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Neuroprotective And Anticonvulsant Effects Of Stigmasterol: A Preclinical Study On Modulation Of Oxidative Stress And Seizure Activity In PTZ-Induced Epileptic Rats

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Abstract: *Epilepsy is a chronic neurological disorder marked by recurrent and unprovoked seizures, often accompanied by neurocognitive and behavioral impairments. This study investigates the anticonvulsant and neuroprotective potential of stigmasterol, a naturally occurring plant-derived phytosterol, using a pentylenetetrazol (PTZ)-induced seizure model in Wistar albino rats. PTZ (75 mg/kg, i.p.) was administered to induce seizures, while stigmasterol was evaluated at two oral doses (4 mg/kg and 8 mg/kg) for its dose-dependent effects. Diazepam (5 mg/kg) was used as a standard reference drug. Seizure activity was assessed based on latency, duration, and severity. Behavioral outcomes were measured using the photoactometer test for motor activity, elevated plus maze for anxiety-like behavior, and Morris water maze for memory and spatial learning. In addition, oxidative stress markers such as superoxide dismutase (SOD), catalase, and lipid peroxidation (MDA levels) were evaluated. Stigmasterol administration significantly delayed seizure onset, reduced seizure severity, and improved both motor coordination and cognitive performance in PTZ-challenged rats. Biochemical analysis revealed a substantial restoration of antioxidant enzyme activity and reduced oxidative damage in brain tissues. Histopathological examination showed decreased neuronal degeneration, preservation of hippocampal structure, and reduced gliosis in stigmasterol-treated groups compared to PTZ controls. These findings suggest that stigmasterol exerts marked anticonvulsant and neuroprotective effects, likely through antioxidant and anti-inflammatory pathways. The results highlight stigmasterol's potential as a therapeutic agent in epilepsy management, especially for mitigating oxidative stress and preserving neuronal architecture.*

Keywords: *Epilepsy, stigmasterol, pentylenetetrazol, neuroprotection, oxidative stress, anticonvulsant*

1. INTRODUCTION

Antiepileptic drugs" are employed as medicines to manage symptoms. "Anti-seizure drugs," to distinguish from disease-modifying treatment with duration-dependent modulatory effect on the underlying epileptic disease that is on the susceptibility to generate spontaneous recurrent seizures and/or concurrent reduction treatment for comorbidity newer antiseizure drugs are the product of strict screening [1, 2, 3]. For patients, not much has actually changed over the last couple of years. Still not capable of verifying that which drug has side effects that will hamper quality of life or lessen dosing to less adequate for seizure control. Seizures are focal or generalized. Footnote from onset of seizure, abnormal neuronal (nerve cell) activity on both sides of brain leads in seizures [4, 5, and 6]. Hippocampal region ca1 which extremely high densities of NMDA receptors throughout the brain. Reduced cellular energy metabolism in ischemia and epilepsy leads to increased release and reduced uptake of glutamate and increased extracellular concentrations of k+ due to na+/k+-atpase stop control of the injury and death of the neurons and intracellular influx of ca2+ is by nmda receptor antagonists. Antiseizure therapy: treatment stopping or preventing recurrence or frequency of seizures. Anticomorbidity therapy treatment that is reducing or abolishing manifestations of many comorbidities of epilepsy, ex neurocognitive deficit, neuropsychiatric syndromes, and cardiovascular events [7, 8, and 9].

Epileptic Syndromes in Pediatrics

Benign familial neonatal epilepsy (BFNE) typically presents within the first week of life, characterized by focal clonic or tonic seizures. These infants are otherwise healthy, and no underlying cause is generally identified apart from the presence of seizures. Another age-specific condition, **West syndrome (WS)**, usually begins within the first year of life, with the highest onset between four to six months. This syndrome is marked by a unique EEG pattern known as hypsarrhythmia [10, 11, and 12].

Febrile seizure plus generally presents around the age of five. Children affected by this condition not only experience seizures during febrile episodes but may also suffer from afebrile seizures [13, 14]. The long-term prognosis remains uncertain, although some children do outgrow these episodes. **Dravet syndrome (DS)** is a severe, inherited form of epilepsy typically beginning before 18 months of age. It involves mutations in neuronal sodium channels and GABA receptors. DS is often drug-resistant, requiring multiple antiepileptic drugs (AEDs), which may lead to toxicity symptoms such as sedation, weakness, nausea, ataxia, and other side effects, though polypharmacy may sometimes achieve optimal seizure control [15, 16].

Landau-Kleffner syndrome (LKS) is a rare acquired epileptic condition characterized by the progressive loss of language skills in children who had previously developed speech normally. These children may exhibit epileptiform EEG changes and also show signs of behavioral regression, including features of autism. The language and social impairments observed in some autistic children may overlap with LKS, making differentiation difficult in the absence of seizures [17, 18].

Childhood absence epilepsy (CAE) typically appears between the ages of four and ten and is characterized by frequent, brief seizures lasting 5–20 seconds. These seizures often begin suddenly and can occur up to 100 times a day, frequently triggered by stress or sleep deprivation. Fortunately, the prognosis is favorable, with approximately 75% of children outgrowing the condition by adolescence [19, 20].

Juvenile myoclonic epilepsy (JME) is another age-dependent epilepsy syndrome, typically manifesting during adolescence. It includes generalized tonic-clonic seizures (GTCs), often accompanied by myoclonic jerks—sudden, brief muscle contractions that may cause individuals to drop or throw objects, particularly after waking. In about 90% of JME cases, GTC seizures are a defining feature [21, 22].

Focal epilepsy syndromes, including **temporal lobe epilepsy (TLE)**, often arise from structural brain abnormalities. One classic example is mesial temporal sclerosis, characterized by hippocampal scarring and often resistant to drug therapy but potentially treatable through surgical intervention. Seizure activity in TLE may manifest as altered consciousness, posturing, or behavioral changes, and diagnosis typically relies on EEG, neuroimaging, and neuropsychological assessments. In some cases, extrahippocampal lesions or genetic factors also contribute to seizure activity [23, 24].

Neonatal seizures occur early in life and may be the first sign of central nervous system dysfunction in newborns. These seizures often present as subtle behavioral changes, such as sucking motions, leg or arm pedaling, or eye deviation. Tonic posturing and deep side-to-side movements are also observed. The causes may range from focal issues like perinatal stroke to diffuse brain insults such as asphyxia, infections, or metabolic disturbances. Due to the immature and unmyelinated cortex in neonates, generalized epileptic discharges may not be well-sustained or evident on EEG, making diagnosis more challenging [25, 26, 27].

Neonatal epilepsy syndromes (NES) represent a particularly severe form, where clinical differentiation from GTC seizures is difficult. A key feature is the asynchronous jerking of limbs, unlike the symmetrical motor activity seen in classic generalized seizures. NES is often associated with a poor prognosis due to its complex pathophysiology and limited treatment response [28, 29].

2. MATERIAL AND METHODS

2.1 Inducing Agent (Pentylenetetrazole): Rats with threshold PTZ seizures serve as a model for absence seizures because of their varying therapeutic responses to medications used to treat absence seizures. To cause excitation, myoclonic jerks, and clonic seizures, 75 mg/kg of PTZ was used. There may also be a fatal tonic seizure on occasion. In at least 97% of the animals, seizures are induced [30, 31].

Thirty minutes after the test medication, PTZ is given. Following injection, the PTZ reaction takes place about five to ten minutes later. After administering medicines to the mice, they are monitored for 30 minutes. A raise in the length of seizure latency was recorded as a protective indicator and proves that test compound 15 possessed anticonvulsant activity [32].

2.2 Experimental design

Group 1: Control Group This group received normal saline solution administered orally. The dosage was adjusted according to the body weight of each animal. A total of 6 animals were included in this group.

Group 2: Disease Control Group Animals in this group were administered pentylenetetrazole (PTZ) at a dose of 75 mg/kg via intraperitoneal injection (i.p.) daily. This group included 6 animals.

Group 3: Standard Drug Group This group received a combination of diazepam (5 mg/kg) and normal saline (10 ml/kg), both administered orally on a daily basis. A total of 6 animals were used.

Group 4: Test Drug Group 1 Animals were treated with stigmasterol (4 mg/kg) and normal saline (2.5 ml/kg) administered orally each day, along with PTZ (75 mg/kg) administered intraperitoneally daily. This group also consisted of 6 animals.

Group 5: Test Drug Group 2 This group received stigmasterol (8 mg/kg) and normal saline (2.5 ml/kg) orally each day, along with PTZ (75 mg/kg) given intraperitoneally daily. A total of 6 animals were included in this group.

2.3 Tissue preparation: Three groups (n=6) were present. An hour following the injection, PTZ (75 mg/kg) was administered intraperitoneally to each animal in the groups. Following PTZ administration, the animals (control group not excluded) were decapitated, and their brains were removed and homogenized using a Remi motor RQT-1.2.7A in 0.9% NaCl when convulsions or seizures began.

2.4 Brain lipid peroxidation: 10% tissue was homogenized in order to prepare 2 milliliters of 30% trichloroacetic acid and 2 milliliters of 0.8% thiobarbituric acid (TBA) reagent. The aluminum foil-covered tube was then dipped in a shaky water bath at 80 degrees Celsius for 30 minutes, removed, and immersed in cold ice water before being centrifuged for 15 minutes at 3000xg. The absorbance of the supernatant at 535 nm at stp was measured and compared to a blank consisting of 2 milliliters of distilled water, 0.8% TBA, and 30% TCA. MDA content is calculated using the formula A × (V/E) × P [33, 34].

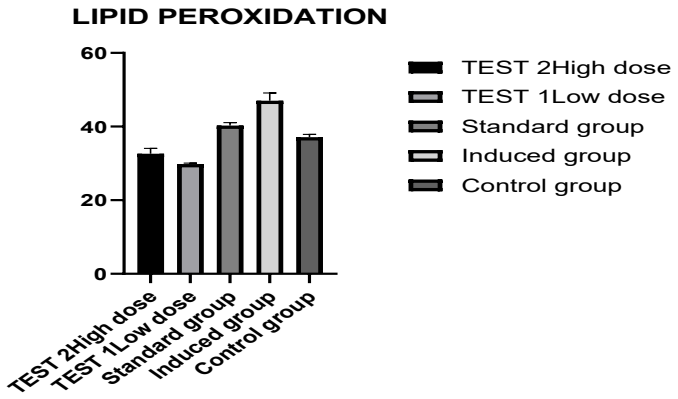

Fig.2 Lipid Peroxidation activity

2.5 Estimation of catalase: The 0.03 ml supernatant in 3 ml of phosphate buffer solution and H2O2 portion is used in the UV spectrophotometer to measure the amount of catalase activity. Catalase activity is expressed as a mole of decomposed H2O2/min/mg protein, and absorbance is measured at 240 nm for 2 minutes at intervals of 30 to 60 s [35, 36].

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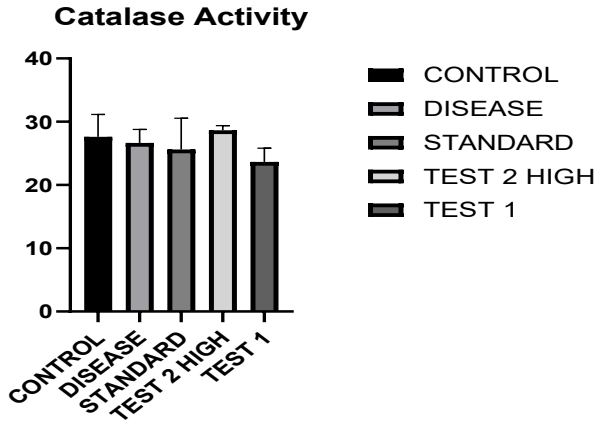


Fig 3 Catalase Activity

2.6 Superoxide dismutase (SOD): 0.5 ml of hydroxylamine hydrochloride, 0.1 ml of homogenate, and 2 ml of nitazo-blueterazolium [NTB] are combined, and using UV spectroscopy, the absorbance at 560 nm is measured for two minutes at 30 to 60 seconds, Units/mg are the units to be measured. PTZ significantly lowers SOD activity due to oxidative stress. Diazepam and Stigmasterol restore SOD levels, showing antioxidant effect [37, 38].

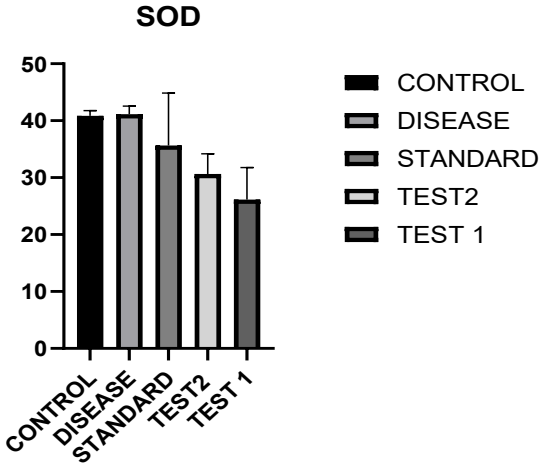
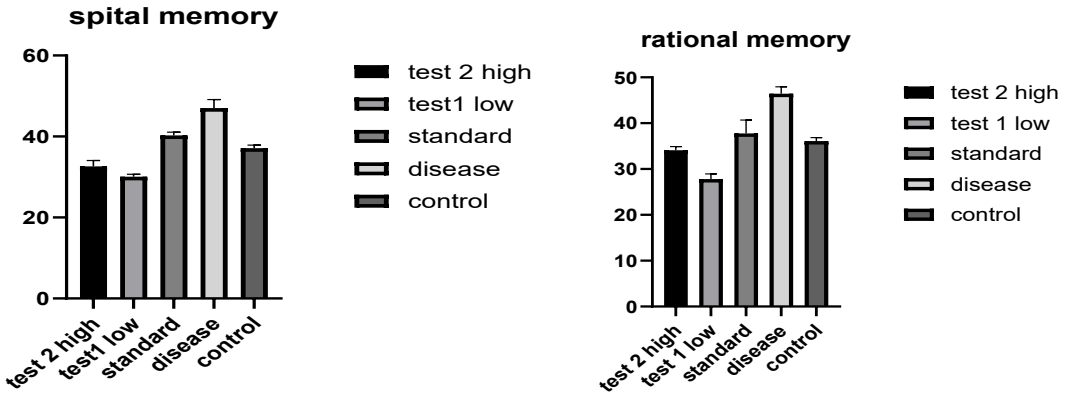


Fig 4 SOD activity

2.7 Behavioural Observations Motor Activity: Two groups of six mice each were created from the animals. One by one, the mice were put inside the photoactometer, and their regular movements were observed. The counter was shut off and the reading was taken five minutes later. The counter was reset to zero after the animal was taken out. All animals received the same treatment. After that, each animal was housed in the photoactometer separately for 0.5, 1, 2, 3, 4, and 5 hours, and a reading was taken. To make calculations easier, the findings were tallied and transformed into percentages. PTZ lowers motor activity as a result of seizure and CNS disturbance. Diazepam further suppresses activity due to sedative action. Stigmasterol exhibits recovery of motor activity, suggesting potential neuroprotective and anticonvulsant activity [39, 40].



2.8 Elevated Plus maze: This test is used to test common behavioral tests in neurotoxicity research to evaluate anxiety state in rats. The plus maze has two open arm and close arm, above the ground a rat is placed in middle and plus maze and freedom is given for movement. More the time spended in open arm the less anxius behaviour is observed, the test is used in determining how neurotoxic drug shows effect on anxiety behaviour PTZ disrupts memory → increased Stigmasterol enhances retention → considerably lesser. Used to measure cognitive effects of treatments in epilepsy models [41, 42].

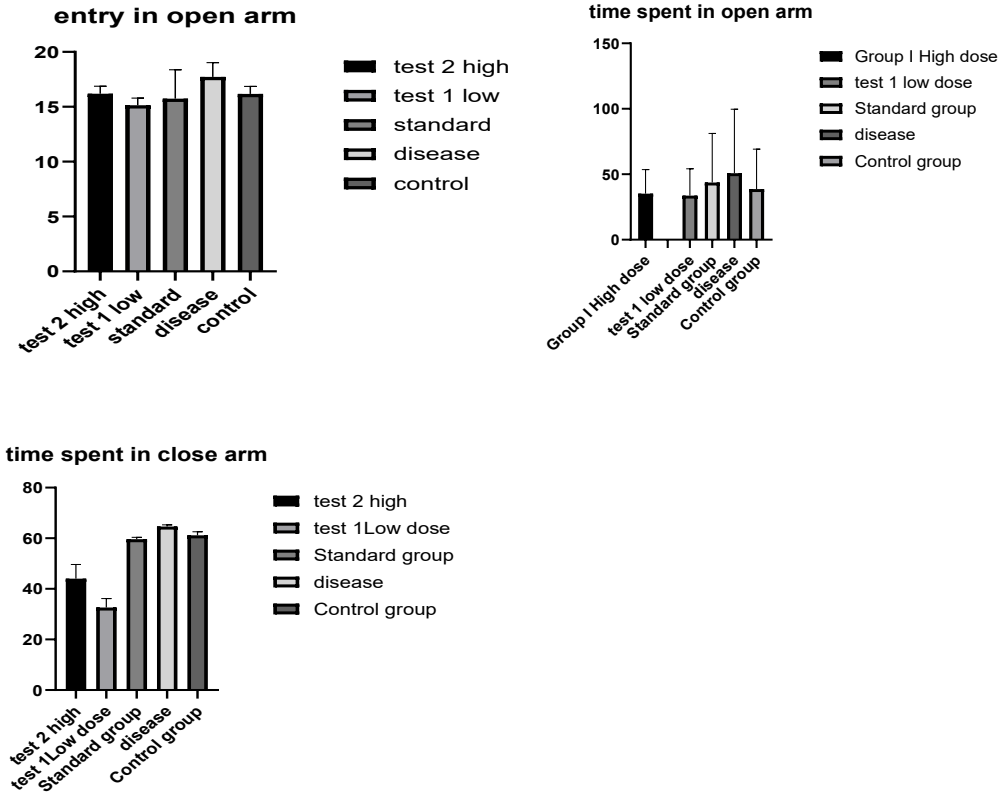


Fig 7

2.9 Morris Water Maze Test: It is employed to assess memory. 90-cm-diameter, water-filled circular pool. According to the protocol, every rat finished both the visible and hidden trials. In the visible trial, the rats

could see the platform because it was level with the water's surface. Each rat in the pool used sixty seconds after climbing on. The platform was dyed and submerged in water the next time the rats were tested covertly so they wouldn't be able to detect it. The test was replicated as in the visible trial. Treatment with stigmasterol plus diazepam improved memory (more crossings, more time in the target quadrant) and learning (lower latency). The results of stigmasterol and diazepam are comparable, suggesting that stigmasterol has neuroprotective or cognitive-enhancing properties [43, 44].

Fig 8 SPITAL MEMORY

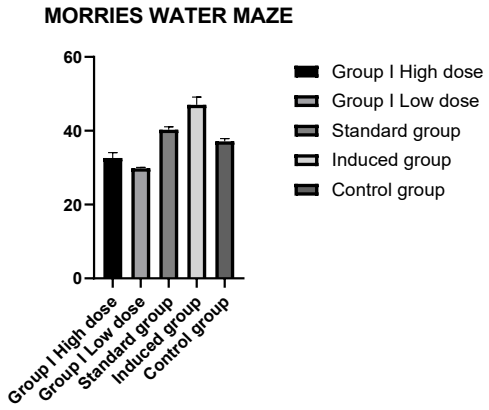
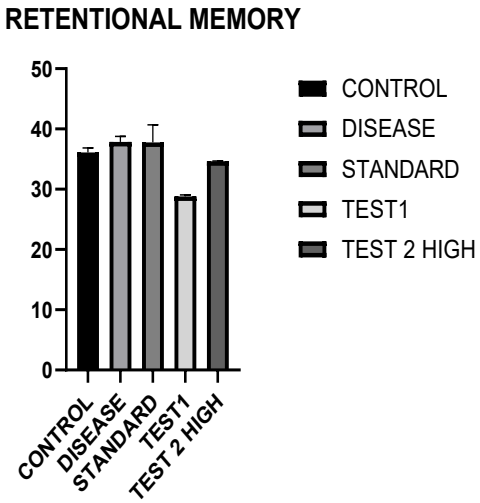


Fig 9 morris water maze test



3. HISTOPATHOLOGY BY MICROSCOPIC EVALUATION

The histopathological evaluation provided valuable insight into the protective effects of stigmasterol against PTZ-induced neuronal damage. In the disease control group that received only PTZ, extensive neuronal degeneration was evident. Key features included hippocampal disorganization, neuronal loss, gliosis, and cellular necrosis, particularly in the CA1 region of the hippocampus, which is highly vulnerable to excitotoxic damage. These changes are consistent with the neuropathological patterns commonly observed in chemically

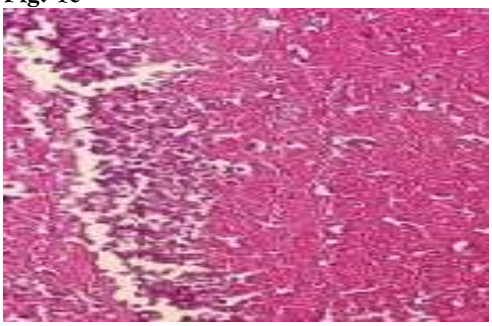
induced epilepsy models, where excessive glutamate activity and oxidative stress lead to widespread cellular injury [45, 46, 47].

In contrast, animals treated with stigmasterol, especially at the higher dose of 8 mg/kg, showed significant preservation of hippocampal architecture. The neuronal layers appeared intact, with minimal signs of cellular disruption or inflammatory infiltration. The reduction in gliosis and necrotic areas indicates that stigmasterol may help prevent glial cell over activation, which is often triggered during epileptic activity. Moreover, the lower presence of fragmented or pyknotic nuclei suggests reduced neuronal apoptosis in the test groups [48, 49].

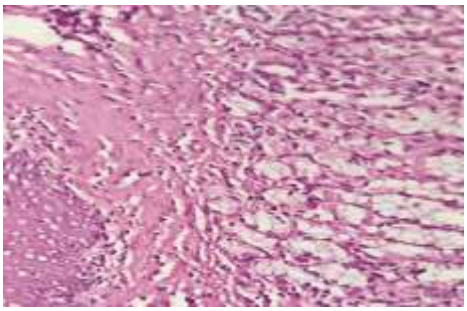
Compared to the standard drug diazepam, which also demonstrated a neuroprotective pattern, stigmasterol produced comparable preservation of brain tissue with fewer signs of toxicity. The extent of damage seen in the PTZ-alone group underscores the protective influence of stigmasterol, reinforcing its role in stabilizing neural membranes and possibly modulating excitatory neurotransmitter activity [50, 51].

Altogether, the histopathological outcomes align closely with the behavioral and biochemical findings in this study—supporting the conclusion that stigmasterol mitigates PTZ-induced brain injury by limiting oxidative stress, preserving neuronal structure, and maintaining hippocampal integrity [52].

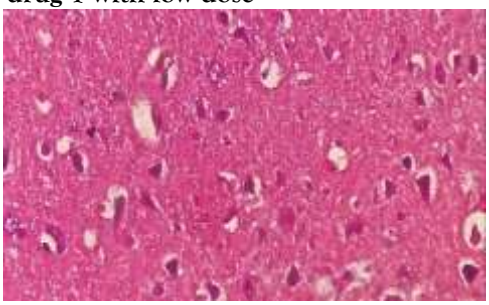
Fig. 10

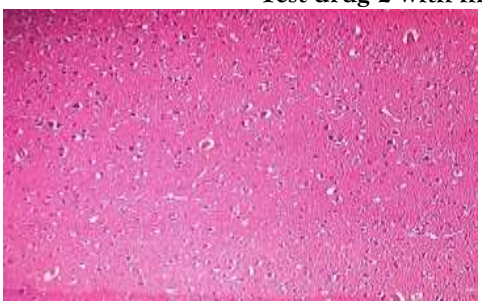


Test drug 1 with low dose



Test drug 2 with high dose





Standard Disease control

4. STATISTICAL ANALYSIS

For data reporting, the average mean of the standard of mean, or mean +- SEM, was utilized; in ANOVA, the difference in gp was compared to the T test. Where the statistical significance of the difference is determined by the p-value.

5. DISCUSSION

This study was conducted to evaluate the anticonvulsant and neuroprotective potential of stigmasterol in a PTZ-induced epilepsy model using Wistar albino rats. PTZ is widely recognized for inducing seizure activity by altering the excitatory-inhibitory balance in the brain, making it a valuable tool for studying potential

antiepileptic agents. As expected, animals treated with PTZ showed prominent signs of seizure activity, confirming successful induction of epileptic episodes. However, when treated with stigmasterol, both at 4 mg/kg and 8 mg/kg doses, a marked reduction in seizure severity and frequency was observed. This suggests that stigmasterol may offer protective effects against PTZ-induced neuroexcitation. Biochemical assays further supported these behavioural findings. PTZ administration significantly reduced superoxide dismutase (SOD) activity, reflecting increased oxidative stress in the brain. Treatment with stigmasterol restored SOD activity, indicating its antioxidant role. In the motor activity test, PTZ led to noticeable suppression of locomotion due to central nervous system (CNS) disturbance. Diazepam, while effective in controlling seizures, also showed sedative effects. In contrast, stigmasterol demonstrated a favorable recovery of motor activity, implying it may help preserve or restore normal CNS function without inducing sedation. The Elevated Plus Maze and Morris Water Maze tests were used to assess memory and cognitive functions. PTZ-treated rats showed signs of cognitive decline and memory impairment, consistent with previous findings that link epilepsy to neurocognitive deficits. Stigmasterol significantly improved performance in both behavioural paradigms, suggesting that it not only prevents seizures but may also offer cognitive protection and enhance memory retention. These effects were comparable to those seen with diazepam, indicating that stigmasterol has potential as a cognitive enhancer in epilepsy management. Histopathological analysis of brain tissues revealed that PTZ exposure led to structural damage in the hippocampus, including neuronal degeneration, gliosis, and signs of necrosis. In contrast, stigmasterol-treated groups exhibited more preserved brain architecture with reduced signs of damage. This provides histological evidence for stigmasterol's neuroprotective efficacy.

6. CONCLUSION

The findings of this study clearly suggest that stigmasterol possesses significant antiepileptic activity against PTZ-induced seizures in rats. Both tested doses—4 mg/kg and 8 mg/kg—produced protective effects, reducing seizure incidence and associated neurological deficits. In addition to its anticonvulsant properties, stigmasterol showed strong antioxidant and cognitive-protective effects, demonstrated by improved enzyme profiles, behavioural performance, and preserved brain histology. The neuroprotective effects observed in the stigmasterol-treated groups likely stem from its ability to counteract oxidative stress, reduce inflammation, and stabilize cell membranes. Compared to the PTZ-only group, stigmasterol helped maintain hippocampal integrity, reduced neuronal loss, and minimized cellular disorganization. These properties indicate its potential to limit or prevent long-term damage caused by epileptic seizures. In conclusion, stigmasterol shows promise as a natural compound with multiple therapeutic benefits in epilepsy. Its potential role as a neuroprotective and antiepileptic agent warrants further investigation and may contribute to future drug development targeting seizure disorders and related neurodegeneration.

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