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RESEARCH ARTICLE

EVALUATION OF ANTICONVULSANT AND NEUROPHARMACOLOGICAL ACTIVITY OF ETHANOLIC EXTRACT OF TRIDAX PROCUMBENS FLOWERS IN EXPERIMENTAL ANIMAL MODELS

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ABSTRACT

Epilepsy is a chronic neurological disorder characterized by recurrent and uncontrolled seizures resulting from abnormal neuronal activity in the brain. Despite the availability of several antiepileptic drugs, many patients continue to experience inadequate seizure control and adverse effects, necessitating the search for safer and more effective therapeutic agents from natural sources. The present study was designed to evaluate the anticonvulsant and neuropharmacological activity of the ethanolic extract of *Tridax procumbens* flowers in experimental animal models. The flowers of *Tridax procumbens* were collected, shade dried, powdered, and subjected to ethanolic extraction using a Soxhlet apparatus. Preliminary phytochemical screening of the extract revealed the presence of flavonoids, alkaloids, tannins, saponins, and phenolic compounds. Acute toxicity studies were conducted according to standard guidelines to determine the safe dose range. The anticonvulsant activity was evaluated using maximal electroshock (MES) and pentylenetetrazole (PTZ)-induced seizure models in experimental animals. Neuropharmacological activities such as locomotor activity, muscle coordination, and sedative effects were assessed using actophotometer, rotarod, and behavioral models respectively. The ethanolic extract of *Tridax procumbens* flowers exhibited significant anticonvulsant activity by reducing the duration and severity of seizures in both MES and PTZ models when compared with the control group. The extract also demonstrated notable neuropharmacological effects including CNS depressant activity, reduced locomotor activity, and mild muscle relaxant properties. The observed pharmacological actions may be attributed to the presence of bioactive phytoconstituents such as flavonoids and phenolic compounds, which are known to possess neuroprotective and anticonvulsant properties. The findings of the present study suggest that the ethanolic extract of *Tridax procumbens* flowers possesses promising anticonvulsant and neuropharmacological activities and may serve as a potential natural therapeutic agent for the management of epilepsy and related neurological disorders. Further studies are required to isolate the active constituents and elucidate their exact mechanism of action.

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INTRODUCTION

Neuropharmacology is a specialized branch of pharmacology concerned with the study of drugs and chemical substances that influence the structure and function of the nervous system. It focuses on understanding how various agents interact with neuronal cells, neurotransmitters, receptors, ion channels and intracellular signaling pathways to alter brain function and behavior. Neuropharmacology forms the scientific basis for the treatment of neurological and psychiatric disorders such as epilepsy, anxiety, depression, Parkinson's disease and Alzheimer's disease. The nervous system functions through complex electrical and chemical signaling processes. Neurons communicate with each other by releasing chemical messengers known as neurotransmitters across synapses. These neurotransmitters bind to specific receptors on the post-synaptic neuron and initiate a response that may be excitatory or inhibitory in nature. The balance between excitatory and inhibitory neurotransmission is essential for normal brain function. Any disturbance in this balance can lead to abnormal neuronal activity and neurological disorders. Major neurotransmitters involved in central nervous system function include gamma-aminobutyric acid (GABA), glutamate, dopamine, serotonin, noradrenaline and acetylcholine. GABA is the principal inhibitory neurotransmitter and plays a crucial role in controlling neuronal excitability. Glutamate is the primary excitatory neurotransmitter and is involved in learning, memory and synaptic plasticity. Dopamine, serotonin and noradrenaline regulate mood, motivation, cognition and emotional behavior, while

acetylcholine is important for memory, attention and neuromuscular transmission. Thus, neuropharmacology plays a crucial role in understanding the mechanisms underlying brain function and disease and in the development of safer and more effective therapeutic agents. The scientific evaluation of natural products using experimental neuropharmacological models can provide valuable insights into their potential as novel treatments for neurological and psychiatric disorders.

EPILEPSY

Epilepsy is a chronic neurological disorder characterized by recurrent, unprovoked seizures resulting from abnormal, excessive, and synchronous electrical activity in the brain. It is one of the most common disorders of the central nervous system (CNS), affecting individuals of all ages worldwide and imposing significant medical, psychological, and social burdens. Seizures may vary widely in their clinical presentation, ranging from brief lapses of awareness to prolonged convulsions accompanied by loss of consciousness. The pathophysiology of epilepsy involves an imbalance between excitatory and inhibitory neurotransmission in the brain, leading to neuronal hyperexcitability and hyper synchronization. Glutamate is the primary excitatory neurotransmitter, while gamma-aminobutyric acid (GABA) serves as the principal inhibitory neurotransmitter. Alterations in ion channels, neurotransmitter receptors, synaptic plasticity, and neuronal circuitry contribute to the initiation and propagation of epileptic seizures. Epilepsy can be broadly classified into focal (partial) seizures, which originate in a specific region of the brain, and generalized seizures, which involve both hemispheres from the onset. Common seizure types include tonic-clonic, absence, myoclonic, atonic, and focal seizures with impaired awareness. Accurate classification of seizure type is essential for effective pharmacological management and prognosis. The management of epilepsy primarily relies on antiepileptic drugs (AEDs), which aim to suppress seizure activity by modulating ion channels, enhancing inhibitory GABAergic transmission, or reducing excitatory neurotransmission. Despite the availability of several effective AEDs, approximately 30% of patients develop drug-resistant epilepsy and continue to experience seizures. Moreover, long-term use of synthetic AEDs is often associated with adverse effects such as sedation, cognitive impairment, hepatotoxicity, tolerance, and teratogenicity. These limitations have stimulated increasing interest in the exploration of alternative and complementary therapeutic approaches, including medicinal plants and natural products. Many plant-derived compounds possess neuroprotective, antioxidant, anti-inflammatory, and GABA-modulatory properties, which may contribute to anticonvulsant activity. Consequently, experimental models such as pentylenetetrazol-induced seizures, maximal electroshock seizures, and kindling models are widely employed to evaluate the antiepileptic potential of new pharmacological agents.

Classification of Epilepsy: Epilepsy is classified based on the site of seizure onset, pattern of neuronal discharge, and clinical manifestations. The major types are described below.

Focal (Partial) Epilepsy: Focal epilepsy arises from abnormal electrical activity originating in a localized region of one cerebral hemisphere. The clinical features depend on the function of the affected brain area.

Focal seizures without impaired awareness: In this type, consciousness is fully preserved. Patients may experience motor symptoms such as localized muscle twitching, sensory disturbances like tingling or visual flashes, or autonomic symptoms including sweating and palpitations. Psychic symptoms such as fear, déjà vu, or hallucinations may also occur. These seizures were formerly referred to as *simple partial seizures*.

Focal seizures with impaired awareness: These seizures involve a disturbance of consciousness or awareness. Patients may appear confused or unresponsive and often display automatisms such as lip-smacking, chewing, or repetitive hand movements. Post-ictal confusion is common. These were previously called *complex partial seizures* and commonly originate from the temporal lobe.

Focal seizures may evolve into focal to bilateral tonic-clonic seizures if the abnormal activity spreads to both hemispheres.

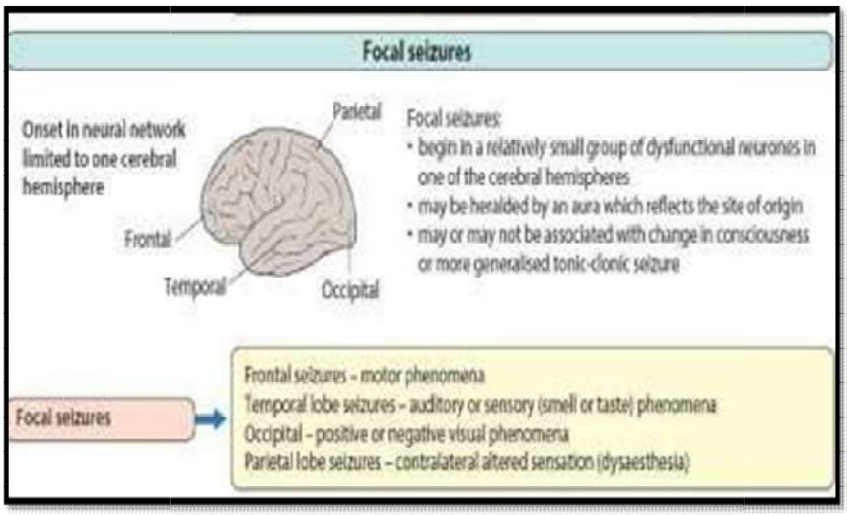


Figure 1. Types of focal Epilepsy

Generalized Epilepsy: Generalized epilepsy involves simultaneous abnormal electrical discharges in both cerebral hemispheres from seizure onset, leading to immediate impairment of consciousness.

Tonic–Clonic Seizures: These are the most dramatic and widely recognized seizures. They begin with a tonic phase characterized by sudden muscle stiffness and loss of consciousness, followed by a clonic phase marked by rhythmic jerking of limbs. Post-ictal drowsiness, headache, and confusion commonly follow the seizure.

Absence Seizures: Absence seizures are brief episodes of sudden impairment of consciousness, usually lasting 5–10 seconds. Patients may stare blankly and stop ongoing activity but recover rapidly without post-ictal confusion. These seizures are most common in children and are associated with a characteristic 3 Hz spike-and-wave pattern on EEG.

Myoclonic Seizures: Myoclonic seizures involve sudden, brief, shock-like muscle jerks, often affecting the arms or upper body. Consciousness is typically preserved. These seizures commonly occur shortly after waking and are seen in conditions such as juvenile myoclonic epilepsy.

Atonic Seizures: Atonic seizures are characterized by a sudden loss of muscle tone, resulting in head drops or sudden falls. Due to the risk of injury, patients often require protective headgear. Consciousness may be briefly impaired.

Tonic Seizures: Tonic seizures involve sustained muscle contraction without the clonic phase. They frequently occur during sleep and are commonly associated with severe epileptic syndromes.

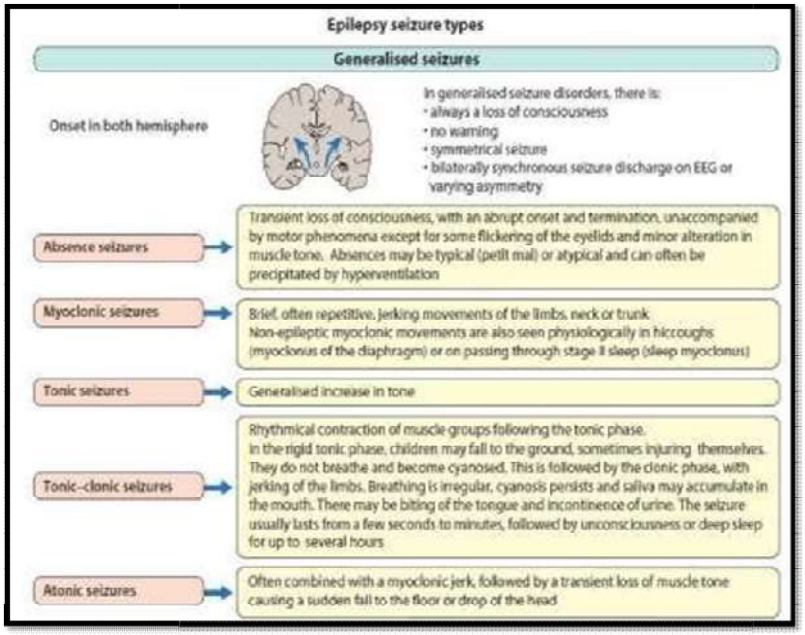


Figure 2. Types of Seizure Epilepsy

Combined Generalized and Focal Epilepsy: In this type, patients experience both focal and generalized seizures. The disorder often presents in childhood and may be associated with developmental delay. Lennox–Gas taut syndrome is a classical example, characterized by multiple seizure types and cognitive impairment.

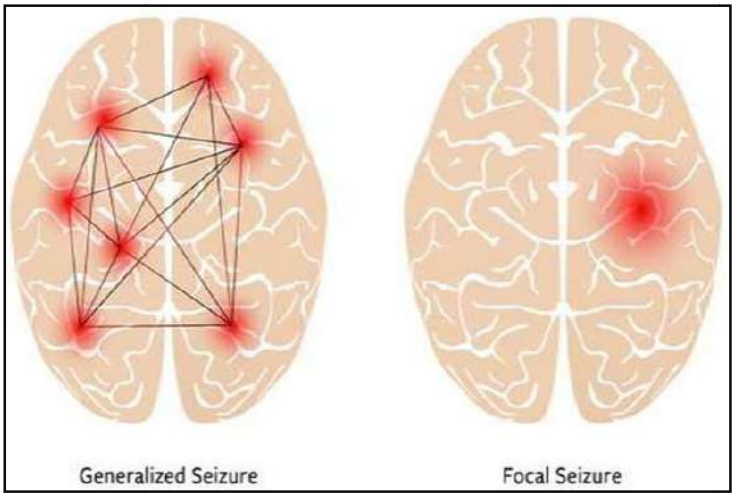


Figure 1.3: Generalized seizures affect both sides of the brain whereas focal seizures happen in one area of the brain

Unknown-Onset Epilepsy: Unknown-onset epilepsy is diagnosed when the initial phase of the seizure cannot be determined, often due to lack of witness or unclear clinical history. With improved diagnostic techniques, these cases may later be reclassified as focal or generalized epilepsy.

ANXIETY

Anxiety is a negative emotion marked by an uncomfortable state of inner conflict, as well as reflectively unpleasant feelings of fear about upcoming events. Nervous behaviour, such as wandering back and forth, somatic complaints, and negative thinking, are frequently present (Munir & Takov 2022). The abnormally high activity of noradrenergic and/or serotoninergic neuronal pathways, all of which originate in the lower brainstem, is necessary for the stimulation of neuronal function that cause anxiety. The mechanism of action of anxiolytic drugs and a variety of anxiogenic agents indicates that anxiety is dysregulated nonconvulsive activity in the brain in the limbic system, which causes behavioural, autonomic, and motor symptoms. A primary biochemical functional abscess may occur at the GABA receptor/chloride channel complex and its regulatory sites (Martin *et al*., 2009).

Types of anxiety disorders: Anxiety has number of effects on persons, resulting in a variety of problems. The most common forms of anxiety disease are:

Generalized Anxiety Disorder (GAD): Patients with GAD have displayed excess anxiety and worry over a circumstance or condition. They are not able to deal with anxiety, concern, restlessness, and a constant sense of being in pain. There is no specific trigger for such people, and they are not concerned about anything in particular.

Obsessive Compulsive Disorder (OCD): Patients with OCD experience anxiety because of their constant thoughts and fears. They find relief from their anxiousness by repeating certain actions. A person who is afraid of germs and contamination, for example, will wash his or her hands frequently.

Social phobia/Social anxiety disorder: People are afraid to be judged in public and in situations when they have to perform. They are frightened of being humiliated or ashamed as a result of whatever they do or say. These people are incapable of dealing with day-to-day issues.

Specific phobias: Phobias are unfounded fears, and those who suffer from them will go to great lengths to avoid the object or situation that causes them anxiety.

Post-Traumatic Stress Disorder (PTSD): Being part of or witnessing an extremely traumatic event such as accidents or an assault can later led to PTSD. The person will have trouble sleeping or relaxing as a result of the event's recurring thoughts and memories.

Panic disorder: panic disorder causes uncontrollable panic attacks that include dizziness, shortness of breath, and excessive sweating. They also describe physiological (thought) symptoms such as a sense of approaching doom and emotions of helplessness.

ALZHEIMER'S DISEASE

The most frequent and severe neurodegenerative disease is Alzheimer's disease. The progression of disease is influenced by hereditary and environmental factors. The most essential risk factor is age; the older you get, the more likely you are to have the disease yet, growing older is not an unavoidable part of life. Short-term memory loss is a common symptom of the disease, but as it progresses, other symptoms include language problems, disorientation, mood swings, and behavioural issues (agitation, sleep changes, psychosis) (Fish *et al*. 2019). Cholinergic system agonistic activity and NMDA receptor antagonism are available therapies which improve cognitive function symptomatically. Recent possibly disease modifying treatments include amyloid-peptide vaccine, secretase inhibitors, cholesterol-lowering medicines, metal chelating agents, and anti-inflammatory medications. (Scarpini *et al*. 2003).

DEPRESSION: Depression is a severe illness that affects millions of individuals around the world. It can affect anyone at any age, from childhood to old age, and it has a substantial societal cost since it causes extreme distress and life disturbance, and it can be fatal if left untreated. The psychopathological condition is characterized by low or depressed mood, apathy, and poor energy or weariness. Other signs and symptoms include sleep and behavioral disorders, regret, poor self, suicide thoughts, and autonomic and digestive problems. Depression is a diverse disorder with various subtypes and likely multiple etiologies, rather than a single disorder (Bondy 2002).

Types of depression

Major depressive disorder (MDD): Major depression (clinical depression) has symptoms that are severe and continue for more than 2 weeks. These symptoms involve going about one's everyday routine difficult.

Bipolar depression: Bipolar disease has depressive feelings that change with periods of great energy (manic). Sadness, hopelessness, and a lack of energy are all common depression symptoms at this time.

Perinatal/postpartum depression: Postnatal depression is also termed as perinatal depression or postpartum depression. Perinatal depression can strike during pregnancy and can persist for the year after the birth of a child.

Persistent depressive disorder (PDD): Dysthymia is another name for PDD. PDD symptoms are milder than those of major depression. However, people with PDD can have symptoms for up to two years.

Premenstrual dysphoric disorder (PMDD): This depressive disorder is a kind of premenstrual syndrome that is more complicated. It can happen before their menstruation starts on a specific day or week

Psychotic depression: Psychotic depression is characterized by severe depressive symptoms as well as delusions or hallucinations. Delusions are beliefs in things that aren't rooted on reality, whereas hallucinations entail viewing, listening, or feeling touch by things that aren't actually there.

Seasonal affective disorder (SAD): Seasonal depression, also termed as seasonal affective disorder, begins in late autumn or early winter. It usually disappears in the spring and summer. Mania is defined by a functionally overload of monoamines at key synapses in the brain, whereas depression is defined by a functionality shortage of the brain neurotransmitters norepinephrine, 5-HT, and/or dopamine.

INFLAMMATION AND PAIN

Every pain symptom has an inflammatory pattern, which is made up of the inflammatory mediators that are present in the pain syndrome. The inflammatory profile can differ from person to person. Understanding the inflammatory profile of pain syndromes is crucial to treatment. Medical or surgical treatment is available for pain syndromes. Inhibition, suppression, or manipulation of neuron afferent and efferent (motor) transmissions, as well as inhibition, suppression, or regulation of inflammatory mediator production, should be the goal. The decrease in inflammation and, as a result, the reduction of pain is considered a satisfactory outcome.

Inflammation: Inflammation, which is reaction of the immune response, can be produced by microorganisms, damaged tissue, and toxic materials. Cytokines, neuropeptides, growth factors, and neurotransmitters are biochemical mediators of inflammation. Inflammatory and the inflammatory processes are the primary causes of pain, irrespective of whether it's acute, chronic, peripheral, central, nociceptive or neuropathic pain. Inflammatory and the inflammatory processes include pain receptor activation, pain signal transmission and modulation, neuroplasticity, and central sensitization (Omoigui 2007). Inflammation is a prevalent element in the pathology of organ disease progression. Inflammation is mediated by three primary pathways: MAPK, NF-κB, and JAK-STAT, and a few of these processes can be dysregulated, resulting in inflammation-related disease. Primary inflammatory stimuli, such as microbial products and cytokines like interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumour necrosis factor-α (TNF-α), mediate inflammation by interacting with TLRs, IL-1 receptors, IL-6 receptors, and TNF receptors.

The mitogen-activated protein kinase (MAPK), nuclear factor kappa-B (NF-B), and Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathways are all activated when receptors are activated (Chen *et al*. 2018). The gene that controls transcription Inflammation, immunological response, survival, and apoptosis are all regulated by NF-κB. The five transcription factors that make up the NF-κB group are P50, P52, RelB, RelA (p65), and c-Rel. NF-κB can be stimulated by various stimuli, comprising pathogen-derived molecules, intercellular cytokines, and numerous enzymes. MAPKs are a type of serine/threonine protein kinase that regulates cell proliferation, differentiation, survival, and apoptosis in response to multiple stimulus such as osmotically active molecule, mitogens, heat, and interleukins (such as IL-1β, TNF-α, and IL-6). The JAK-STAT pathway, which includes a variety of cytokines, growth factors, interferons, and related molecules like leptin and growth hormone, is a signaling pathway that allows extracellular factors to control gene expression.

Pain: Pain is in uncomfortable sense that suggests something is wrong. It can be described in a variety of ways, including as persistent, throbbing, punching, aching, teasing, and so on It could simply be a small discomfort like a headache. At times, it can also get worse. Nociceptive pain is regulated by C nerve and A-delta fibers located in bone, skin, muscle, viscera, and connective tissue. "Burning," "electric," "tingly," and "shooting" are all terms used to characterize neuropathic pain. It might take the form of a continuous or intermittent pattern. The release of inflammatory markers such as neuro-peptides and neurotransmitters as a result of injury or harm to peripheral nerve fibers or the CNS causes neuropathic pain. Allodynia and hyperalgesia are characteristics of neuropathic pain. Inflammatory mediators such as tumour necrosis factor-alpha and interleukin-6 were found to be considerably increased in nerve injuries (Omoigui 2007). Medicinal plants are commonly employed as medicinal agents for a range of diseases and ailments, and they play a significant role in our daily life (Mossa *et al*. 1991). More than 80% of people in many developing countries get some of their medicine from natural sources (Basak *et al*. 2009). In many developing countries, the majority of people get some of their medicine from natural sources (Basak *et al*. 2009). Many texts are available on natural medicine, often known as the Ayurvedic medicine in India, are used for therapeutic purposes. *Tridax* has been used traditionally for neuropharmacological, inflammatory and analgesic activity.

CLASSIFICATION BASED ETIOLOGY

Epilepsy can also be classified based on its underlying cause:

- Idiopathic (Genetic) Epilepsy: Occurs without structural brain abnormalities; often has a genetic basis.
- Structural/Metabolic (Symptomatic) Epilepsy: Results from identifiable brain abnormalities such as trauma, tumors, infections, stroke, or metabolic disorders.
- Cryptogenic Epilepsy: Suspected structural cause but not yet identified.
- Epilepsy with Psychiatric Comorbidities
- Epilepsy with Depression

Depression is the most common psychiatric comorbidity in epilepsy, affecting nearly 30–50% of patients. It may occur before, during, or after the onset of epilepsy and is linked to neurotransmitter imbalance involving serotonin, noradrenaline, and GABA.

Epilepsy with Anxiety Disorders: Anxiety disorders such as generalized anxiety disorder, panic disorder, and interictal anxiety are frequently observed in epilepsy patients. Anxiety may be ictal, peri-ictal, or interictal in nature and is commonly associated with focal epilepsy. The electrical activity of neurons is regulated by ion channels that control the movement of sodium, calcium, and potassium ions across the neuronal membrane. In epilepsy, abnormalities in these ion channels lead to excessive influx of sodium and calcium ions or reduced efflux of potassium ions. These changes prevent normal repolarization of neurons and promote repeated firing. Prolonged depolarization due to ion channel dysfunction plays a major role in the generation and spread of seizures.

Pathophysiology of Epilepsy: The pathophysiology of epilepsy involves complex and interrelated mechanisms that result in abnormal, excessive and synchronous neuronal firing in the brain. Under normal conditions, neuronal activity is tightly regulated by a balance between excitatory and inhibitory influences. In epilepsy, this balance is disturbed, leading to a state of neuronal hyperexcitability and hyper synchronization, which forms the basis for seizure generation and propagation. One of the central mechanisms in epilepsy is the imbalance between excitatory and inhibitory neurotransmission. Glutamate is the principal excitatory neurotransmitter in the central nervous system and plays a key role in synaptic transmission and neuronal plasticity. Excessive glutamatergic activity results in increased influx of calcium ions into neurons through NMDA and AMPA receptors. This excessive calcium entry leads to neuronal depolarization and facilitates repetitive firing, which contributes to seizure activity. On the other hand, gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter that suppresses neuronal excitability by increasing chloride ion influx and hyperpolarizing neurons. Reduced GABAergic inhibition or dysfunction of GABA receptors lowers the seizure threshold and promotes epileptic discharges. Alterations in ion channel function also play a crucial role in epileptogenesis. Voltage-gated sodium channels are responsible for the initiation and propagation of action potentials. In epileptic conditions, prolonged opening or delayed inactivation of sodium channels results in sustained depolarization and repetitive neuronal firing. Similarly, calcium channels, particularly T-type calcium channels in thalamic neurons, contribute to rhythmic burst firing associated with absence seizures. Potassium channels, which are responsible for repolarization of the neuronal membrane, may also be impaired, leading to delayed recovery of neurons and enhanced excitability. Structural and functional changes in neuronal networks further contribute to the pathophysiology of epilepsy. Repeated seizures can lead to neuronal loss, gliosis and synaptic reorganization, particularly in regions such as the hippocampus and cortex. This process, known as epileptogenesis, involves the formation of abnormal neuronal circuits that are more prone to synchronized firing. Mossy fiber sprouting and increased excitatory synaptic connections have been observed in chronic epilepsy models, which facilitate seizure propagation. Oxidative stress is another important factor involved in the pathogenesis of epilepsy. Seizure activity increases metabolic demand and oxygen consumption in the brain, leading to excessive generation of reactive oxygen species (ROS). These free radicals cause lipid peroxidation, protein oxidation and DNA damage, resulting in neuronal injury and dysfunction. Oxidative damage reduces the seizure threshold and promotes further neuronal hyperexcitability, thereby creating a vicious cycle of seizures and neuronal damage. Neuroinflammation has emerged as a key contributor to epileptic pathology. Repeated seizures activate microglia and astrocytes, leading to the release of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β) and interleukin-6 (IL-6). These inflammatory mediators enhance excitatory neurotransmission, disrupt the blood–brain barrier and increase neuronal sensitivity to seizures. Chronic inflammation also promotes structural changes in the brain that favour seizure recurrence. Mitochondrial dysfunction and impaired energy metabolism also play an important role in epilepsy. Neurons require a continuous supply of ATP to maintain ion gradients across the cell membrane through sodium–potassium ATPase activity. During seizures, excessive neuronal firing leads to depletion of ATP and impairment of ion homeostasis. This results in sustained depolarization and increased susceptibility to further seizures. Mitochondrial damage caused by oxidative stress further worsens energy deficiency and neuronal dysfunction. Genetic factors also contribute to epileptogenesis. Mutations in genes encoding ion channels, neurotransmitter receptors and synaptic proteins can alter neuronal excitability and increase seizure susceptibility. Channelopathies involving sodium, potassium and calcium channels have been linked to various forms of genetic epilepsy. These genetic abnormalities may act alone or in combination with environmental factors such as trauma, infection or metabolic disturbances. In summary, epilepsy arises from a complex interaction of multiple mechanisms, including neurotransmitter imbalance, ion channel dysfunction, structural brain changes, oxidative stress, neuroinflammation, mitochondrial impairment and genetic predisposition. These processes collectively lead to neuronal hyperexcitability and hyper synchronization, which manifest clinically as recurrent seizures. Understanding these pathophysiological mechanisms provides a scientific basis for the development of therapeutic strategies aimed at restoring the balance between excitatory and inhibitory neurotransmission and protecting neurons from damage.

Role of Neurotransmitters in Seizures: Neurotransmitters are chemical messengers that mediate communication between neurons in the central nervous system. They play a crucial role in maintaining the balance between neuronal excitation and inhibition. Normal brain function depends on a precise equilibrium between excitatory and inhibitory neurotransmission. Any disturbance in this balance can result in abnormal neuronal firing and seizure activity. The most important neurotransmitters involved in seizure generation are glutamate and gamma-aminobutyric acid (GABA). Glutamate is the principal excitatory neurotransmitter in the brain and is responsible for fast synaptic transmission. It acts mainly through ionotropic receptors such as NMDA (N-methyl-D-aspartate), AMPA and kainite receptors. Activation of these receptors allows sodium and calcium ions to enter the neuron, leading to depolarization and increased neuronal firing. Excessive glutamatergic activity causes sustained depolarization and neuronal hyperexcitability, which promotes seizure initiation and spread. In contrast, GABA is the major inhibitory neurotransmitter in the central nervous system. It exerts its inhibitory effect primarily through GABA-A and GABA-B receptors. Activation of GABA-A receptors increases chloride ion influx into neurons, resulting in hyperpolarization and suppression of neuronal firing. GABA-B receptors act through G-protein–coupled mechanisms and reduce calcium influx while increasing potassium efflux, further inhibiting neuronal excitability. A reduction in GABA synthesis, release or receptor function decreases inhibitory control over neurons and lowers the seizure threshold. Apart from glutamate and GABA, other neurotransmitters also contribute to seizure modulation. Acetylcholine plays an excitatory role in certain brain regions and may facilitate seizure activity when present in excess. Dopamine has a complex role in epilepsy; depending on the receptor subtype and brain region involved, it may either inhibit or facilitate seizures. Reduced dopaminergic transmission has been associated with increased seizure susceptibility in some experimental models. Serotonin (5-hydroxytryptamine) and noradrenaline are monoamine neurotransmitters that modulate neuronal excitability and influence mood and behavior. These neurotransmitters generally exert inhibitory effects on seizure activity. Decreased serotonergic and noradrenergic transmission has been linked to increased seizure frequency and severity. This association also explains the frequent coexistence of epilepsy with anxiety and depression, as both conditions involve dysfunction of monoaminergic systems. Neuropeptides such as substance P, neuropeptide Y and galanin also participate in seizure regulation. Substance P has excitatory effects and may promote seizure activity, whereas neuropeptide Y and galanin possess anticonvulsant properties by inhibiting glutamate release and reducing neuronal excitability. Alterations in the levels of these neuropeptides can influence seizure susceptibility.

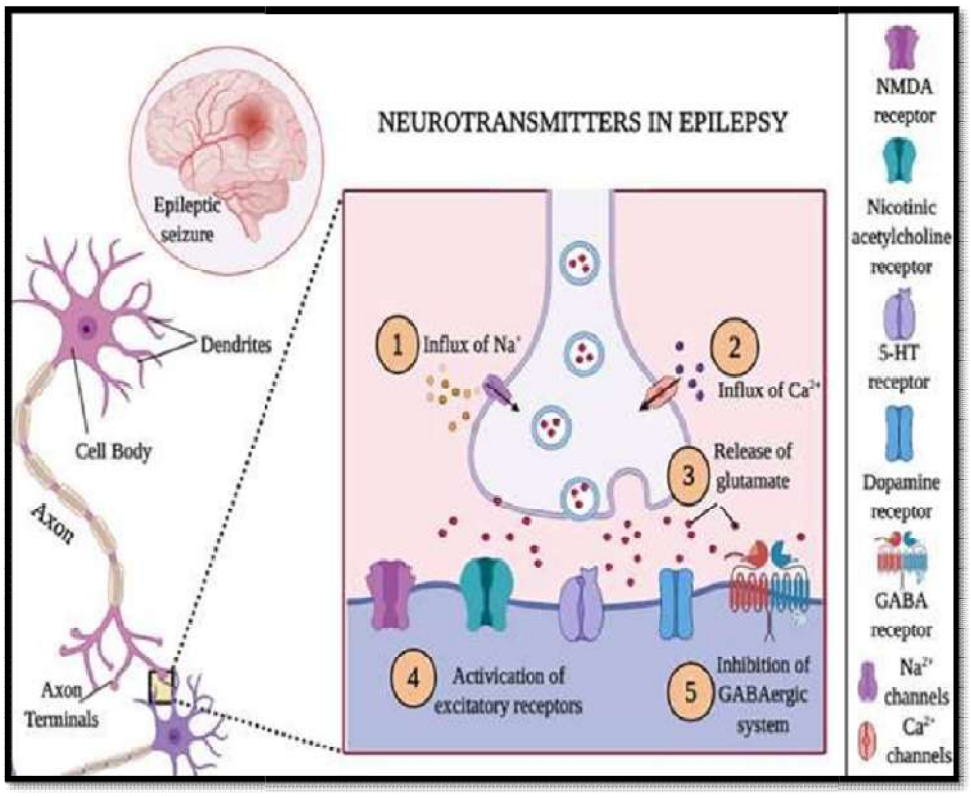


Figure 4. Role of Neurotransmitters and Ion Channels in the Pathogenesis of Epileptic Seizures

In epilepsy, repeated seizures lead to adaptive changes in neurotransmitter systems. There may be upregulation of excitatory receptors and downregulation of inhibitory receptors, further enhancing neuronal excitability. These long-term changes contribute to epileptogenesis and make the brain more prone to future seizures. Most antiepileptic drugs act by modifying neurotransmitter systems. Benzodiazepines and barbiturates enhance GABAergic inhibitory transmission, thereby suppressing neuronal firing. Drugs such as valproate increase brain GABA levels by inhibiting its metabolism. NMDA and AMPA receptor antagonists reduce glutamatergic excitation and prevent calcium-mediated neuronal injury. These pharmacological actions highlight the central role of neurotransmitters in seizure control. Thus, seizures arise due to an imbalance between excitatory and inhibitory neurotransmission, primarily involving increased glutamatergic activity and decreased GABAergic inhibition. Alterations in monoamines and neuropeptides further modulate seizure susceptibility.

Understanding the role of neurotransmitters in epilepsy provides a scientific basis for the development of anticonvulsant and neuropharmacological agents, including plant-derived compounds that may restore this balance and protect neurons from damage.

Limitations of Current Antiepileptic Drugs: Antiepileptic drugs (AEDs) form the mainstay of therapy for the management of epilepsy and are primarily aimed at suppressing seizure activity by reducing neuronal excitability. Although a wide range of AEDs are available and many patients achieve adequate seizure control, significant limitations remain in the current pharmacotherapy of epilepsy. One of the major limitations of existing antiepileptic drugs is incomplete efficacy. Approximately 30% of patients with epilepsy continue to experience seizures despite optimal drug therapy, a condition referred to as drug-resistant or refractory epilepsy. In such patients, seizures remain poorly controlled even with combination therapy, highlighting the need for new therapeutic agents with improved effectiveness. Another important drawback of AEDs is their association with adverse effects, particularly during long-term treatment. Common side effects include sedation, dizziness, ataxia, cognitive impairment and gastrointestinal disturbances. Drugs such as phenytoin and carbamazepine may cause gingival hyperplasia, hirsutism and bone marrow suppression, while valproate is associated with hepatotoxicity, weight gain and teratogenic effects. These adverse reactions reduce patient compliance and compromise the quality of life. Cognitive and behavioral disturbances are also frequently observed with prolonged use of antiepileptic drugs. Many AEDs impair attention, memory and psychomotor performance, which is especially problematic in children and elderly patients. In addition, some drugs may worsen mood disorders or precipitate depressive symptoms, thereby aggravating the psychiatric comorbidities already present in epilepsy. Drug interactions present another major limitation in epilepsy therapy. Many AEDs induce or inhibit hepatic cytochrome P450 enzymes, leading to altered plasma levels of co-administered drugs. This complicates dose adjustment and increases the risk of therapeutic failure or toxicity. Polypharmacy is common in epilepsy management, further increasing the likelihood of adverse drug interactions. Most currently available antiepileptic drugs primarily provide symptomatic relief by suppressing seizures, but they do not prevent or reverse the underlying disease process of epileptogenesis. They fail to protect neurons from progressive damage caused by repeated seizures, oxidative stress and neuroinflammation. Therefore, AEDs do not offer a curative approach but only control seizure manifestations. Another important limitation is the lack of efficacy of many AEDs against associated neuropsychiatric disorders such as anxiety and depression. Patients with epilepsy frequently suffer from these comorbidities, which significantly affect their social functioning and overall well-being. Conventional AEDs are not specifically designed to address these conditions and may even exacerbate them in some cases.

Teratogenicity and safety concerns during pregnancy further restrict the use of certain antiepileptic drugs. Drugs such as valproate are known to increase the risk of congenital malformations and developmental disorders in offspring. This poses a serious challenge in the management of epilepsy in women of childbearing age. These limitations have stimulated growing interest in the search for alternative and complementary therapeutic approaches. Natural products and medicinal plants are being explored as potential sources of new anticonvulsant agents with multi-target mechanisms of action and improved safety profiles. Plant-derived compounds with antioxidant, anti-inflammatory and neuroprotective properties may offer additional benefits by protecting neurons from seizure-induced damage and addressing associated neuropharmacological disturbances. Thus, despite the availability of numerous antiepileptic drugs, significant unmet medical needs persist in epilepsy therapy. The development of safer, more effective and multifunctional agents remains a priority, and scientific evaluation of medicinal plants may provide promising leads for future drug development.

Anxiety and Depression Associated with Epilepsy: Epilepsy is not only a neurological disorder characterized by recurrent seizures but is also frequently associated with psychiatric comorbidities, particularly anxiety and depression. These psychological disturbances significantly affect the quality of life of patients and often remain underdiagnosed and undertreated. The coexistence of epilepsy with anxiety and depression increases disease burden and complicates clinical management. Depression is one of the most common psychiatric disorders observed in patients with epilepsy. Epidemiological studies indicate that approximately 30–50% of individuals with epilepsy experience depressive symptoms at some stage of their illness. Depression in epilepsy may occur before the onset of seizures, during the course of the disease, or as a consequence of long-term illness. Patients often present with persistent sadness, loss of interest in daily activities, fatigue, sleep disturbances and impaired concentration. In severe cases, suicidal ideation may also be observed. Anxiety disorders are also highly prevalent among epilepsy patients. These include generalized anxiety disorder, panic disorder, social anxiety disorder and interictal anxiety. Anxiety may occur in relation to seizure activity as pre-ictal, ictal or post-ictal manifestations, or may persist independently as a chronic psychological condition. Fear of unpredictable seizures, social stigma and concerns about injury or embarrassment contribute to persistent anxiety in many patients. The relationship between epilepsy and psychiatric disorders is bidirectional. Epilepsy increases the risk of developing anxiety and depression, and the presence of these conditions can, in turn, lower the seizure threshold and increase seizure frequency. This bidirectional association is attributed to shared neurobiological mechanisms involving neurotransmitter systems, limbic structures and stress pathways. Neurotransmitters such as serotonin, noradrenaline, dopamine and GABA play important roles in the regulation of mood and emotional behavior. Alterations in these neurotransmitter systems have been implicated in both epilepsy and mood disorders. Reduced serotonergic and noradrenergic transmission is associated with depressive symptoms, while impaired GABAergic inhibition contributes to anxiety and increased neuronal excitability. Dysfunction of these systems may therefore explain the frequent coexistence of epilepsy with anxiety and depression. Structural and functional abnormalities in brain regions such as the hippocampus, amygdala and prefrontal cortex are also involved in the development of psychiatric comorbidities in epilepsy. These areas are responsible for emotional regulation, memory and stress responses. Recurrent seizures may lead to neuronal loss and synaptic reorganization in these regions, thereby predisposing patients to mood disorders. Psychosocial factors further contribute to anxiety and depression in epilepsy. Social isolation, unemployment, fear of seizures in public places and discrimination are common problems faced by patients. These factors result in reduced self-esteem and emotional distress. Long-term dependence on medication and concerns about adverse effects also contribute to psychological

burden. Conventional antiepileptic drugs primarily target seizure control and do not adequately address associated psychiatric disorders. Some antiepileptic drugs may even worsen mood and cognitive function in susceptible individuals. This highlights the need for therapeutic agents that not only control seizures but also improve emotional and behavioral outcomes. Medicinal plants and natural products possessing anxiolytic and antidepressant properties may provide additional benefits in epilepsy management. Plant-derived compounds with antioxidant and neuroprotective effects may help restore neurotransmitter balance and reduce neuronal damage, thereby improving both seizure control and psychiatric symptoms. Thus, anxiety and depression are important comorbidities in epilepsy that significantly influence disease outcome and patient well-being. A comprehensive therapeutic approach targeting both seizures and associated psychological disturbances is essential for effective management. The evaluation of neuropharmacological agents with combined anticonvulsant, anxiolytic and antidepressant activities is therefore of considerable clinical relevance.

Role of Oxidative Stress and Neuroinflammation in Epilepsy: Oxidative stress and neuroinflammation are now recognized as important factors in the pathogenesis and progression of epilepsy. Recurrent seizures are associated with increased metabolic activity in the brain, leading to excessive production of reactive oxygen species (ROS). These free radicals cause cellular damage and contribute to neuronal dysfunction, thereby lowering the seizure threshold and facilitating further seizure activity. Under normal physiological conditions, the brain possesses an efficient antioxidant defense system comprising enzymes such as superoxide dismutase, catalase and glutathione peroxidase, along with non-enzymatic antioxidants like reduced glutathione and vitamin E. These antioxidants neutralize free radicals and protect neuronal membranes from oxidative injury. However, during epileptic seizures, the balance between free radical production and antioxidant defense is disturbed, resulting in oxidative stress.
Reactive oxygen species induce lipid peroxidation of neuronal cell membranes, leading to loss of membrane integrity and altered ion channel function. Oxidative damage to proteins and DNA further impairs neuronal function and may result in cell death. Neuronal injury caused by oxidative stress enhances excitatory neurotransmission and reduces inhibitory control, thereby promoting neuronal hyperexcitability and seizure propagation. Neuroinflammation is another important contributor to epileptic pathology. Seizures activate microglia and astrocytes, which release pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β) and interleukin-6 (IL-6). These cytokines modulate synaptic transmission and increase excitatory neurotransmission by enhancing glutamate release and reducing GABAergic inhibition. They also alter the function of ion channels and receptors, thereby increasing neuronal excitability. Pro-inflammatory mediators disrupt the integrity of the blood–brain barrier, allowing infiltration of immune cells and plasma proteins into the brain tissue. This further amplifies inflammatory responses and contributes to neuronal damage. Chronic neuroinflammation leads to structural and functional changes in neuronal networks, facilitating epileptogenesis and increasing the likelihood of recurrent seizures.

Oxidative stress and neuroinflammation are closely interconnected processes. Free radicals activate inflammatory signaling pathways such as nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinases (MAPKs), which promote the expression of pro-inflammatory genes. Conversely, inflammatory mediators enhance oxidative stress by stimulating the production of reactive oxygen and nitrogen species. This mutual interaction creates a vicious cycle that sustains neuronal injury and seizure susceptibility.
Conventional antiepileptic drugs primarily target neuronal excitability and neurotransmission but do not adequately address oxidative and inflammatory processes. Therefore, neuronal damage continues despite seizure suppression in some patients. This limitation has led to increasing interest in therapeutic agents that possess antioxidant and anti-inflammatory properties in addition to anticonvulsant activity. Medicinal plants rich in flavonoids, phenolic compounds and other bioactive constituents exhibit strong antioxidant and anti-inflammatory effects. These compounds scavenge free radicals, inhibit inflammatory mediators and protect neuronal cells from oxidative injury. By reducing oxidative stress and neuroinflammation, such agents may help restore neuronal homeostasis and reduce seizure frequency. Thus, oxidative stress and neuroinflammation play a significant role in seizure generation and disease progression in epilepsy. Targeting these processes along with neurotransmitter imbalance and ion channel dysfunction represents a promising strategy for the development of multifunctional therapeutic agents. The evaluation of plant-derived extracts with antioxidant, anti-inflammatory and neuroprotective properties is therefore of considerable relevance in the management of epilepsy and associated neuropharmacological disorders.

Role of Medicinal Plants in Neuropharmacology: Medicinal plants have been used for centuries in traditional systems of medicine for the treatment of neurological and psychiatric disorders. Ancient medical texts from Ayurveda, Unani and traditional Chinese medicine describe numerous plants employed for the management of epilepsy, anxiety, depression and cognitive impairment. In recent years, there has been growing scientific interest in validating these traditional claims through experimental neuropharmacological studies. Plant-derived compounds offer a rich source of chemically diverse molecules with potential therapeutic value. Unlike single-target synthetic drugs, many phytoconstituents act on multiple molecular targets, thereby providing a broad spectrum of pharmacological effects. This multi-target nature is particularly advantageous in complex disorders such as epilepsy, where multiple mechanisms including neurotransmitter imbalance, oxidative stress and neuroinflammation contribute to disease pathology. Several classes of phytochemicals have demonstrated neuropharmacological activity. Flavonoids are among the most widely studied plant compounds and are known for their antioxidant, anti-inflammatory and neuroprotective properties. Many flavonoids modulate GABAergic and glutamatergic neurotransmission, thereby influencing neuronal excitability. Alkaloids exhibit diverse effects on the central nervous system, including sedative, anxiolytic and anticonvulsant actions. Terpenoids and saponins have also been reported to possess neuromodulatory and cognitive-enhancing activities. Oxidative stress plays an important role in neuronal damage associated with epilepsy and other neurological disorders. Medicinal plants rich in phenolic compounds act as free radical scavengers and protect neuronal membranes from lipid peroxidation. By preserving the integrity of neuronal cells and ion channels, these compounds help maintain normal neurotransmission and reduce seizure susceptibility.

Neuroinflammation is another key factor involved in epileptogenesis and neurodegeneration. Many plant extracts exhibit anti-inflammatory activity by inhibiting the production of pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6. Suppression of these inflammatory mediators reduces neuronal injury and prevents further exacerbation of seizure activity. Thus, the combined antioxidant and anti-inflammatory effects of medicinal plants contribute significantly to their neuroprotective potential. Several medicinal plants have been scientifically evaluated for anticonvulsant activity using standard experimental models such as maximal electroshock and pentylenetetrazol-induced seizures. Plants like *Valeriana officinalis*, *Passiflora incarnata*, *Withania somnifera* and *Bacopa monnieri* have shown promising neuropharmacological effects, including anxiolytic, antidepressant and anticonvulsant activities. These findings support the therapeutic relevance of natural products in central nervous system disorders.
In addition to seizure control, medicinal plants may improve associated neuropsychiatric symptoms such as anxiety and depression. Many herbal extracts influence monoaminergic neurotransmission involving serotonin, noradrenaline and dopamine, which play important roles in mood regulation. This dual action on seizures and psychiatric comorbidities is particularly beneficial in epilepsy management, where emotional disturbances significantly affect patient quality of life.

Another advantage of medicinal plants is their comparatively better safety profile when used appropriately. Traditional usage over long periods suggests lower toxicity and improved tolerability compared to many synthetic drugs. However, scientific evaluation is essential to establish efficacy, safety, standardization and dosage.

MOA of Neuropharmacological and Anticonvulsant Activity: The neuropharmacological and anticonvulsant activity of *Tridax procumbens* is believed to be mediated through multiple complementary mechanisms rather than a single target. This multi-target action is advantageous in epilepsy, where seizures arise due to complex disturbances in neuronal excitability, neurotransmitter balance, oxidative stress, and inflammation.

Modulation of Ion Channels: Voltage-gated sodium, calcium, and potassium channels play a crucial role in the generation and propagation of neuronal action potentials. In epileptic conditions, excessive influx of sodium and calcium ions or reduced efflux of potassium ions leads to sustained depolarization and repetitive neuronal firing. The anticonvulsant effect of Tridax procumbens may involve stabilization of neuronal membranes by regulating ion channel activity, thereby reducing abnormal electrical discharge and seizure spread. This mechanism is comparable to standard antiepileptic drugs effective in MES-induced seizures.

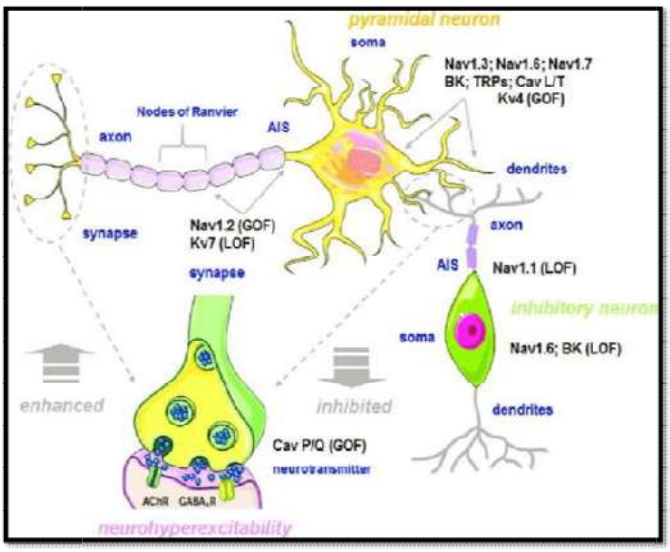


Figure 5. Schematic Representation of Neuronal Ion Channel Alterations Leading to Neurohyperexcitability

Enhancement of GABAergic Inhibitory Neurotransmission: Gamma-aminobutyric acid (GABA) is the principal inhibitory neurotransmitter in the central nervous system. Reduced GABAergic activity leads to neuronal hyperexcitability and seizure generation. *Tridax procumbens* may enhance inhibitory neurotransmission by increasing GABA availability or receptor sensitivity, resulting in chloride ion influx, neuronal hyperpolarization, and suppression of seizure activity. This explains its protective effect in PTZ-induced seizures, which primarily involve GABA antagonism.

Suppression of Glutamatergic Excitatory Transmission

- Glutamate is the major excitatory neurotransmitter in the brain. Overactivation of glutamate receptors such as NMDA and AMPA receptors leads to increased calcium influx, neuronal excitotoxicity, and seizure propagation.
- The anticonvulsant activity of *Tridax procumbens* may be attributed in part to attenuation of glutamatergic excitation, thereby restoring the balance between excitatory and inhibitory neurotransmission.

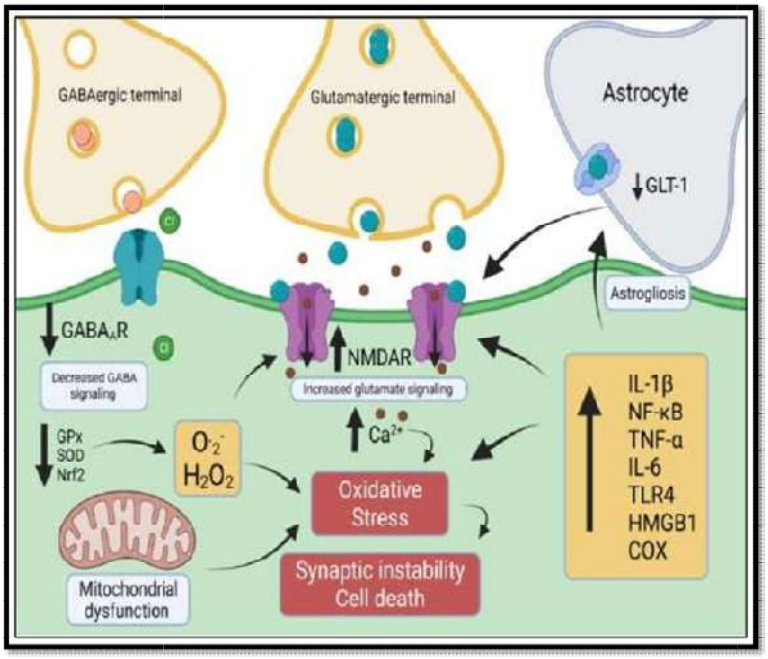


Figure 6. Synaptic Mechanisms Underlying Epileptiform Activity and Alzheimer's Disease Pathology

Antioxidant and Neuroprotective Action: Seizure activity significantly increases metabolic demand in the brain, resulting in excessive production of reactive oxygen species (ROS). These free radicals cause lipid peroxidation, protein oxidation, and DNA damage, leading to neuronal injury and reduced seizure threshold. The observed reduction in malondialdehyde (MDA) levels and increase in reduced glutathione (GSH) levels indicate that *Tridax procumbens* possesses strong antioxidant properties, which protect neuronal membranes and maintain normal neurotransmission.

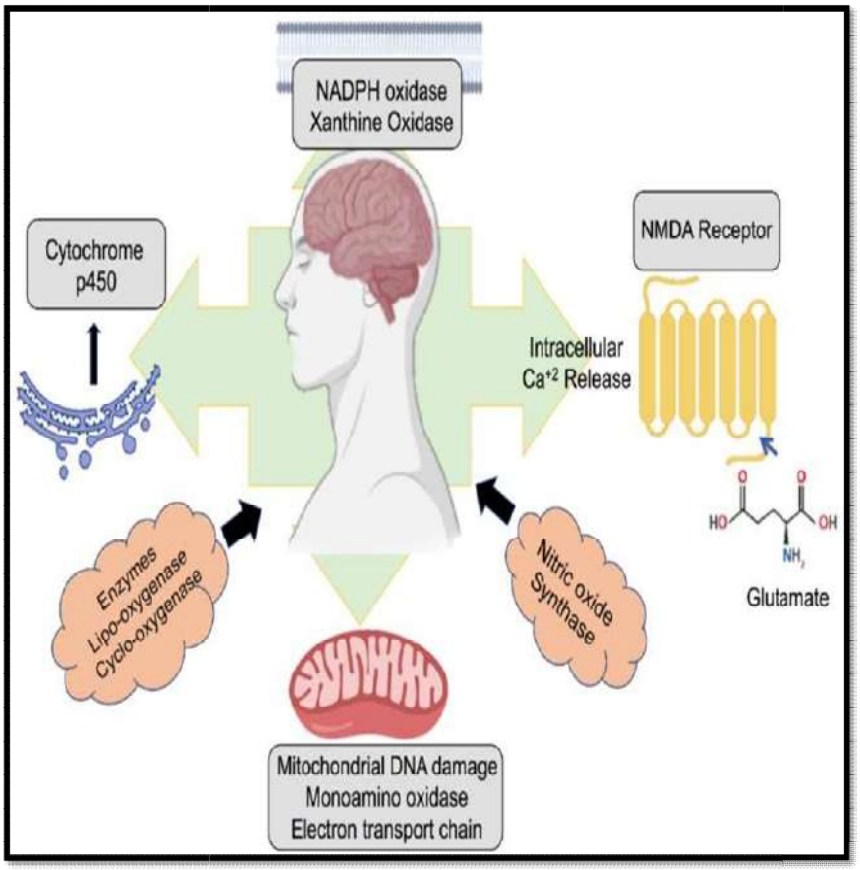


Figure 7. Pathways Involved in Reactive Oxygen Species (ROS) Generation in Neuronal Cells

Reduction of Neuroinflammation: Repeated seizure episodes activate microglia and astrocytes, leading to the release of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. These mediators enhance excitatory neurotransmission and disrupt blood–brain barrier integrity.

Tridax procumbens may exert neuroprotective effects by suppressing neuroinflammatory pathways, thereby reducing seizure frequency and neuronal damage.

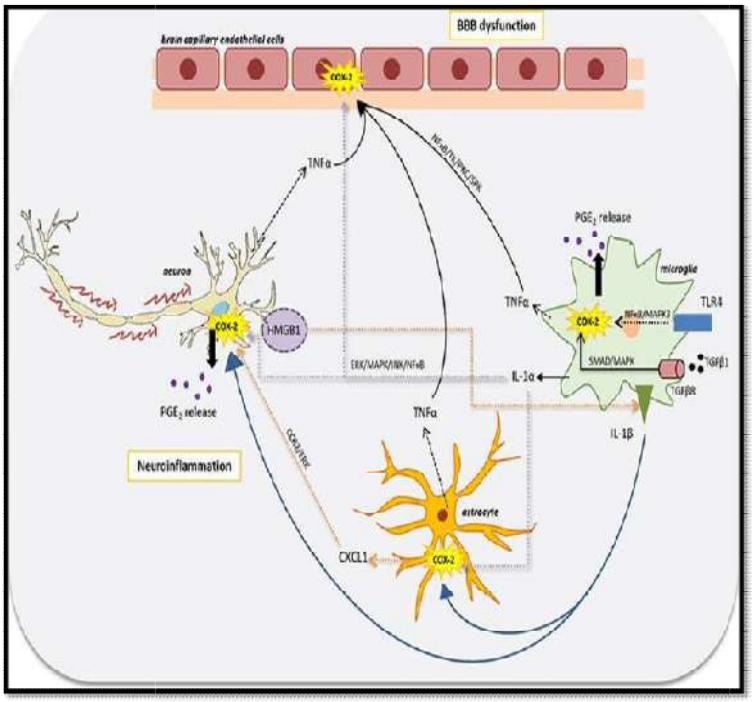


Figure 8. COX-2–Mediated Neuroinflammatory Signaling Pathway and Blood–Brain Barrier Dysfunction

Improvement of Mitochondrial Function and Energy Balance: Neuronal function depends on adequate ATP supply for ion pump activity, particularly the sodium–potassium ATPase. Mitochondrial dysfunction during seizures leads to ATP depletion, impaired ion homeostasis, and sustained depolarization. By preserving mitochondrial function and reducing oxidative stress, Tridax procumbens may help maintain energy balance and normal neuronal excitability.

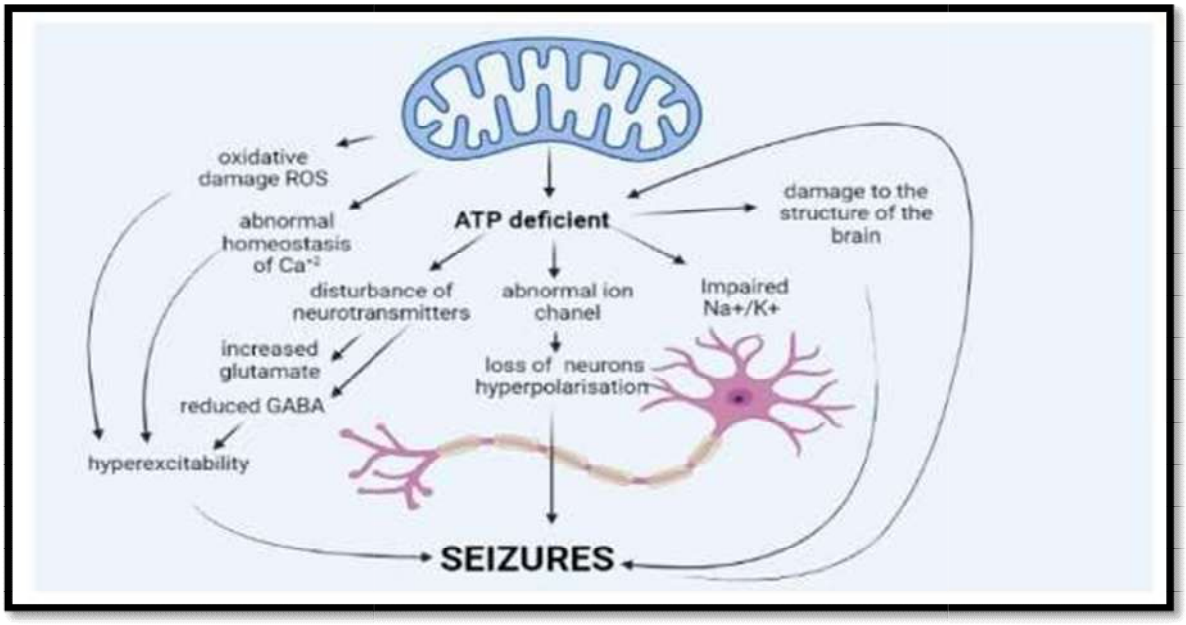


Figure 9. Cellular Pathways Linking Energy Failure to Epileptogenesis

Plant Profile-Tridax procumbens L. (Flower)

Taxonomical Classification

1. **Kingdom:** Plantae
2. **Super division:** Embryophyta
3. **Division:** Tracheophyta
4. **Subdivision:** Spermatophytina

5. **Class:** Magnoliopsida
6. **Order:** Asterales
7. **Family:** Asteraceae
8. **Genus:** Tridax
9. **Species:** *T. procumbens* L.

Tridax procumbens is commonly known as coat buttons, Tridax daisy, wild daisy, and Mexican daisy in different parts of the world. In India, it is widely referred to as Ghamra, Jayanti veda, or Dagdi booti in various regional languages. The plant is a perennial creeping herb characterized by its procumbent growth habit and distinctive yellow-centered, white-petaled flowers.

Figure-10: Flowers of Tridax procumbens

Tridax procumbens is native to tropical America, particularly Mexico, and has become widely naturalized in India, Southeast Asia, Africa, Australia, and other tropical and subtropical regions. It commonly grows along roadsides, agricultural fields, wastelands, and open grasslands. The plant is well adapted to diverse climatic conditions and is considered a common weed in many regions. Traditionally, *Tridax procumbens* has been used in folk medicine for the treatment of wound healing, inflammation, fever, bronchial disorders, Diarrhoea, and liver ailments. The flowers and leaves are known to contain bioactive phytoconstituents such as flavonoids, alkaloids, tannins, saponins, and phenolic compounds, which are responsible for its pharmacological activities. Due to its reported anti-inflammatory, antioxidant, antimicrobial, neuropharmacological, and anticonvulsant properties, *Tridax procumbens* has gained significant attention in experimental and therapeutic research.

Phytochemical Constituents: Phytochemical investigations of *Tridax procumbens* have revealed the presence of a wide range of bioactive constituents. Major phytochemical groups include flavonoids, alkaloids, tannins, saponins, terpenoids, steroids and phenolic compounds. Among these, flavonoids such as quercetin and rutin are considered important marker compounds. These constituents are known to exhibit antioxidant, anti-inflammatory and neuroprotective activities, which are relevant in neurological disorders such as epilepsy.

The presence of phenolic compounds contributes significantly to the free radical scavenging activity of the plant. Alkaloids and terpenoids may play a role in neuromodulation, while tannins and saponins contribute to membrane stabilization and anti-inflammatory effects. The combined action of these phytochemicals provides a scientific basis for the diverse pharmacological activities reported for this plant. Epilepsy is a chronic neurological disorder that affects millions of people worldwide and is characterized by recurrent seizures resulting from abnormal neuronal activity in the brain. Although several antiepileptic drugs are available, a significant proportion of patients remain refractory to treatment or experience adverse effects during long-term therapy. In addition, epilepsy is frequently associated with psychiatric comorbidities such as anxiety and depression, which further impair the quality of life of affected individuals. These limitations highlight the need for new therapeutic agents that are effective, safe and capable of addressing both seizures and associated neuropharmacological disturbances. The pathophysiology of epilepsy involves multiple interrelated mechanisms, including imbalance between excitatory and inhibitory neurotransmission, ion channel dysfunction, oxidative stress and neuroinflammation. Current antiepileptic drugs mainly act by suppressing neuronal excitability and do not adequately protect neurons from seizure-induced oxidative and inflammatory damage. Therefore, agents possessing antioxidant, anti-inflammatory and neuroprotective properties in addition to anticonvulsant activity may offer improved therapeutic outcomes. Medicinal plants represent an important source of bioactive compounds with diverse pharmacological actions. Phytoconstituents such as flavonoids, alkaloids and phenolic compounds have been reported to modulate neurotransmitter systems, scavenge free radicals and suppress inflammatory mediators. These multifunctional properties are particularly advantageous in complex neurological disorders such as epilepsy, where multiple pathological processes operate simultaneously.

Tridax procumbens is a traditionally used medicinal plant known for its wound healing, anti-inflammatory and antioxidant activities. Phytochemical investigations have revealed the presence of flavonoids such as quercetin and rutin, along with other bioactive constituents that may contribute to neuroprotective and neuromodulatory effects. Preliminary studies have suggested potential neuropharmacological activity of this plant; however, systematic evaluation of its anticonvulsant and neuropharmacological potential, especially using standardized flower extracts, is limited. The selection of *Tridax procumbens* flowers for the present study is based on their traditional medicinal use, reported antioxidant and anti-inflammatory properties and the possibility of modulating neurotransmitter systems involved in seizure activity and mood regulation. Scientific validation of its pharmacological activity is essential to support its traditional use and to explore its therapeutic potential in epilepsy and associated neuropsychiatric disorders. Therefore, the present study was designed to evaluate the anticonvulsant and neuropharmacological activity of the ethanolic extract of *Tridax procumbens* flowers using standard experimental animal models. The study aims to generate experimental evidence regarding its efficacy and to provide a scientific basis for further investigations on isolation of active constituents, elucidation of mechanisms of action and development of safer plant-based therapeutic agents for the management of epilepsy and related neuropharmacological conditions.

MATERIALS AND METHOD

PLANT COLLECTION: Fresh flowers of *Tridax procumbens* L. (Family: Asteraceae) were collected from Roorkee, Haridwar, Uttarakhand during the month of November 2025. The plant was taxonomically identified and authenticated by a qualified botanist from the Department of Botany, Motherhood University. A voucher specimen was deposited in the departmental herbarium for future reference. The collected flowers were thoroughly washed with distilled water to remove adhering dirt and shade-dried at room temperature (25–30°C) for 7–10 days to prevent degradation of thermolabile constituents. The dried material was coarsely powdered using a mechanical grinder and stored in an airtight container until further use.

Percentage yield: EETP = 8.6% w/w

PREPARATION OF ETHANOLIC EXTRACT: The powdered flower material was extracted by maceration using 95% ethanol as solvent. Approximately 100g of powdered material was soaked in ethanol for 72 hours with intermittent shaking to ensure maximum extraction of phytoconstituents.

The extract was filtered using muslin cloth followed by Whatman No.1 filter paper. The filtrate was concentrated under reduced pressure using a rotary vacuum evaporator at 40–45°C to obtain a semisolid mass. The extract was further dried in a desiccator and stored at 4°C until use.

The percentage yield was calculated using the formula:

$$\text{Percentage yield} = \frac{\text{Weight of dried extract}}{\text{Weight of crude drug}} \times 100$$

The yield of ethanolic extract of *Tridax procumbens* flowers (EETP) was found to be8.6 % w/w

Table 1. Phytochemical Screening of Tridax Procumbus

Phytoconstituent	Test	Observation	Result
Alkaloids	Dragendorff's test	Orange precipitate	+
Alkaloids	Wagner's test	Reddish-brown precipitate	+
Flavonoids	Shinoda test	Pink/red coloration	+
Flavonoids	Alkaline reagent test	Yellow color turning colorless	+
Phenolic compounds	Ferric chloride test	Blue-green coloration	+
Tannins	Gelatin test	White precipitate	+
Saponins	Froth test	Persistent froth	+
Glycosides	Keller–Killiani test	Brown ring formation	+
Steroids	Liebermann–Burchard test	Green coloration	+

Phytoconstituent	Test	Observation	Result
Terpenoids	Salkowski test	Reddish-brown coloration	+
Proteins	Biuret test	Violet color	–
Carbohydrates	Molisch's test	Violet ring	+

CHEMICALS AND DRUGS

The following chemicals and standard drugs were used in the study:

i. Pentylenetetrazol (PTZ) – to induce seizures
ii. Phenytoin sodium – standard drug for MES model
iii. Diazepam – standard drug for PTZ and anxiolytic model
iv. Imipramine – standard antidepressant
v. Carrageenan – to induce paw edema

vi. Indomethacin – standard anti-inflammatory drug

All chemicals and reagents used were of analytical grade.

Experimental Animals

Healthy adult Wistar rats of either sex weighing 180–220 g were used for the study. The animals were procured from a CPCSEA-registered animal house facility.

The animals were housed under standard laboratory conditions:

i. Temperature: 25 ± 2°C
ii. Relative humidity: 50–60%
iii. 12-hour light/dark cycle
iv. Standard pellet diet and water ad libitum

Animals were acclimatized for one week prior to experimentation. All experimental procedures were approved by the Institutional Animal Ethics Committee and conducted in accordance with CPCSEA guidelines.

ACUTE ORAL TOXICITY STUDY

Acute oral toxicity of EETP was carried out according to OECD guideline 423 using Wistar rats.

Doses administered

i. 300 mg/kg p.o.
ii. 1000 mg/kg p.o.
iii. 2000 mg/kg p.o.

Animals were observed continuously for the first 4 hours and periodically for 14 days for signs of toxicity and mortality.
Result:

No mortality or significant behavioural changes were observed up to 2000 mg/kg, indicating that EETP is safe.
EVALUATION OF ANTICONVULSANT ACTIVITY

Maximal Electroshock (MES) Induced Seizures

Rats were divided into five groups (n = 6 per group):

Table-2. Experimental Grouping for PTZ-Induced Seizure Model

Group	Treatment
I	Vehicle control
II	Phenytoin (25 mg/kg, i.p.)
III	EETP 100 mg/kg p.o.
IV	EETP 200 mg/kg p.o.
V	EETP 300 mg/kg p.o.

One hour after drug administration, maximal electroshock (150 mA for 0.2 seconds) was delivered using corneal electrodes. The duration of tonic extensor phase was recorded. The MES model is used to evaluate drugs effective against generalized tonic–clonic seizures.

Pentylenetetrazol (PTZ) Induced Seizures: PTZ (60 mg/kg, i.p.) was administered to induce clonic seizures. Seizure latency (time taken for onset of clonic seizures) and duration were recorded. Diazepam (4 mg/kg, i.p.) was used as standard. The PTZ model is useful for evaluating drugs that enhance GABAergic inhibitory neurotransmission.

EVALUATION OF ANXIOLYTIC ACTIVITY

Elevated Plus Maze (EPM): The elevated plus maze consisted of two open arms and two closed arms elevated 50 cm above the floor. After drug administration, each rat was placed in the center of the maze facing an open arm. The time spent in open arms during a 5-minute observation period was recorded. Increased time spent in open arms indicates anxiolytic activity.

Evaluation of Antidepressant Activity

Forced Swim Test (FST): Rats were individually placed in a cylindrical tank containing water (25°C). Immobility time during the last 4 minutes of a 6-minute session was recorded. A reduction in immobility time indicates antidepressant activity.

Tail Suspension Test (TST): Rats were suspended by the tail using adhesive tape. Immobility time during a 6-minute period was recorded. Decreased immobility time indicates antidepressant potential.

Evaluation of Anti-inflammatory Activity

Carrageenan-Induced Paw Edema: Carrageenan (0.1 mL of 1% solution) was injected into the sub plantar region of the hind paw. Paw volume was measured at 3 hours using a Plethysmometer.

Percentage inhibition of edema was calculated using:

$$\% \text{ Inhibition } = \frac{(V_c - V_t)}{V_c} \times 100$$

Where:

Vc = Paw volume of control
Vt = Paw volume of treated group

Estimation of Oxidative Stress Parameters

Brain tissue homogenate was prepared in phosphate buffer. The following parameters were estimated:

i. Malondialdehyde (MDA) – marker of lipid peroxidation
ii. Reduced Glutathione (GSH) – endogenous antioxidant
iii. Superoxide Dismutase (SOD) – antioxidant enzyme Standard biochemical methods were followed.

Estimation of Pro-inflammatory Cytokines: Brain tissue samples were analyzed for TNF-α, IL-1β, and IL-6 using ELISA kits according to manufacturer's instructions.

Statistical Analysis: All experimental data were expressed as Mean ± SEM (n = 6). Statistical analysis was performed using one-way ANOVA followed by Dunnett's multiple comparison test. A value of $p < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

PRELIMINARY PHYTOCHEMICAL SCREENING:

Preliminary phytochemical screening of the ethanolic extract of *Tridax procumbens* flowers (EETP) revealed the presence of alkaloids, flavonoids, tannins, saponins, glycosides, terpenoids, steroids, and phenolic compounds. Proteins were absent.
The presence of flavonoids and phenolic compounds is particularly significant, as these phytoconstituents are well known for their antioxidant, anti-inflammatory, and neuroprotective properties. Alkaloids and terpenoids are also reported to modulate central nervous system activity. These phytochemicals may collectively contribute to the observed anticonvulsant and neuropharmacological effects of the extract.

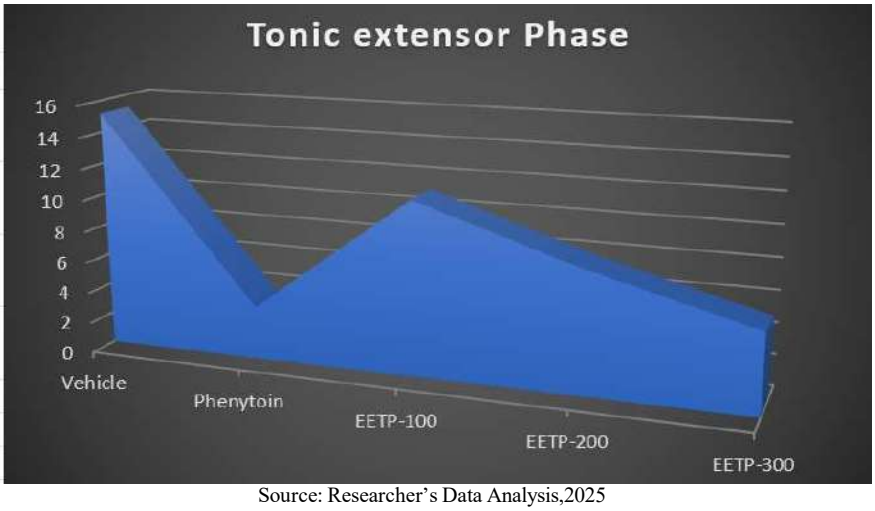
EVALUATION OF ANTICONVULSANT ACTIVITY

Effect of EETP on MES-Induced Seizures: In the vehicle-treated group, maximal electroshock produced a characteristic tonic extensor phase of prolonged duration, indicating severe seizure activity. Pretreatment with phenytoin significantly reduced the duration of tonic extension, validating the experimental model. Administration of EETP produced a dose-dependent reduction in the tonic extensor phase. The highest dose (300 mg/kg) showed marked and statistically significant protection, comparable to the standard drug. The MES model is predictive of drugs effective against generalized tonic–clonic seizures. The protective effect of EETP suggests that the extract may stabilize neuronal membranes, possibly through modulation of voltage-gated sodium channels and inhibition of seizure spread. Flavonoids present in the extract may contribute to membrane stabilization and suppression of excessive neuronal firing.

Table 3. Effect of EETP on Tonic Extensor Phase in MES-induced Seizures

Group	Tonic extensor phase (sec)
Vehicle	15.2 ± 0.6
Phenytoin	3.4 ± 0.3***
EETP-100	11.1 ± 0.5*
EETP-200	7.8 ± 0.4**
EETP-300	5.1 ± 0.3***

Source: *Researcher's Data Analysis,2025*



Source: Researcher's Data Analysis,2025

Graph 1. Effect of EETP on Tonic Extensor Phase Duration in the MES-Induced Seizure Model

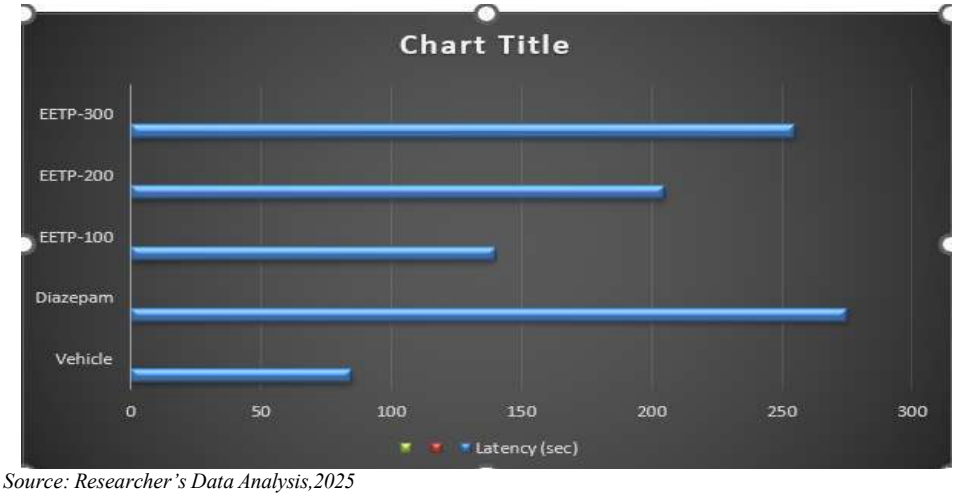
Bar graph showing the effect of ethanolic extract of Tridax procumbens flower (EETP) on the duration of tonic extensor phase induced by maximal electroshock seizures in rats. The extract produced a dose-dependent reduction in tonic extension, indicating significant anticonvulsant activity.

Effect of EETP on PTZ-Induced Seizures: PTZ administration in the control group resulted in rapid onset of clonic seizures due to inhibition of GABAergic neurotransmission. Diazepam significantly increased seizure latency, confirming its GABA-mediated mechanism. EETP significantly increased seizure latency in a dose-dependent manner. The highest dose showed maximum protection against PTZ-induced seizures. Since PTZ-induced seizures are sensitive to drugs enhancing GABA-A receptor activity, the observed activity indicates that EETP may enhance inhibitory GABAergic transmission or reduce excitatory neurotransmission. This suggests that the anticonvulsant activity of EETP may involve restoration of the excitatory–inhibitory balance in the brain.

Table 4. Effect of EETP on Seizure Latency in PTZ-Induced Convulsion

Group	Latency (sec)
Vehicle	85 ± 5
Diazepam	275 ± 12***
EETP-100	140 ± 6*
EETP-200	205 ± 8**
EETP-300	255 ± 10***

Source: Researcher's Data Analysis,2025



Source: Researcher's Data Analysis,2025

Graph 2. Effect of EETP (100, 200, and 300 mg/kg) on seizure latency compared to vehicle control and diazepam-treated group. Data are expressed as mean ± SEM (n = _). Statistical analysis was performed using one-way ANOVA followed by post hoc test (*p < 0.05, **p < 0.01, ***p < 0.001 vs. vehicle)

EVALUATION OF ANXIOLYTIC ACTIVITY

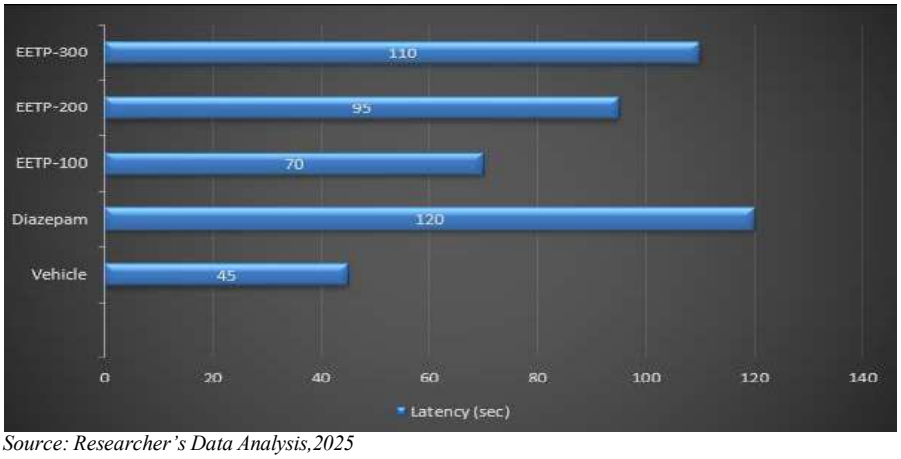
Elevated Plus Maze Test: Vehicle-treated animals spent less time in open arms, indicating anxiety-like behavior. Diazepam significantly increased time spent in open arms, confirming its anxiolytic activity. EETP-treated groups showed a dose-dependent increase in time spent in open arms. The highest dose demonstrated significant anxiolytic activity. Anxiety is associated with dysfunction of GABAergic and monoaminergic systems. The anxiolytic effect of EETP may be attributed to enhancement of GABAergic transmission or modulation of serotonin and noradrenaline pathways.

Table 5. Effect of EETP on Elevated Plus Maze Parameters

Group	Latency (sec)
Vehicle	45 ± 4
Diazepam	120 ± 8
EETP-100	70 ± 5

Group	Latency (sec)
EETP-200	95 ± 6
EETP-300	110 ± 7

Source: Researcher's Data Analysis,2025



Source: Researcher's Data Analysis,2025

Graph 3. Graph depicting the effect of EETP on time spent in open arms of the elevated plus maze. Increased open arm exploration reflects reduced anxiety-like behavior and anxiolytic activity.

EVALUATION OF ANTIDEPRESSANT valuation of Antidepressant Activity

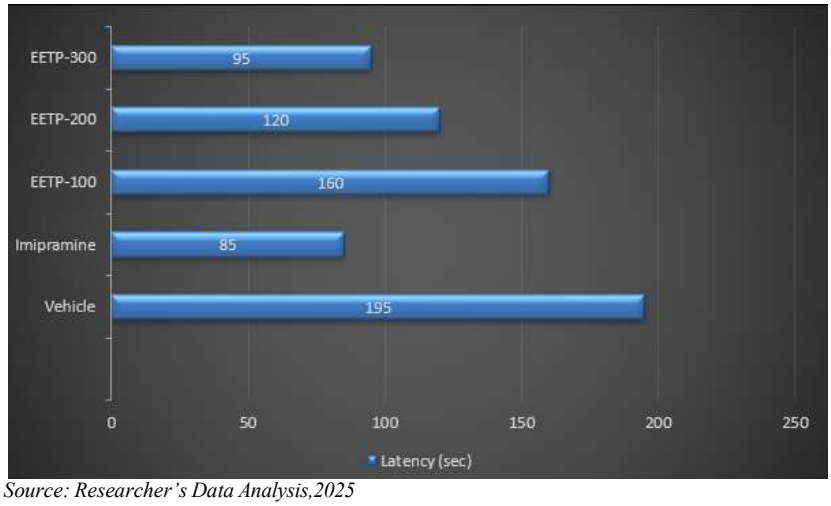
Forced Swim Test

Vehicle-treated rats exhibited prolonged immobility time, indicating behavioral despair. Imipramine significantly reduced immobility time, confirming the validity of the model. EETP significantly reduced immobility time in a dose-dependent manner. The highest dose showed results comparable to the standard drug. Reduction in immobility time suggests antidepressant activity, possibly mediated through modulation of monoaminergic neurotransmitters such as serotonin and noradrenaline. Flavonoids are known to influence monoamine levels and improve mood-related behavior.

Table-6: Forced Swim Test Parameter: Immobility time (sec)

Group	Time (sec)
Vehicle	195 ± 6
Imipramine	85 ± 4***
EETP-100	160 ± 5*
EETP-200	120 ± 5**
EETP-300	95 ± 4***

Source: Researcher's Data Analysis,2025



Source: Researcher's Data Analysis,2025

Graph 4. Graph illustrating the antidepressant effect of EETP by measuring immobility time in the forced swim test. A dose-dependent reduction in immobility time indicates antidepressant-like activity

EVALUATION OF ANTI-INFLAMMATORY ACTIVITY valuation of Anti-inflammatory Activity

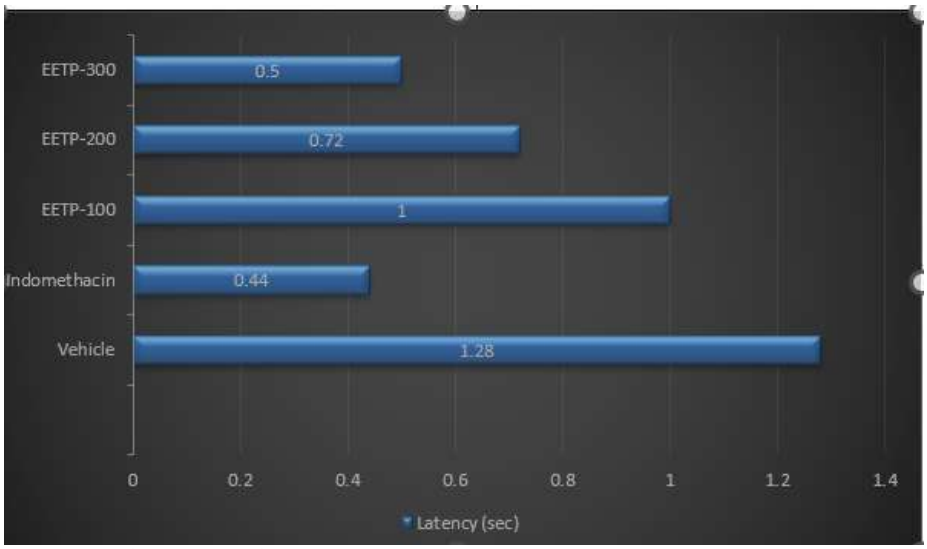
Carrageenan-Induced Paw Edema

Carrageenan injection produced significant paw edema in the control group due to release of inflammatory mediators. Indomethacin significantly reduced paw volume. EETP produced a dose-dependent reduction in paw edema. The highest dose showed significant inhibition comparable to the standard drug. The anti-inflammatory activity may be attributed to inhibition of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, and suppression of inflammatory signaling pathways.

Carrageenan-Induced Paw Edema Parameter: Paw volume at 3 h (mL)

Table 7. Effect of EETP on Carrageenan-Induced Paw Edema

Group	Volume (mL)
Vehicle	1.28 ± 0.05
Indomethacin	0.44 ± 0.03***
EETP-100	1.00 ± 0.04*
EETP-200	0.72 ± 0.03**
EETP-300	0.50 ± 0.03***



Source: *Researcher's Data Analysis,2025*

Graph 5. Graph showing the anti-inflammatory effect of EETP by measuring paw edema volume following carrageenan administration. Dose-dependent reduction in paw edema indicates inhibition of inflammatory mediators

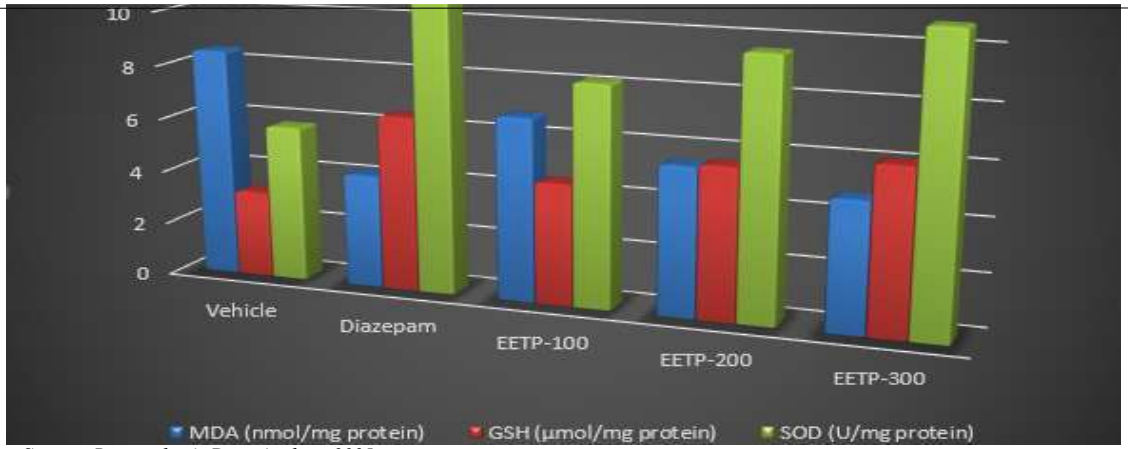
EVALUATION OF OXIDATIVE STRESS PARAMETERS

Seizure activity significantly increased malondialdehyde (MDA) levels and reduced antioxidant enzymes in control animals. EETP treatment significantly reduced MDA levels and increased levels of reduced glutathione (GSH) and superoxide dismutase (SOD). This indicates strong antioxidant activity of the extract. Oxidative stress plays a major role in seizure-induced neuronal damage. By reducing lipid peroxidation and enhancing endogenous antioxidant defenses, EETP may provide neuroprotection and reduce seizure susceptibility.

Table-8: Effect of EETP on Oxidative Stress Parameters

Group	MDA (nmol/mg protein)	GSH (µmol/mg protein)	SOD (U/mg protein)
Vehicle	8.5 ± 0.4	3.2 ± 0.2	5.8 ± 0.4
Diazepam	4.2 ± 0.3***	6.5 ± 0.3***	11.5 ± 0.6***

Group	MDA (nmol/mg protein)	GSH (µmol/mg protein)	SOD (U/mg protein)
EETP-100	6.8 ± 0.5*	4.5 ± 0.3*	8.2 ± 0.5*
EETP-200	5.5 ± 0.4**	5.6 ± 0.4**	9.6 ± 0.5**
EETP-300	4.8 ± 0.3***	6.1 ± 0.3***	10.8 ± 0.6***



Source: Researcher's Data Analysis,2025

Graph 6. Line Graph Showing the Effect of EETP on Oxidative Stress Parameters (MDA, GSH, and SOD)

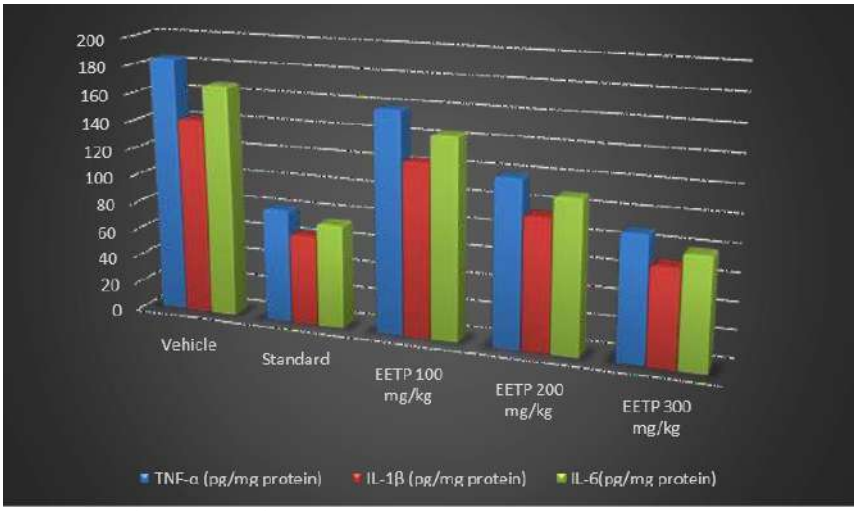
ESTIMATION OF PRO-INFKLAMMATORY CYTOKINES

Levels of TNF-α, IL-1β, and IL-6 were elevated in control animals. EETP treatment significantly reduced cytokine levels in a dose-dependent manner. Neuroinflammation enhances neuronal excitability and seizure propagation. Suppression of pro-inflammatory cytokines suggests that EETP exerts neuroprotective effects by reducing neuroinflammation.

Table 9. Effect of EETP on Pro-inflammatory Cytokines (TNF-α, IL-1β, IL-6)

Group	TNF-α (pg/mg protein)	IL-1β (pg/mg protein)	IL-6(pg/mg protein)
Vehicle	185 ± 8	142 ± 6	168 ± 7

Group	TNF-α (pg/mg protein)	IL-1β (pg/mg protein)	IL-6(pg/mg protein)
Standard	82 ±	65 ± 4***	75 ± 5***
EETP 100 mg/kg	160 ± 7*	125 ± 5*	145 ± 6*
EETP 200 mg/kg	120 ±	95 ± 4**	110 ± 5*
EETP 300 mg/kg	90 ±	70 ± 3***	80 ± 4*



Source: Researcher's Data Analysis,2025

Graph 7. Effect of Ethanolic Extract of Tridax procumbens Flowers on Pro-inflammatory Cytokines (TNF-α, IL-1β, and IL-6) in Experimental Animals

Levels of TNF-α, IL-1β, and IL-6 were significantly elevated in the vehicle-treated group, indicating enhanced neuroinflammatory response associated with seizure activity. Treatment with the ethanolic extract of *Tridax procumbens* flowers (EETP) significantly reduced cytokine levels in a dose-dependent manner. The highest dose (300 mg/kg) showed marked suppression of pro-inflammatory mediators comparable to the standard drug. Neuroinflammation enhances neuronal excitability and facilitates seizure propagation through activation of microglia and release of inflammatory mediators. Suppression of TNF-α, IL-1β, and IL-6

suggests that EETP exerts neuroprotective effects by attenuating inflammatory pathways, possibly through inhibition of NF-κB and related signaling mechanisms.

CONCLUSION

The present study was undertaken to scientifically evaluate the anticonvulsant and neuropharmacological potential of the ethanolic extract of *Tridax procumbens* flowers using well-established experimental models. The findings of the study clearly demonstrate that the extract possesses significant neuroprotective and therapeutic properties. Preliminary phytochemical screening confirmed the presence of important bioactive constituents such as flavonoids, phenolic compounds, alkaloids, tannins, saponins, terpenoids, and glycosides. These phytoconstituents are widely recognized for their antioxidant, anti-inflammatory, and neuromodulatory activities. Their combined presence provides a strong scientific basis for the pharmacological effects observed in this investigation.
In the MES-induced seizure model, the extract produced a dose-dependent reduction in the tonic extensor phase, indicating its ability to prevent seizure spread and stabilize neuronal membranes. In the PTZ-induced seizure model, the extract significantly increased seizure latency, suggesting possible enhancement of inhibitory GABAergic transmission and restoration of excitatory–inhibitory balance in the brain. These results confirm the anticonvulsant potential of the extract. Behavioural studies further revealed that the extract exhibited significant anxiolytic and antidepressant activities in models such as the Elevated Plus Maze, Forced Swim Test, and Tail Suspension Test. These findings indicate that the extract may modulate monoaminergic and GABAergic neurotransmitter systems, which are commonly involved in epilepsy-associated psychiatric comorbidities. The biochemical analysis demonstrated that the extract significantly reduced oxidative stress by decreasing MDA levels and enhancing endogenous antioxidant defenses such as GSH and SOD. Additionally, it reduced pro-inflammatory cytokines including TNF-α and IL-6, confirming its anti-inflammatory activity. Since oxidative stress and neuroinflammation play crucial roles in epileptogenesis and neuronal damage, these protective effects strongly support its therapeutic relevance. Acute toxicity studies indicated that the extract is safe up to 2000 mg/kg, suggesting a favourable safety profile.

Overall, the study establishes that the ethanolic extract of *Tridax procumbens* flowers exhibits multifunctional activity by targeting seizures, oxidative stress, inflammation, and associated neuropsychiatric disturbances. This multi-target action makes it a promising natural candidate for the management of epilepsy and related neurological disorders. Although the present findings are encouraging, further investigations are required to strengthen and expand these observations. Isolation and characterization of the specific active compounds responsible for the observed pharmacological effects should be undertaken using advanced analytical techniques such as HPLC, LC-MS, and NMR. Identification of bioactive markers will facilitate standardization and reproducibility. Detailed molecular studies are necessary to clarify the exact mechanisms involved, particularly regarding ion channel modulation, receptor interactions, and intracellular signalling pathways such as GABAergic, glutamatergic, NF-κB, and MAPK pathways. Long-term toxicity and chronic treatment studies should be conducted to evaluate the safety of prolonged administration, as epilepsy requires extended therapy. Advanced experimental models such as kindling and genetic models of epilepsy may further validate its anticonvulsant efficacy. Ultimately, well-designed clinical studies will be required to confirm its safety and therapeutic effectiveness in human subjects. Development of standardized formulations and dosage forms would be essential for translating these findings into clinical practice. Furthermore, due to its demonstrated antioxidant and anti-inflammatory properties, *Tridax procumbens* may also have potential applications in other neurodegenerative and stress-related disorders, opening new avenues for future research. In conclusion, the present study provides a strong experimental foundation for further scientific exploration of *Tridax procumbens* as a safe and effective plant-based therapeutic agent for epilepsy and associated neuropharmacological disorders.

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