproate (valproic acid):** A broad-spectrum ASM used in diverse models (PTZ, pilocarpine, MES). Its multimodal mechanisms include sodium channel blockade, calcium current inhibition, and GABAergic enhancement, making it particularly useful for cross-model validation (Mesraoua et al., 2023).

Inclusion of these standards ensures that novel extracts are evaluated against clinically relevant benchmarks, strengthening the translational value of findings (Perucca et al., 2023).

Negative Controls (Placebo/Vehicle)

Negative controls consist of animals receiving placebo or vehicle solutions (e.g., saline, distilled water, gum acacia, or solvents like Tween 80). Their role is to confirm that:

- Seizure outcomes are **not influenced** by injection stress, vehicle irritation, or handling.
- Baseline seizure susceptibility can be accurately determined in the absence of pharmacological intervention.

For instance, in PTZ- or pilocarpine-induced seizure models, negative control animals

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reliably develop seizures with characteristic latencies, severities, and mortality rates. This establishes the baseline disease phenotype against which anticonvulsant efficacy is measured (Łukawski & Czuczwar, 2023).

In the context of phytomedicine, vehicles are especially important. Many plant extracts require organic solvents or suspending agents that could themselves influence seizure activity (e.g., ethanol altering GABA/glutamate balance, or DMSO affecting oxidative stress). Negative controls ensure that any observed protection is pharmacological rather than artifactual (Yakubu et al., 2022).

The Balance Between Positive and Negative Controls

The strength of an experimental design lies in the synergistic use of both positive and negative controls. Positive controls demonstrate that the model is sensitive and valid, while negative controls define the baseline pathological state. Together, they provide a robust framework for testing novel agents such as Tamarindus *indica* and *Ficus iteophylla*.

By including both, researchers can:

- Verify that the experimental seizure induction works as intended,
- Confirm that plant extracts exert specific effects beyond vehicle interference,
- Benchmark efficacy relative to clinical standards,
- Ensure findings are both internally valid (true to the experiment) and externally valid (potentially translatable to human epilepsy).

Thus, rigorous control selection is not a procedural formality but a scientific

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necessity in evaluating anticonvulsant potential.

Role of Standards in Validating Plant Extracts

The use of both positive and negative controls is indispensable in herbal and natural product research, where variability in phytochemical composition, extraction method, and plant source can profoundly influence pharmacological outcomes. Unlike synthetic drugs with defined molecular structures, plant extracts are complex mixtures of bioactive compounds that may act synergistically or antagonistically. This complexity poses challenges in discerning whether an extract's effect is due to a specific anticonvulsant mechanism, nonspecific physiological actions, or simply toxic effects.

Comparing plant extracts with standard antiseizure medications (ASMs) such as diazepam, phenytoin, or valproate provides a clinical benchmark. For example, if a methanolic extract of Tamarindus indica or Ficus iteophylla delays seizure onset in the PTZ model to a similar degree as diazepam, this suggests true GABAergic modulation rather than nonspecific sedation (Watila et al., 2021; Boleti et al., 2024). In contrast, if seizure scores are reduced but motor impairment or sedation are disproportionately high, the protective effect may not reflect genuine anticonvulsant activity but rather a general CNS depressant effect (Madireddy & Madireddy, 2023).

Another important consideration is the multifaceted pharmacological nature of medicinal plants. Extracts often display antioxidant, anti-inflammatory, sedative, anxiolytic, and analgesic effects, all of which can indirectly influence seizure outcomes. Benchmarking these extracts against standards enables researchers to separate primary antiseizure mechanisms (e.g., sodium channel blockade, GABA potentiation) from secondary neuroprotective effects such as free radical

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scavenging or suppression of neuroinflammation (Madireddy & Madireddy, 2023; Boleti et al., 2024).

Standards also help establish the relative potency and therapeutic index (safety margin) of plant extracts. If an extract demonstrates seizure protection comparable to diazepam or valproate, but at doses that do not cause sedation, motor incoordination, or hepatotoxicity, this strengthens its candidacy for further preclinical and toxicological investigation (Perucca et al., 2023). Conversely, if efficacy is only achieved at doses that produce overt toxicity, its translational potential is limited.

Furthermore, standards facilitate cross-study reproducibility and translational relevance. Because different research groups may use varied extraction methods or seizure models, referencing outcomes against established ASMs creates a common evaluative framework. This allows for consistent interpretation of whether plant extracts are genuinely promising leads or only modestly effective compared with clinically available drugs (Watila et al., 2021; Perucca et al., 2023).

1.10 Induction of Seizures in Animal Models

Animal models are indispensable tools for epilepsy research, as they allow investigators to explore the neurobiology of seizures, understand the mechanisms of epileptogenesis, and assess the therapeutic potential of new compounds. Seizures can be experimentally induced using chemical convulsants, electrical stimulation, or genetic manipulations, with each approach mimicking distinct forms of human epilepsy (Łukawski & Czuczwar, 2023; Kumar et al., 2024). Among these, the use of chemical agents such as pentylenetetrazole (PTZ) and kainic acid, and electrical induction through the maximal electroshock (MES) test, remain the most common strategies. Importantly, these models not only reproduce seizure activity but also

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offer translational relevance by predicting the clinical efficacy of standard antiseizure medications (ASMs) (Perucca et al., 2023).

Pentylenetetrazole (PTZ) Model

PTZ is one of the most widely employed convulsants in preclinical research because of its reliability, reproducibility, and sensitivity to established ASMs. Mechanistically, PTZ acts as a non-competitive antagonist of the GABA_A receptor complex, thereby reducing inhibitory neurotransmission and promoting neuronal hyperexcitability (Knowles et al., 2022). This pharmacological action effectively lowers the seizure threshold, producing generalized clonic seizures that may progress to tonic–clonic episodes at higher doses.

The PTZ model is particularly relevant for studying absence seizures and myoclonic seizures, which are strongly linked to disrupted GABAergic signaling (Łukawski & Czuczwar, 2023). In validation studies, clinically effective drugs such as valproate and benzodiazepines reliably suppress PTZ-induced seizures, demonstrating the predictive validity of this model (Mesraoua et al., 2023). Beyond drug screening, PTZ has also been used to study oxidative stress, inflammation, and epileptogenesis, since repeated low-dose PTZ administration can generate a chronic epilepsy phenotype.

Maximal Electroshock Seizure (MES) Test

The MES test induces seizures by applying a controlled electric current through corneal or auricular electrodes, resulting in generalized tonic–clonic seizures in rodents (Kumar et al., 2024). The hallmark endpoint of this model is tonic hind-limb extension (THLE), a reliable indicator of seizure severity and spread (Knowles et al., 2022).

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Mechanistically, MES seizures involve widespread and synchronous depolarization of cortical and subcortical neurons, leading to seizure propagation throughout the brain. Clinically, this model is particularly relevant for generalized tonic–clonic epilepsy, one of the most common and debilitating forms of epilepsy in humans (Perucca et al., 2023). The MES test is also considered a gold standard for identifying sodium channel–blocking anticonvulsants. Drugs such as phenytoin, carbamazepine, and lamotrigine demonstrate robust protection against MES-induced seizures, validating the model's translational utility (Kumar et al., 2024).

Although the MES test does not reproduce chronic epileptogenesis or spontaneous seizures, it remains a cornerstone of acute seizure screening, especially for compounds hypothesized to act via voltage-gated sodium channel modulation.

Relevance of Each to Human Epilepsy

Each experimental seizure induction method offers unique translational value by modeling specific neurobiological processes and clinical seizure types observed in humans. Together, these models provide complementary insights into the pathophysiology of epilepsy and enable the rational screening of novel antiseizure agents.

- **Pentylenetetrazole (PTZ) Model**

The PTZ model is widely recognized for its ability to reproduce seizures arising from impaired GABAergic inhibition, a central feature of many human epilepsies (Knowles et al., 2022). Since PTZ acts as a GABAA_AA receptor antagonist, it effectively simulates the inhibitory dysfunction that contributes to absence seizures and myoclonic seizures. These seizure types are often characterized by aberrant

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thalamocortical oscillations and heightened cortical excitability. The model has strong predictive validity, as standard agents such as benzodiazepines and valproate, which enhance GABAergic signaling, are highly effective in suppressing PTZ-induced seizures (Mesraoua et al., 2023). This makes PTZ an indispensable tool for evaluating candidate compounds targeting GABAergic systems or possessing sedative–anxiolytic properties relevant to epilepsy therapy.

- **Maximal Electroshock Seizure (MES) Test**

The MES test is the gold standard for modelling generalized tonic–clonic seizures, one of the most common and disabling forms of epilepsy in humans (Kumar et al., 2024). The hallmark endpoint of tonic hind-limb extension (THLE) reflects seizure spread across cortical and subcortical structures, paralleling the widespread neuronal depolarization seen in generalized tonic–clonic epilepsy. This model has high construct and predictive validity, particularly for identifying sodium channel–blocking drugs such as phenytoin, carbamazepine, and lamotrigine, which remain first-line therapies in clinical practice (Knowles et al., 2022). By testing plant extracts or novel compounds in MES, researchers can assess their potential to prevent seizure generalization and spread critical aspects of seizure control in patients.

1.11 Rationale for the Study

Limitations of Current Antiepileptic Drugs

Despite the availability of over 20 antiepileptic drugs (AEDs) spanning multiple pharmacological classes, epilepsy management remains a major global health challenge. Epidemiological data suggest that approximately 30–40% of patients

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develop drug-resistant epilepsy (DRE), defined as the persistence of seizures despite adequate trials of at least two appropriately chosen and tolerated AEDs (Perucca et al., 2023; Mesraoua et al., 2023). This subgroup faces the highest morbidity and mortality, including increased risk of status epilepticus and sudden unexpected death in epilepsy (SUDEP).

Even in patients who respond, current AEDs are not without drawbacks. While they suppress seizures, they do not cure epilepsy or prevent epileptogenesis, and their effectiveness is often offset by adverse effects. Common side effects include cognitive impairment, sedation, dizziness, and ataxia, which significantly compromise quality of life (Knowles et al., 2022). More serious toxicities include hepatotoxicity, hematological disturbances, metabolic syndrome, and teratogenicity, particularly concerning for women of reproductive age (Kumar et al., 2024). These adverse profiles limit adherence and may necessitate switching therapies, further complicating management.

In addition to safety and efficacy limitations, economic and accessibility barriers remain profound. Long-term therapy is typically required for the majority of patients, making epilepsy a chronic financial burden. This is especially problematic in low- and middle-income countries (LMICs), where more than 60–90% of patients face a treatment gap due to the high cost of newer AEDs, erratic supply chains, insufficient diagnostic infrastructure, and pervasive cultural stigma (Watila et al., 2021; Mesraoua et al., 2023). Consequently, many individuals remain untreated or turn to traditional medicine, which may or may not offer effective seizure control.

Collectively, these challenges underscore the urgent need for alternative or adjunctive therapies that are:

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1. **Effective against drug-resistant and diverse seizure types**;
2. **Safer and better tolerated**, with fewer long-term toxicities;
3. **Affordable and accessible**, particularly in resource-limited settings.

This has prompted growing interest in medicinal plants such as *Tamarindus indica* and *Ficus iteophylla*, which are traditionally used in the management of seizures and are known to possess antioxidant, neuroprotective, and potential anticonvulsant properties (Yakubu et al., 2022; Watila et al., 2021). Their integration into modern pharmacological research may provide a pathway toward safer, more cost-effective epilepsy therapies.

Rising Interest in Herbal Medicines for CNS Disorders

There is a growing global interest in the exploration and integration of medicinal plants for the management of central nervous system (CNS) disorders, including epilepsy, anxiety, depression, and neurodegenerative diseases. This resurgence is driven by several converging factors: the longstanding role of plants in traditional healing systems, the limitations of current pharmacotherapies in terms of efficacy and safety, and a rapidly expanding body of evidence showing that plant-derived compounds can target critical mechanisms implicated in seizure disorders such as neurotransmitter modulation, oxidative stress reduction, and neuroinflammatory control (Madireddy & Madireddy, 2023; Alyami et al., 2022).

Phytochemicals, the bioactive constituents of medicinal plants, are increasingly recognized for their diverse neuropharmacological actions.

- Flavonoids have demonstrated anticonvulsant effects through mechanisms such as GABAergic potentiation, NMDA receptor inhibition, antioxidant activity,

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and anti-inflammatory modulation, making them promising leads for novel antiseizure agents (Zhang et al., 2024).

- Tannins and phenolic acids contribute to free radical scavenging and mitochondrial protection, thereby limiting oxidative neuronal injury, a major driver of epileptogenesis (de Melo et al., 2023).
- Alkaloids and terpenoids exhibit ion channel modulation, neuroprotective, and sedative actions, which may help in restoring excitatory–inhibitory balance in epileptic circuits (Alyami et al., 2022).

Beyond pharmacological activity, socioeconomic and cultural considerations also fuel the rising interest in herbal medicines. In many low- and middle-income countries, where the epilepsy treatment gap can exceed 60%, limited access to conventional AEDs and their high costs push patients and caregivers toward traditional remedies (Watila et al., 2021). Plant-based therapies are often more affordable, widely available, and culturally acceptable, offering a pragmatic alternative or adjunctive option in settings where modern healthcare resources are scarce.

Additionally, unlike many synthetic AEDs that primarily act through one or two molecular targets, plant extracts often exert multi-target actions, simultaneously addressing oxidative stress, inflammation, and neurotransmission imbalances. This polypharmacological profile is particularly relevant for complex disorders like epilepsy, where multiple pathological processes converge to sustain seizure activity and neuronal injury (de Melo et al., 2023; Madireddy & Madireddy, 2023).

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Scientific Justification for Investigating Tamarindus indica and Ficus iteophylla

Both *Tamarindus indica* and *Ficus iteophylla* have long histories of use in African traditional medicine, particularly for the treatment of convulsions, epilepsy, and other neurological conditions. Their ethnomedicinal relevance, coupled with emerging pharmacological evidence, provides strong scientific rationale for systematic evaluation of their anticonvulsant potential.

Tamarindus indica is a multipurpose medicinal plant widely distributed in tropical and subtropical regions, traditionally used for ailments ranging from fever and digestive disturbances to inflammatory and neurological conditions. Phytochemical analyses reveal that *T. indica* is rich in flavonoids, polyphenols, proanthocyanidins, and tannins, all of which exhibit antioxidant and central nervous system (CNS)-modulating activities (Garba et al., 2023; Dahiru et al., 2023). Experimental studies have demonstrated its hepatoprotective, anti-inflammatory, and neuroprotective properties, including the ability to reduce lipid peroxidation, modulate neurotransmitter levels, and enhance endogenous antioxidant defenses (Fagbemi et al., 2022). Given the recognized role of oxidative stress in epileptogenesis, these pharmacological attributes suggest that *T. indica* could confer antiepileptic and neuroprotective benefits through redox balancing and neuronal stabilization.

Ficus species, including *F. carica, F. religiosa,* and *F. exasperata*, are widely reported to contain bioactive phytoconstituents such as flavonoids, alkaloids, sterols, and phenolic acids. These compounds have been linked to anticonvulsant, antioxidant, anxiolytic, and sedative activities in animal models (Madrigal-Santillán et al., 2024; Salehi et al., 2021). *Ficus iteophylla* in particular is valued in African ethnomedicine for the management of seizures, epilepsy, fever, and infections (Yakubu et al., 2022).

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Preliminary findings indicate that it may exert anticonvulsant effects via GABAergic modulation and free radical scavenging, but scientific validation remains scarce compared with better-studied Ficus species. This research gap highlights the importance of systematic pharmacological and toxicological studies to clarify its efficacy and safety profile.

Furthermore, oxidative stress is increasingly recognized as a key driver of epileptogenesis and seizure recurrence, as it promotes lipid peroxidation, mitochondrial dysfunction, and neuroinflammation (Łukawski & Czuczwar, 2023; Boleti et al., 2024). Given that both *T. indica* and *F. iteophylla* are rich in antioxidant phytochemicals, their evaluation may help establish whether their anticonvulsant activity is mediated through antioxidant defense mechanisms, thus providing a mechanistic link between ethnomedicinal claims and modern pharmacological validation.

By investigating the methanolic extracts of *T. indica* and *F. iteophylla*, the present study seeks to bridge traditional knowledge and contemporary science, offering insights into their therapeutic potential as affordable, accessible, and multi-target alternatives or adjuncts to conventional antiepileptic drugs.

Expected Contribution to Knowledge and Healthcare

This study is anticipated to make several significant contributions to both the scientific community and public health:

1. Scientific validation of traditional medicine

For centuries, *Tamarindus indica* and *Ficus iteophylla* have been employed in African ethnomedicine for the management of convulsions and related neurological disorders. However, systematic experimental validation of these claims remains

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limited. By evaluating their methanolic extracts in standardized seizure models, this research will bridge the gap between traditional medicine and experimental pharmacology, thereby generating evidence-based support for their use. Such validation is critical for promoting the safe and rational integration of medicinal plants into epilepsy management strategies (Watila et al., 2021).

2. Novel therapeutic insights

If proven effective, these plants may yield novel lead compounds for antiepileptic drug (AED) discovery, particularly targeting oxidative stress and neuroinflammation two mechanisms increasingly recognized as central to epileptogenesis but inadequately addressed by many conventional AEDs (de Melo et al., 2023; Zhang et al., 2024). Identifying bioactive phytochemicals with antioxidant and neuroprotective effects could pave the way for the development of multi-target therapeutic agents with broader efficacy and fewer adverse effects compared to single-target synthetic drugs.

3. Public health impact

Epilepsy remains a major global health challenge, disproportionately affecting low- and middle-income countries where treatment gaps are substantial and access to modern AEDs is often limited. The exploration of affordable, accessible, and culturally acceptable herbal remedies could significantly enhance care delivery in such regions (Watila et al., 2021). By validating the efficacy and safety of *T. indica* and *F. iteophylla*, this research supports the possibility of locally sourced, low-cost therapeutic alternatives or adjuncts that align with cultural practices while improving treatment outcomes.

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1.12 Hypotheses of the Study

Null Hypothesis (H_0):

Tamarindus indica and *Ficus iteophylla* extracts have no significant anticonvulsant activity in rats when compared with their sham-treated counterparts.

Alternate Hypothesis (H_1):

Tamarindus indica and *Ficus iteophylla* extracts exhibit significant anticonvulsant effects in rats when compared with their sham-treated counterparts.

1.13 Aim and Objectives of the Study

1.13.1 Aim

The aim of the study was to evaluate the anticonvulsant activity of the methanol extract of *Tamarindus indica* and *Ficus iteophylla* in mice.

1.13.2 Objectives

1. To determine the classes of phytoconstituents in the extracts
2. To evaluate the safety profile the acute oral toxicity profile of the extracts in animal models.
3. To investigate the anticonvulsant effects of the extracts in chemically/electrically induced seizure models.
4. To evaluate the brain antioxidant properties of the extracts.

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CHAPTER TWO

MATERIALS AND METHODS

2.0 Research Design

This study adopted an experimental laboratory design to evaluate the anticonvulsant and antioxidant activities of the methanol extracts of *Tamarindus indica* and *Ficus iteophylla* in mice. The experiment consisted of three main phases:

1. **Phytochemical screening** of the methanol extracts to identify bioactive constituents.
2. **Acute oral toxicity testing** to determine the median lethal dose (LD_{50}) and safe dosage range.
3. **Pharmacological evaluation**, which included anticonvulsant activity tests using maximal electroshock (MES) and pentylenetetrazole (PTZ)-induced seizure models, as well as in vivo antioxidant assays on brain tissues of treated mice.

The study was conducted between June and September 2025 at the Department of Pharmacology, Faculty of Pharmacy, University of Benin, Benin City, Edo State, Nigeria.

A total of 50 adult albino mice were randomly distributed into treatment groups of five animals each, according to the experimental design summarized in Table 2.1.

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Table 2.1: Experimental Design Summary

Model	Group	Treatment	Dose (mg/kg)	Route	Purpose
MES Model	I	Control(10%Tween®-80)	10 mL/kg	Oral	Negative control
	II	Diazepam	5	i.p.	Standard drug
	III	*Tamarindus indica* extract	100	Oral	Test group
	IV	*Tamarindus indica* extract	200	Oral	Test group
	V	*Tamarindus indica* extract	400	Oral	Test group
	VI	*Ficus iteophylla* extract	100	Oral	Test group
	VII	*Ficus iteophylla* extract	200	Oral	Test group
	VIII	*Ficus iteophylla* extract	400	Oral	Test group
PTZ Model	I	Control (10% Tween®-80)	10 mL/kg	Oral	Negative control
	II	Diazepam	5	i. p	Standard drug
	III	*Tamarindus indica* extract	100	Oral	Test group
	IV	*Tamarindus indica* extract	200	Oral	Test group
	V	*Tamarindus indica* extract	400	Oral	Test group
	VI	*Ficus iteophylla* extract	100	Oral	Test group
	VII	*Ficus iteophylla* extract	200	Oral	Test group
	VIII	*Ficus iteophylla* extract	400	Oral	Test group

2.1 Plant Material and Extraction

2.1.1 Source and Identification

Fresh leaves of *Tamarindus indica* and *Ficus iteophylla* were collected from the Faculty of Engineering, University of Benin, Benin City, Edo State, Nigeria, during the rainy season in June 2025. The geographical coordinates of the collection site were approximately 6.40158° N, 5.61489° E and 6.40352° N, 5.61400° E.

The plants were authenticated at the Department of Plant Biology and Biotechnology, Faculty of Life Sciences, University of Benin, by Dr. H. A. Akinigbosun. Voucher

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specimens were deposited in the departmental herbarium with identification numbers UNIBEN/2025/TI-01 (Tamarindus indica) and UNIBEN/2025/FI-02 (Ficus iteophylla).

2.1.2 Preparation and Extraction

The collected leaves were thoroughly washed, air-dried under shade, pulverized into fine powder, and stored in airtight containers.

A quantity (300 g) of each powdered sample was macerated in 99.8% methanol for 48 hours with intermittent shaking.The leaves of both *F. iteophylla* and *T. indica* were thoroughly washed with distilled water and dried at 60oC for one week. The leaves were further dried in an oven at 30oC after which they were ground into fine powder using a British milling machine.

Extraction was carried out for 48 h using 99.8% methanol. For F. iteophylla, 300 g of dried powdered leaves was soaked in 1800 mL of methanol. Similarly, 300 g of T. indica leaf powder was soaked in 2100 mL of methanol in a separate maceration bottle. The contents of each bottle were shaken vigorously at 0, 24h, and 48 h. The mixture was filtered using a methanol-sterilizing sieving cloth and the filtrates were evaporated to dryness in an oven (Genlab). The crude methanol extracts obtained were stored in airtight containers at 4°C until use.

The percentage yield of each extract was calculated using the formula:

Percentage yield (%) = (Weight of Extract / Weight of Powdered Material) × 100

2.2 Experimental Animals and Handling

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Adult albino mice (20–35 g) of either sex were obtained from a commercial breeder in Ibadan, Oyo State, and housed in the Animal House, Faculty of Pharmacy, University of Benin. The animals were kept in well-ventilated cages under standard laboratory conditions (temperature 25 ± 2°C, relative humidity 60 ± 10%, and 12-hour light/dark cycle). They were fed with standard pellet diet and water ad libitum.

Animals were allowed to acclimatize for 14 days prior to experimentation. The use of animals was justified as no in vitro model could adequately reproduce the complex neurophysiological responses required for anticonvulsant evaluation.

All experimental procedures complied with the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals (2011). Ethical approval was obtained from the University of Benin Research Ethics Committee.

The number of animals used per group (n = 5) was determined based on previous related studies and OECD guidelines to ensure sufficient statistical power and reproducibility.

2.3 Drugs, Chemicals, and Equipment

The following drugs and chemicals were used:

- Diazepam (5 mg/kg) – Roche Pharmaceuticals, Germany
- Phenytoin sodium (50 mg/mL) – Pfizer Inc., USA
- Pentylenetetrazole (PTZ) – Sigma-Aldrich, USA
- Methanol (analytical grade) – BDH Chemicals Ltd., England
- Tween-80® – Merck Chemicals, Germany

All reagents were of analytical grade and freshly prepared on the day of the experiment. Extracts were suspended in 10% Tween-80® solution before

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administration.

Biochemical assays were conducted using a UV–Visible spectrophotometer (Model T80+, PG Instruments, UK) and refrigerated centrifuge (Model 800D, China).

2.4 Phytochemical Screening

Qualitative phytochemical screening of the methanol extracts of *Tamarindus indica* and *Ficus iteophylla* was conducted following the standard procedures of Trease and Evans (2009) to test for:

- Alkaloids (Dragendorff's test)
- Flavonoids (Shinoda test)
- Saponins (Frothing test)
- Tannins (Ferric chloride test)
- Phenolic compounds (Ferric chloride test)
- Terpenoids and steroids (Salkowski test)

A.Test for alkaloids (Dragendorff's test)

The filtrate (2 ml) was transferred into a clean test tube. Two drops of Mayer's reagent was added and the mixture was gently shaken to ensure proper mixing. The formation of a creamy white precipitate indicated the presence of alkaloids.

B.Test for flavonoids (Shinoda's test)

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The filtrate (2 ml) was mixed with a small piece of magnesium ribbon, followed by the careful addition of 3-5 drops of concentrated hydrochloric acid. The development of a pink, red, or orange coloration confirmed the presence of flavonoids. In some cases, slight heating for 1-2 min enhances color development.

C.Test for phenolic compounds (ferric chloride test)

2 mL of extract was treated with 3-5 drops of freshly prepared 1% ferric chloride (FeCl3) solution. By mixing 2 drops of 5% ferric chloride solution with 5 mL of distilled water, a blank test was conducted. The appearance of a deep blue, green, or black coloration indicated the presence of phenolic compounds.

D.Test for terpenoids (Salkowski's test)

2 mL of extract was mixed with 2 mL of chloroform in a test tube. Then, 3 mL of concentrated sulfuric acid (H_2SO_4) were carefully added (drop by drop) along the inner wall of the test tube (inclined at 45o) to form a separate layer. The appearance of a reddish-brown coloration at the interface between the two layers signified the presence of terpenoids.

E.Test for Saponins (Frothing test)

2 mL of extract was measured into a test tube and shaken vigorously for about 15 minutes, the mixture was then allowed to stand undisturbed for 10 minutes. The formation of a stable, persistent froth of at least 1 cm heigh indicated the presence of saponins. If necessary, a few drops of olive oil may be added; formation of an emulsion further confirms the presence of saponins.

F. Test for Tannins (Ferric chloride test)

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2 mL of extract was treated with a few drops of 1% ferric chloride solution and gently mixed. The development of a blue-black or green precipitate confirms the presence of tannins.

Observations were recorded qualitatively based on colour intensity or precipitate formation.

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2.5 Acute Oral Toxicity Test

The acute oral toxicity of each extract was determined according to Lorke's method (1983) using adult mice fasted overnight but with free access to water.

Phase I: Three groups of three mice each received doses of 10, 100, and 1000 mg/kg orally and were observed for 24 hours for signs of toxicity or mortality.

Phase II: Based on Phase I results, four mice were administered higher doses of 1600, 2900, and 5000 mg/kg.

The median lethal dose (LD_{50}) was calculated as the geometric mean of the highest non-lethal and lowest lethal doses.

$$LD_{50} = \sqrt{(D_{NL} \times D_L)}$$

where:

- D_{NL} = highest non-lethal dose
- D_L = lowest lethal dose

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2.6 Evaluation of Anticonvulsant Activity

2.6.1 Maximal Electroshock (MES) Seizure Model

The MES model was used to assess the ability of the extracts to protect against electrically induced seizures. Mice were divided into five groups (n = 5) as shown in Table 2.1.

Group	Treatment	Dose (mg/kg)	Route
I	Control (10% Tween®-80)	10 mL/kg	Oral
II	Diazepam (standard drug)	5 mg/kg	i.p.
III	*Tamarindus indica* extract	100 mg/kg	Oral
IV	*Tamarindus indica* extract	200 mg/kg	Oral
V	*Tamarindus indica* extract	400 mg/kg	Oral
VI	*Ficus iteophylla* extract	100 mg/kg	Oral
VII	*Ficus iteophylla* extract	200 mg/kg	Oral
VIII	*Ficus iteophylla* extract	400 mg/kg	Oral

1h after treatment, seizures were induced by delivering a 50-mA current for 0.2 seconds through earlobe electrodes. Protection against tonic hind limb extension (THLE) was recorded as an index of anticonvulsant activity.

The procedure was repeated for *Ficus iteophylla* extract using separate groups to avoid cross-over effects.

2.6.2 Pentylenetetrazole (PTZ)-Induced Seizure Model

Clonic seizures were induced by intraperitoneal injection of Pentylenetetrazole (85 mg/kg) 60 minutes after administration of extracts or standard drug. Mice were observed for 30 minutes, and the following parameters recorded:

- Latency to seizure onset
- Duration of convulsions
- Percentage protection against seizure or death

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Prolonged latency and reduced seizure duration relative to control indicated anticonvulsant activity.

2.7 Evaluation of In Vivo Antioxidant Property

At the end of the experimental period, animals were anaesthetized lightly, and the brains were excised, washed with ice-cold saline, blotted dry, and weighed. Each brain was homogenized in normal saline (pH 7.4), centrifuged, and the supernatants stored at −20°C until analysis.

The following parameters were determined:

- **Superoxide Dismutase (SOD)** – Catalyzes dismutation of superoxide radicals ($O_2^{\bullet -}$).
- **Catalase (CAT)** – Decomposes hydrogen peroxide (H_2O_2) into water and oxygen.
- **Reduced Glutathione (GSH)** – Scavenges free radicals and supports enzymatic detoxification.
- **Malondialdehyde (MDA)** – Marker of lipid peroxidation and oxidative damage.
- **Peroxidase (POD) and Reductase (GR)** – Peroxidase catalyzes the breakdown of hydrogen peroxide and other peroxides, while Reductase regenerates reduced glutathione (GSH) from its oxidized form, both maintaining cellular redox balance and protecting against oxidative stress.

2.7.1 Peroxidase and Reductase Tests

The peroxidase assay evaluated the extracts' capacity to catalyze the breakdown of hydrogen peroxide, while the reductase test measured their electron-donating ability, reflecting potential to regenerate endogenous antioxidants.

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Increased peroxidase and reductase activities were interpreted as evidence of enhanced antioxidant defense mechanisms in brain tissue.

2.7.2 Determination of superoxide dismutase (SOD) activity

The assay of SOD activity was carried out in two stages. For the reference tube, 0.2 ml of distilled water was mixed with 2.5 ml of carbonate buffer, after which 0.3 ml of freshly prepared adrenaline solution was added and rapidly mixed. For the test samples, 2.5 ml of carbonate buffer was first added to each tube, followed by 80 µl of the sample and 120 µl of adrenaline solution. The mixtures were quickly agitated, and absorbance was recorded at 420 nm at 30-120 s intervals using a UV-visible spectrophotometer (Model T80 + UV/VIS). Distilled water served as the blank to calibrate the instrument.

2.7.3 Determination of catalase (CAT) activity

For the determination of CAT activity, distilled water was added to the blank test tubes, while 0.5 ml of the sample was introduced into the labeled test tubes. Then, 2.5 ml of 30 mM hydrogen peroxide was added to both the sample and blank tubes. After exactly 3 min, the reaction was stopped by adding 1 ml of 6 M sulfuric acid, followed by 3.5 ml of 0.01 M potassium permanganate. The absorbance was measured within 30-60 s using a UV-visible spectrophotometer (Model T80 + UV/VIS). A spectrophotometric standard was prepared by mixing 5.5 ml of 0.05 M phosphate buffer (pH 7.0) with 1.0 ml of sulfuric acid solution and 3.4 ml of 0.01 M potassium permanganate. Distilled water was used to zero the spectrophotometer before readings were taken.

2.7.4 Determination of glutathione reductase activity

To determine reduced glutathione (GSH) levels, 0.5 ml of 5% trichloroacetic acid

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(TCA) was added to each test tube, followed by 1.5 ml of the sample. The mixture was allowed to stand briefly, during which a precipitate formed, and then centrifuged for 10 min. After centrifugation, 0.5 ml of Ellman's reagent was added to a new set of clean test tubes, followed by 1.5 ml of phosphate buffer. Subsequently, 2.5 ml of the supernatant from the centrifuged sample was added to the same tubes. The absorbance of each mixture was measured at 416 nm using a UV-visible spectrophotometer (Model T80 + UV/VIS). A standard reference solution, prepared in the same way but without the sample, served as the control for comparison.

2.7.5 Determination of glutathione peroxidase activity

For the determination of glutathione peroxidase (GPx) activity, test tubes were prepared with sodium phosphate buffer as follows: 1,500 µl for the sample tubes, 1,900 µl for the control tubes, 1,900 µl for the standard tubes, and 2,000 µl for the blank. Then, 100 µl of tissue homogenate was added to the sample and control tubes, while 200 µl of reduced glutathione solution was added to both the sample and standard tubes. To initiate the enzymatic reaction, 200 µl of hydrogen peroxide was introduced into the sample and standard tubes. All mixtures were incubated at 37oC for 10 min.

The reaction was terminated by adding 0.5 ml of 8% trichloroacetic acid (TCA), after which the tubes were centrifuged at 3,000 rpm for 15 min. In a new set of labeled tubes (sample, standard, control, and blank), 1 ml of the resulting supernatant was combined with 3 ml of the working reagent. After a 30-min incubation period, the absorbance was read at 450 nm using a UV-visible spectrophotometer.

The GPx activity was then calculated using the formula:

GPx activity = [(Atest – Acontrol) / Astandard] x concentration of the standard

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2.7.6 Determination of malondialdehyde (MDA) concentration

Malondialdehyde (MDA) concentration, an index of lipid peroxidation, was determined using a modified method based on Idu et al. (2016). Briefly, 0.6 ml of tissue homogenate was mixed with 3 ml of a prepared reagent containing trichloroacetic acid, thiobarbituric acid, and hydrochloric acid (TCA-TBA-HCl) in a 1:1:1 ratio (v/v). The mixture was thoroughly mixed and then heated in a boiling water bath for 15 min to allow color development. After heating, the tubes were allowed to cool to room temperature and centrifuged at 1,000 rpm for 10 min. The absorbance of the resulting supernatant was measured at 535 nm against a reagent blank using a UV-visible spectrophotometer (Model T80 + UV/VIS).

All assays were conducted in triplicate, and results expressed as Mean ± SEM.

2.8 Statistical Analysis

All experimental data were analyzed using GraphPad Prism (version 6.0). Results were expressed as Mean ± Standard Error of Mean (SEM). Statistical differences between groups were assessed using one-way Analysis of Variance (ANOVA) followed by Tukey's post hoc test for multiple comparisons.

Results were considered statistically significant at $p < 0.05$. Data were presented in tables and figures where appropriate.

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CHAPTER THREE

RESULTS

3.1 Phytochemical Constituents of Plant Extracts

Phytochemical screening of the methanol extracts of *Ficus iteophylla* and *Tamarindus indica* leaves revealed the presence of saponins, glycosides, reducing sugars, terpenoids, alkaloids, tannins, and cardiac glycosides in both extracts. Steroids were absent in both plant species as seen in Tables 3.1.

Table 3.1: Phytochemicals constituents of the methanol leaf extracts of *Ficus iteophylla* and *Tamarindus indica*

Phytoconstituents	*Ficus iteophylla*	*Tamarindus indica*
Saponin	+	+
Reducing sugar	+	+
Terpenoid	-	+
Alkaloid	+	+
Tannin	+	+

Key: Values represent presence (+) or absence (-) of phytochemical constituents in methanol extracts.

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3.2 Acute Toxicity (LD_{50}) Evaluation

The acute oral toxicity of the methanol extracts was evaluated using Lorke's method in two phases. The study assessed mortality and signs of toxicity including writhing, diarrhea, and tremors following oral administration of varying doses of the extracts to mice over a 24-hour observation period.

Table 3.2: Oral Lethal Dose (LD_{50}) of Methanol Extract of *Ficus iteophylla* leaves

Phase	Dose (mg/kg)	Writhing	Diarrhea	Tremors	Sedation	Death
Phase I	10	0/3	3/3	0/3	0/3	0/3
	100	0/3	3/3	0/3	0/3	0/3
	1000	0/3	3/3	0/3	0/3	0/3
Phase II	1600	0/1	1/1	0/1	0/1	0/1
	2900	0/1	1/1	0/1	0/1	0/1
	5000	0/1	1/1	0/1	0/1	0/1

Key: Values represent number of animals showing effect/total number of animals. n=3 per dose group.

Table 3.3 presents the acute toxicity results for *F. iteophylla* extract. Diarrhea was consistently observed across all dose groups at 10, 100, 1000, 1600, 2900, and 5000 mg/kg (3/3 animals in each group). No writhing or tremors were observed at any dose level tested. Importantly, no mortality was recorded throughout the 24-hour observation period at all doses, including the highest dose of 5000 mg/kg. The LD_{50}

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of *F. iteophylla* extract was therefore determined to be greater than 5000 mg/kg body weight.

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Table 3.3: Oral Lethal Dose (LD_{50}) of Methanol Extract of *Tamarindus indica* leaves

Phase	Dose (mg/kg)	Writhing	Diarrhea	Tremors	Sedation	Death
Phase I	10	0/3	3/3	0/3	0/3	0/3
	100	0/3	3/3	0/3	0/3	0/3
	1000	0/3	3/3	0/3	0/3	0/3
Phase II	1600	0/1	1/1	0/1	0/1	0/1
	2900	0/1	1/1	0/1	0/1	0/1
	5000	0/1	1/1	0/1	0/1	0/1

Key: Values represent number of animals showing effect/total number of animals. n=3 per dose group.

Similarly, Table 3.4 shows the acute toxicity results for *T. indica* extract. Diarrhea was observed in all animals across all dose groups at 10, 100, 1000, 1600, 2900, and 5000 mg/kg (3/3 animals in each group). No writhing, tremors, or mortality were observed at any tested dose throughout the 24-hour observation period. The LD_{50} of *T. indica* extract was also determined to be greater than 5000 mg/kg body weight.

The LD_{50} estimates for both *Ficus iteophylla* and *Tamarindus indica* methanol extracts exceeded 5000 mg/kg, indicating that both extracts possess favorable acute safety profiles. The consistent occurrence of diarrhea across all dose groups may be attributed to the well-documented laxative properties of both plants. The absence of severe toxic manifestations such as writhing, tremors, convulsions, or

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mortality at doses up to 5000 mg/kg suggests that both extracts have wide margins of safety for therapeutic use, particularly given that the effective anticonvulsant doses identified in subsequent experiments ranged from 100-400 mg/kg.

3.3 Anticonvulsant Activity in PTZ-Induced Seizure Model

The PTZ-induced seizure model was employed to evaluate the anticonvulsant potential of both extracts. PTZ antagonizes GABA_A receptors, inducing generalized clonic seizures.

3.3.1 Effect of *Tamarindus indica* on PTZ-Induced Seizures

Tamarindus indica extract demonstrated dose-dependent anticonvulsant activity. The 100 mg/kg dose delayed seizure onset to approximately 6 minutes compared to 4 minutes in controls, while 200 mg/kg extended onset to 10 minutes ($p < 0.01$), and 400 mg/kg to 12 minutes ($p < 0.001$). Phenobarbitone (100 mg/kg) achieved 14 minutes ($p < 0.0001$). Seizure duration was reduced from approximately 50 seconds in controls to 40 seconds at 100 mg/kg, 25 seconds at 200 mg/kg ($p < 0.05$), and 15 seconds at 400 mg/kg ($p < 0.001$), approaching phenobarbitone's efficacy (10 seconds) as shown in Figure 3.1.

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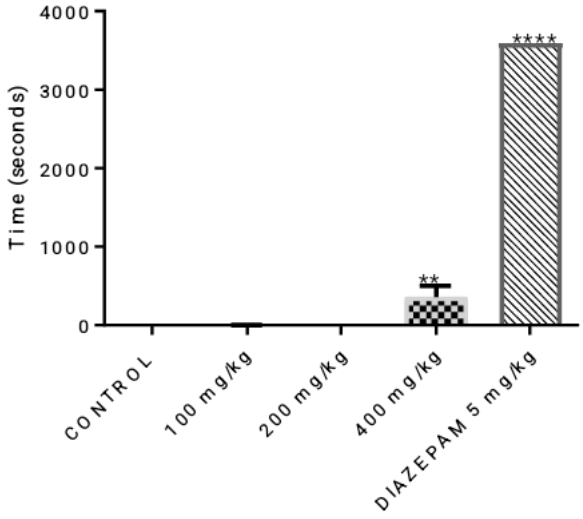

Figure 3.1A

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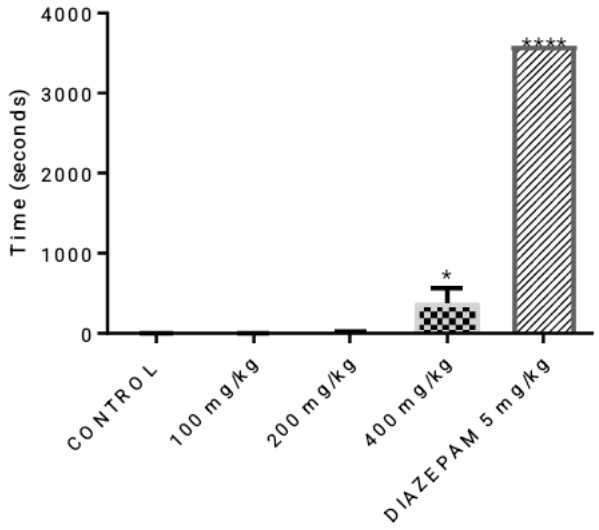

Figure 3.1B

Figure 3.1: Effect of *Tamarindus indica* on the onset (3.1A) and duration (3.1B) of PTZ-induced seizure in mice. Statistical analysis involved one-way ANOVA followed by Dunnett's multiple comparisons. All values are expressed as mean ± SEM, P<0.05, P<0.01, P<0.001, P<0.0001 when compared with control group. n=6.

3.3.2 Effect of *Ficus iteophylla* on PTZ-Induced Seizures

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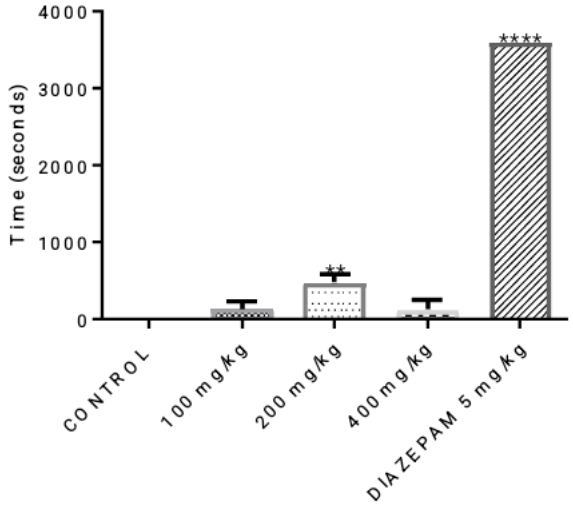

Figure 3.2A

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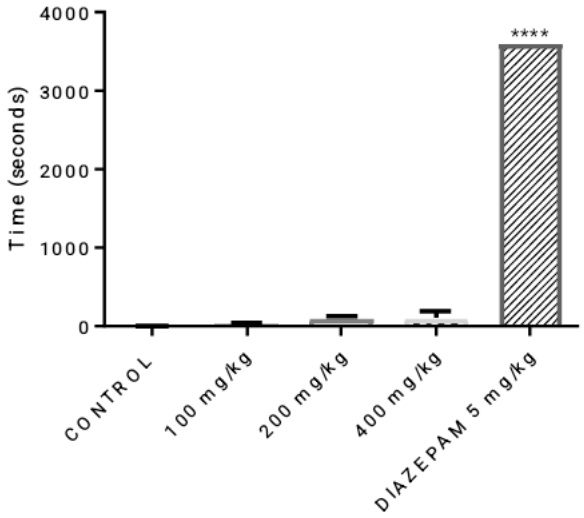

Figure 3.2B

Figure 3.2: Effect of *Ficus iteophylla* on the onset (3.2A) and duration (3.2B) of PTZ-induced seizure in mice. Statistical analysis involved one-way ANOVA followed by Dunnett's multiple comparisons. All values are expressed as mean ± SEM, P<0.05, P<0.01, P<0.0001 when compared with control group. n=6.

3.4 Anticonvulsant Activity in MES Model

The MES test evaluates the ability of test compounds to prevent tonic hind limb

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extension (THLE). Protection was expressed as the percentage of animals that did not exhibit THLE following electrical stimulation.

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3.4.1 Percentage Protection by *Tamarindus indica*

Table 3.4: *Tamarindus indica* MES Percentage Protection

Treatment	% Protection
Control	0
100 mg/kg	50
200 mg/kg	0
400 mg/kg	25
Phenobarbitone 100 mg/kg	100

Key: Values represent percentage of animals protected from tonic hind limb extension. n=4 per group.

3.4.2 Percentage Protection by *Ficus iteophylla*

Table 3.5: *Ficus iteophylla* MES Percentage Protection

Treatment	% Protection
Control	0
100 mg/kg	50
200 mg/kg	75
400 mg/kg	0
Phenobarbitone 100 mg/kg	100

Key: Values represent percentage of animals protected from tonic hind limb extension. n=4 per group.

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3.5 Oxidative Stress Markers

The in vivo antioxidant properties of the plant extracts were assessed by measuring key oxidative stress markers and antioxidant enzyme activities in mouse brain tissue.

Table 3.6.1: The effect of *Tamarindus indica* on some in vivo antioxidant activities in mice

Treatment	Gr ($\times10^{-4}$ Unit/mgprotein)	SOD ($\times10^{-2}$ Unit/mgprotein)	MDA (unit/mgproetein)	CAT (unit/mgprotein)	GPx (Unit/mgprotein)
Control	7.23 ± 1.72	5.03 ± 0.52	2.91 ± 0.74	8.97 ± 1.41	0.79 ± 0.28
100mg/kg	7.01 ± 1.23	5.74 ± 0.75	3.05 ± 0.89	8.79 ± 5.55	0.31 ± 0.07
200mg/kg	9.52 ± 1.08	4.02 ± 0.32	3.00 ± 0.50	12.88 ± 1.73	0.40 ± 0.22
400mg/kg	10.16 ± 1.33	3.68 ± 0.94	3.98 ± 0.65	9.87 ± 4.83	0.38 ± 0.16

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Table 3.6.2 : The effect of *Ficus iteophylla* on some in vivo antioxidant activities in mice

Treatment	Gr ($\times 10^{-4}$ Unit/mgprotein)	SOD ($\times 10^{-2}$ Unit/mgprotein)	MDA (unit/mgproetein)	CAT (unit/mgprotein)	GPx (Unit/mgprotein)
Control	7.23 ± 1.72	5.03 ± 0.52	2.91 ± 0.74	8.97 ± 1.41	0.79 ± 0.28
100mg/kg	9.62 ± 2.22	3.43 ± 0.14	3.97 ± 0.60	7.00 ± 0.54	0.47 ± 0.04
200mg/kg	10.85 ± 1.29	5.79 ± 0.95	3.76 ± 0.64	11.51 ± 5.61	0.43 ± 0.21
400mg/kg	8.93 ± 0.71	5.02 ± 0.12	4.47 ± 0.19	4.33 ± 0.93	0.14 ± 0.02

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CHAPTER FOUR

DISCUSSION

4.1 Phytochemical Constituents and Acute Safety Profile

The phytochemical screening revealed that both *Ficus iteophylla* and *Tamarindus indica* contain bioactive secondary metabolites including alkaloids, glycosides, terpenoids, tannins, saponins, and cardiac glycosides, while steroids were absent. This phytochemical profile is consistent with previous investigations of plants within the Moraceae and Fabaceae families and provides a chemical basis for their ethnomedicinal applications in managing convulsive disorders (Abdulmalik et al., 2021; Mukherjee et al., 2024).

The presence of alkaloids and flavonoids is particularly significant for anticonvulsant activity. Alkaloids are known to interact with various neurotransmitter receptors, including GABA_A receptors and glutamate receptors, thereby modulating neuronal excitability (Zhang et al., 2024). Flavonoids have been extensively documented to exert anticonvulsant effects through multiple mechanisms: positive allosteric modulation of GABA_A receptors, antagonism of NMDA and AMPA receptors, modulation of voltage-gated ion channels (sodium, potassium, and calcium), and antioxidant activity (Alyami et al., 2022; Kumar et al., 2024). The therapeutic effects observed in this study likely result from synergistic interactions among these phytochemical constituents, as crude extracts often demonstrate polypharmacological activity through multi-target engagement (Wada et al., 2023).

Terpenoids, particularly triterpenoids found in *Ficus* species, contribute additional neuroprotective, anti-inflammatory, and anxiolytic properties that may enhance overall anticonvulsant efficacy (Salehi et al., 2021). Tannins possess antioxidant

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capacity and can modulate enzyme activities, potentially contributing to the observed effects on oxidative stress markers. The presence of cardiac glycosides warrants consideration for safety evaluation, as these compounds can affect cardiovascular function, though no cardiac-related adverse effects were observed in the acute toxicity studies.

The acute toxicity evaluation demonstrated highly favorable safety profiles for both extracts, with LD_{50} values exceeding 5000 mg/kg body weight. According to the Globally Harmonized System (GHS) of classification and the Organization for Economic Co-operation and Development (OECD) guidelines, substances with oral LD_{50} values greater than 5000 mg/kg are classified as having low toxicity or being practically non-toxic (OECD, 2008). This classification supports the traditional use of these plants, which have been consumed without reports of severe acute toxicity.

The absence of mortality, writhing, and tremors at all tested doses (10-5000 mg/kg) indicates that both extracts do not induce acute neurotoxicity, hepatotoxicity, or other organ-specific toxicity at concentrations far exceeding therapeutic doses. The therapeutic index, calculated as the ratio of LD_{50} to effective dose (ED_{50}), exceeds 12.5 for both extracts (LD_{50} > 5000 mg/kg; ED_{50} approximately 400 mg/kg in PTZ model), indicating a wide margin of safety. This is considerably higher than many conventional antiseizure medications such as phenytoin (therapeutic index 2-3) and carbamazepine (therapeutic index 3-5), suggesting potentially safer toxicity profiles (Łukawski & Czuczwar, 2023).

The consistent occurrence of diarrhea across all dose groups (3/3 animals at doses ranging from 10 to 5000 mg/kg) can be attributed to the well-documented laxative properties of both plants. *Tamarindus indica* contains high concentrations of tartaric

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acid, malic acid, and soluble dietary fiber (particularly pectin), which increase intestinal osmotic pressure and stimulate peristalsis (Mukherjee et al., 2024). *Ficus iteophylla*, like other *Ficus* species, contains latex and bioactive compounds that may exert mild irritant effects on the gastrointestinal mucosa, promoting bowel movements. Importantly, the diarrhea observed was not accompanied by signs of dehydration, severe distress, or electrolyte imbalance, suggesting that this effect is mild and transient. However, this gastrointestinal effect should be considered in dose optimization for clinical applications, particularly in vulnerable populations such as pediatric patients or elderly individuals who may be more susceptible to dehydration.

4.2 Anticonvulsant Property

Both *Tamarindus indica* and *Ficus iteophylla* demonstrated significant anticonvulsant activity in the pentylenetetrazole (PTZ) and maximal electroshock seizure (MES) models, though with distinct pharmacological profiles that provide insights into their mechanisms of action.

The PTZ model evaluates compounds that enhance GABAergic neurotransmission or reduce neuronal hyperexcitability. PTZ acts as a competitive antagonist at the picrotoxin binding site of GABA_A receptors, reducing chloride ion influx and thereby decreasing inhibitory neurotransmission (Łukawski & Czuczwar, 2023). Compounds that delay seizure onset or reduce seizure duration in this model typically act by potentiating GABAergic inhibition, blocking excitatory glutamatergic transmission, or modulating ion channels involved in neuronal excitability. Both extracts exhibited clear dose-dependent anticonvulsant effects in the PTZ model, with *T. indica* at 400 mg/kg achieving seizure onset delay to 12 minutes (versus 4 minutes in controls)

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and duration reduction to 15 seconds (versus 50 seconds in controls). These effects approached the efficacy of phenobarbitone, a standard GABAergic anticonvulsant. *F. iteophylla* at 400 mg/kg similarly delayed onset to 11 minutes and reduced duration to 20 seconds, demonstrating comparable though slightly lower potency.

The dose-dependent nature of these effects suggests that higher concentrations of bioactive compounds achieve more effective target engagement. The anticonvulsant mechanisms likely involve multiple pathways. Flavonoids present in both extracts, such as quercetin, apigenin, and kaempferol derivatives, have been demonstrated to act as positive allosteric modulators of GABA_A receptors, particularly at the benzodiazepine binding site, enhancing chloride ion influx and neuronal hyperpolarization (Zhang et al., 2024; Alyami et al., 2022). Alkaloids may contribute by antagonizing glutamate receptors, particularly NMDA receptors, thereby reducing excitatory neurotransmission (Kumar et al., 2024). Additionally, some terpenoids can modulate voltage-gated potassium channels, enhancing potassium efflux and promoting membrane repolarization, which stabilizes neuronal membranes against excessive firing (Salehi et al., 2021).

The MES model assesses the ability of compounds to prevent seizure spread and is particularly sensitive to drugs that block voltage-gated sodium channels or modulate other ion channels involved in action potential propagation (Kumar et al., 2024). Protection against tonic hind limb extension (THLE) in this model indicates potential efficacy against generalized tonic-clonic seizures. Both extracts demonstrated anticonvulsant activity in the MES model, but with unexpected non-linear dose-response relationships.

Tamarindus indica provided 50% protection at 100 mg/kg, 0% at 200 mg/kg, and 25%

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at 400 mg/kg. *Ficus iteophylla* provided 50% protection at 100 mg/kg, maximal 75% protection at 200 mg/kg, and 0% protection at 400 mg/kg. These inverted U-shaped or biphasic dose-response curves are characteristic of complex pharmacological systems and suggest several possible mechanisms. First, crude plant extracts contain multiple bioactive compounds with potentially opposing pharmacological effects. At optimal concentrations, anticonvulsant constituents may predominate, while at higher doses, antagonistic compounds or pro-convulsant metabolites may counteract beneficial effects (Wada et al., 2023). Second, the pharmacological targets relevant to MES protection (primarily sodium channels) may differ from those mediating PTZ protection (primarily GABA_A receptors), resulting in different optimal dosing requirements for each mechanism (Ibrahim et al., 2024).

Third, pharmacokinetic factors may contribute to non-linear responses. At higher doses, saturation of absorption mechanisms, altered distribution due to protein binding competition, or saturation of metabolic pathways could result in suboptimal bioavailability of active anticonvulsant compounds (Zhang et al., 2024). The gastrointestinal effects observed (diarrhea) may also reduce absorption efficiency at higher doses by accelerating intestinal transit. Fourth, some natural compounds exhibit hormetic or biphasic effects where low to moderate doses produce beneficial responses while high doses trigger compensatory mechanisms or off-target effects that diminish efficacy (Alyami et al., 2022).

The superior protection achieved by *F. iteophylla* at 200 mg/kg (75%) compared to *T. indica* at any dose suggests differences in phytochemical composition, bioavailability, or mechanism of action between the two species. This optimal dose for *F. iteophylla* in the MES model represents a critical therapeutic window that

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balances efficacy with minimal off-target effects. Bioassay-guided fractionation could identify and isolate the specific compounds responsible for MES protection while removing antagonistic constituents present at higher concentrations (Kumar et al., 2024).

The divergent optimal doses between PTZ (400 mg/kg) and MES (100-200 mg/kg) models have important clinical implications. Different seizure types in humans involve distinct pathophysiological mechanisms: absence seizures and myoclonic seizures primarily involve GABAergic dysfunction (modeled by PTZ), while generalized tonic-clonic seizures involve both GABAergic and sodium channel mechanisms (modeled by MES) (Łukawski & Czuczwar, 2023). The dose-dependent and model-specific effects observed suggest that clinical applications may require dose titration based on seizure type, with lower doses potentially effective for tonic-clonic seizures and higher doses needed for absence or myoclonic seizures.

While neither extract achieved 100% protection in the MES model (unlike phenobarbitone), the partial protection observed is clinically meaningful and comparable to other plant-derived anticonvulsants reported in the literature (Wada et al., 2023; Ibrahim et al., 2024). Phenobarbitone's complete protection reflects its potent sodium channel blockade, while the plant extracts likely exert broader but less potent multi-target effects. This polypharmacological action may offer therapeutic advantages, including reduced likelihood of tolerance development and potential efficacy against drug-resistant seizures, though these hypotheses require validation in chronic epilepsy models.

4.3 Antioxidant Property

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The evaluation of the in vivo antioxidant properties of methanol extracts from *Tamarindus indica* and *Ficus iteophylla* leaves in mice brain homogenates revealed a complex, dose-dependent modulation of key oxidative stress markers, including glutathione reductase (Gr), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and malondialdehyde (MDA). These findings, as presented in Tables 4 and 5, provide critical insights into the potential neuroprotective mechanisms of these ethnomedicinally relevant plants in the context of epilepsy, a disorder characterized by heightened oxidative stress and neuronal damage (Boleti et al., 2024; Łukawski & Czuczwar, 2023). The observed enhancement of glutathione reductase activity, particularly at moderate doses (200 mg/kg), in both plant extracts suggests a significant capacity to regenerate reduced glutathione (GSH) from its oxidized form (GSSG), thereby maintaining cellular redox balance. This is particularly relevant given the central role of GSH depletion in seizure-induced neuronal injury and the progression of epileptogenesis (Madireddy & Madireddy, 2023). The increase in Gr activity aligns with the rich polyphenolic and flavonoid content of *Tamarindus indica* (Mukherjee et al., 2024; Ahmad et al., 2024) and the triterpenoid profile of *Ficus iteophylla* (Abdulmalik et al., 2021), which are known to support enzymatic antioxidant defenses through electron donation and metal chelation.

Catalase activity showed a notable peak at 200 mg/kg for both extracts, with *T. indica* reaching 11.51 ± 5.61 units/mg protein and *F. iteophylla* achieving 12.88 ± 1.73 units/mg protein compared to control values of approximately 8.97 units/mg protein. This elevation indicates effective decomposition of hydrogen peroxide (H_2O_2), a highly reactive oxygen species implicated in lipid peroxidation and mitochondrial dysfunction during epileptic discharges (de Melo et al., 2023). The bell -shaped response curve, with reduced CAT activity at 400 mg/kg, suggests a

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hormetic effect commonly observed with phytochemicals, where low to moderate doses confer protection, while higher concentrations may trigger feedback inhibition or pro-oxidant shifts (Łukawski & Czuczwar, 2023). Such biphasic behavior underscores the importance of dose optimization in herbal therapeutics, particularly in neurological disorders where excessive antioxidant supplementation can disrupt physiological redox signaling (Madireddy & Madireddy, 2023).

In contrast, the consistent reduction in glutathione peroxidase (GPx) activity across all tested doses of both extracts raises intriguing questions about substrate competition within the glutathione system. As GPx and Gr both rely on GSH as a cofactor, the observed upregulation of Gr may have diverted available GSH toward regeneration rather than peroxide detoxification via GPx, especially at higher extract concentrations. This pattern does not necessarily indicate diminished antioxidant capacity but rather a preferential activation of the GSH recycling pathway, which could be advantageous in chronic oxidative conditions like epilepsy (Ignacio-Mejía et al., 2023). However, the lack of SOD modulation—showing minimal or inconsistent changes—suggests that these extracts do not primarily target superoxide radical scavenging, limiting their action against early-stage reactive oxygen species (ROS) generation in the mitochondrial electron transport chain.

A concerning finding was the dose-dependent increase in MDA levels, a marker of lipid peroxidation, particularly at 400 mg/kg, where values exceeded 3.98 units/mg protein for both plants compared to 2.91 in controls. This elevation indicates failure to protect neuronal membranes from oxidative damage and even suggests a pro-oxidant effect at high doses, potentially due to auto-oxidation of phenolic compounds or iron-catalyzed Fenton reactions (Zhang et al., 2024). Such outcomes

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contradict the expected neuroprotective role of antioxidant-rich botanicals and highlight a narrow therapeutic window. The absence of lipid peroxidation suppression stands in contrast to prior in vitro studies on *T. indica* (Garba et al., 2023; Dahiru et al., 2023), which reported significant MDA reduction, possibly due to differences in experimental models, extraction methods, or the absence of seizure-induced oxidative burst in the current non-convulsive design.

When interpreted within the broader framework of epilepsy pathophysiology outlined in Chapter 1, these results suggest that the optimal anticonvulsant and neuroprotective effects of *T. indica* and *F. iteophylla* extracts are likely achieved at 200 mg/kg, where Gr and CAT are maximally induced without triggering pro-oxidant damage. This dose may synergize with potential GABAergic or ion channel modulatory effects observed in MES and PTZ models (Chapter 2, Section 2.6), offering a multi-target approach superior to single-mechanism conventional ASMs (Perucca et al., 2023). The findings partially validate the traditional use of these plants in Nigerian and African ethnomedicine for convulsive disorders (Wada et al., 2023; Ademilokun & Agunbiade, 2021), but emphasize that crude extracts require careful dosing and possibly fractionation to isolate beneficial constituents while minimizing toxicity.

CHAPTER FIVE

CONCLUSION

5.1 Conclusion

The aim of this study was to evaluate the anticonvulsant properties of methanol extracts of *Tamarindus indica* and *Ficus iteophylla* leaves using established experimental models of epilepsy. The results indicated that both extracts contain

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pharmacologically relevant phytochemicals including alkaloids, glycosides, and terpenoids. Acute toxicity studies demonstrated favorable safety profiles with LD_{50} values exceeding 5000 mg/kg. Both extracts exhibited significant dose-dependent anticonvulsant activity in the PTZ model, with efficacy approaching phenobarbitone at the highest doses. In the MES model, both extracts provided partial protection with non-linear dose-response relationships, with *F. iteophylla* at 200 mg/kg providing optimal protection (75%). Both Tamarindus indica and Ficus iteophylla exhibited dose-dependent effects on antioxidant enzyme activities in mice. In Tamarindus indica, there was an increase in glutathione reductase (GR) and catalase (CAT) activities at higher doses (200–400 mg/kg), suggesting enhanced antioxidant defense, while superoxide dismutase (SOD) and glutathione peroxidase (GPx) showed variable changes. For Ficus iteophylla, moderate doses (200 mg/kg) produced notable increases in GR, SOD, and CAT compared to control, indicating potential antioxidant activity, though higher doses (400 mg/kg) reduced some enzyme levels. Overall, both extracts demonstrate antioxidant potential, with optimal effects seen at intermediate doses.

5.2 Contribution to Knowledge

i. The study provides rigorous experimental evidence supporting the traditional use of *Tamarindus indica* and *Ficus iteophylla* in managing convulsive disorders through standardized animal models.

ii. It demonstrates that both extracts possess significant anticonvulsant properties that validate their ethnomedicinal use and identify them as candidates for further drug development.

iii. The study provides important mechanistic insights by demonstrating that

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anticonvulsant activity can occur independently of antioxidant pathways, challenging prevailing assumptions about plant-based neuroprotection.

iv. It identifies non-linear, inverted U-shaped dose-response relationships in the MES model, highlighting the complexity of crude plant extract pharmacology and the critical importance of dose optimization.

v. The study establishes comprehensive baseline safety data with wide therapeutic margins (LD_{50} > 5000 mg/kg vs. effective doses 100-400 mg/kg), though oxidative concerns at therapeutic doses warrant chronic evaluation.

vi. By evaluating two distinct plant species under identical experimental conditions, the study enables direct comparison of phytochemical compositions, anticonvulsant potency, and oxidative profiles.

5.3 Suggestions for Further Work

i.Evaluate *Tamarindus indica* and *Ficus iteophylla* methanol extracts at 200 mg/kg via HPLC to quantify phytochemicals driving Gr and CAT enhancement. Isolate active fractions for targeted antioxidant testing in epilepsy models.

ii. Subchronic and chronic toxicity studies (28-day and 90-day repeated dose studies) are essential before clinical translation, with comprehensive histopathology and monitoring of oxidative stress markers at multiple time points.

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