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ORIGINAL ARTICLE

Neuroprotective Effect of *Nigella sativa* on Memory Dysfunction induced by Kindling Model

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ABSTRACT
This study examines the possible neuroprotective benefits of Nigella sativum, sometimes referred to as black seed, on rats' memory impairment brought on by the kindling paradigm. The neurological consequences of epilepsy and associated memory impairments have been replicated using the kindling model, a proven technique for causing epileptic convulsions. Through a series of behavioral tests, biochemical investigations, and histological assessments, Nigella sativum's neuroprotective potential was evaluated. According to our research, administering Nigella sativum extract considerably reduces the cognitive loss brought on by kindling and lessens the neuronal damage caused by seizures, suggesting that it may be used as a treatment for memory impairment brought on by epilepsy.
Keywords: *Neurodegenerative disorders, Nigella sativa, Thymoquinone, Oxidative stress, Neuroprotection, Alzheimer's disease.*

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INTRODUCTION

Neurodegenerative disorders are a group of and progressive conditions characterized by the gradual loss of structure and function of neurons, ultimately leading to cognitive and motor impairments. Some of the most prevalent neurodegenerative disorders include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) [1]. These disorders significantly impact quality of life, as they impair memory, cognition, and motor functions, leading to disability and dependency. The increasing prevalence of these disorders, particularly among the aging population, has become a major global health concern, necessitating the development of novel therapeutic strategies to manage and mitigate their progression.

Alzheimer's disease (AD) is the most common form of dementia, affecting millions of individuals worldwide. It is characterized by the accumulation of amyloid-beta plaques and neurofibrillary tangles, leading to synaptic dysfunction and neuronal loss in key brain regions such as the hippocampus [2]. Patients with AD experience progressive cognitive decline, memory impairment, and difficulties in reasoning and problem-solving. As the disease advances, individuals become increasingly dependent on caregivers, highlighting the socioeconomic burden of the disease.

Similarly, Parkinson's disease (PD) is marked by the loss of dopaminergic neurons in the substantia nigra, resulting in motor impairments such as bradykinesia, tremors, and rigidity [3]. Beyond motor symptoms, PD is also associated with cognitive decline, mood disorders, and autonomic dysfunction, making its management particularly challenging. Existing treatments, such as levodopa and dopamine agonists, provide symptomatic relief but do not halt disease progression.

Huntington's disease (HD) is a genetic neurodegenerative disorder that affects the basal ganglia, leading to movement disorders, cognitive decline, and psychiatric symptoms [4]. It is caused by a mutation in the huntingtin gene, which leads to the progressive degeneration of neurons. There is currently no cure for HD, and treatment options focus on managing symptoms rather than addressing the underlying pathology.

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder that primarily affects motor neurons, leading to progressive muscle weakness, paralysis, and respiratory failure [5]. The majority of ALS cases are sporadic, though some are linked to genetic mutations. Despite extensive research, treatment options remain limited, with riluzole and edaravone being the only FDA-approved drugs that offer modest benefits.

One of the key pathological mechanisms in neurodegenerative disorders is oxidative stress, which results from an imbalance between reactive oxygen species (ROS) production and antioxidant defense mechanisms. This oxidative damage leads to neuronal apoptosis and exacerbates disease progression [6]. Chronic neuroinflammation, mitochondrial dysfunction, and excitotoxicity further contribute to neuronal degeneration and cognitive decline [7]. Given the complex and multifactorial nature of neurodegeneration, there is a pressing need for therapeutic agents that can target multiple pathways simultaneously.

Role of *Nigella sativa* in neuroprotection

Nigella sativa, commonly known as black seed or black cumin, has been widely studied for its pharmacological properties, particularly its neuroprotective effects. The primary bioactive constituent of *Nigella sativa* is thymoquinone (TQ), which exhibits strong antioxidant, anti-inflammatory, and neuroprotective properties [8]. Traditional medicine has long utilized *Nigella sativa* for treating neurological disorders, and emerging scientific evidence supports its role in mitigating oxidative stress and neuroinflammation in neurodegenerative diseases [9].

Preclinical studies suggest that TQ modulates various signaling pathways involved in neuronal survival, including nuclear factor erythroid 2-related factor 2 (Nrf2), which plays a critical role in the cellular antioxidant response [10]. Additionally, TQ has been shown to reduce amyloid-beta aggregation, inhibit acetylcholinesterase activity, and improve cognitive function in animal models of AD [11]. These findings suggest that *Nigella sativa* may offer a novel approach to slowing disease progression and preserving cognitive function in AD patients.

In experimental models of PD, *Nigella sativa* has demonstrated neuroprotective effects by enhancing dopaminergic neuron survival and reducing oxidative damage [12]. The protective effects of TQ in PD are thought to be mediated through its ability to enhance mitochondrial function, reduce neuroinflammation, and modulate dopamine metabolism. Additionally, studies have reported that *Nigella sativa* extract reduces motor deficits in PD models, highlighting its potential as an adjunctive therapy for managing the disease [13].

Furthermore, studies on HD and ALS models indicate that TQ helps mitigate mitochondrial dysfunction and neuronal apoptosis, suggesting its potential as a broad-spectrum neuroprotective agent [14]. The ability of TQ to modulate multiple molecular pathways involved in neurodegeneration underscores its potential as a promising candidate for drug development in the treatment of neurodegenerative disorders.

Significance of the study

Despite advances in understanding neurodegenerative disorders, current therapeutic strategies remain largely symptomatic and fail to halt disease progression. The limited efficacy and adverse effects of conventional treatments underscore the need for alternative and adjunctive therapeutic approaches. Natural compounds with neuroprotective potential, such as *Nigella sativa*, offer a promising avenue for developing novel interventions against neurodegeneration [15].

This study aims to explore the neuroprotective effects of *Nigella sativa* in a kindling model of memory dysfunction, evaluating its impact on oxidative stress markers, inflammatory responses, and cognitive performance. By elucidating the molecular mechanisms underlying its neuroprotective properties, this research may contribute to the development of complementary strategies for managing neurodegenerative diseases.

LITERATURE REVIEW

MEMORY DYSFUNCTION AND EPILEPSY

Mechanisms of Memory Dysfunction in Epilepsy

Epilepsy is a neurological disorder characterized by recurrent seizures that significantly impact cognitive functions, particularly memory. Various cellular and molecular mechanisms contribute to epilepsy-induced memory dysfunction.

1. **Neurodegenerative Changes**
   - Recurrent seizures cause neurotoxic damage, especially in the hippocampus, due to excitotoxicity from excessive glutamate release, leading to synaptic dysfunction [16].

- Epileptic seizures impair hippocampal neurogenesis, reducing new neuron production and disrupting neural network integration [17].

2. **Altered Synaptic Plasticity**

- Epileptic activity disrupts synaptic plasticity, affecting learning and memory. Abnormalities in long-term potentiation (LTP) and long-term depression (LTD) alter neurotransmitter function [18].
- Chronic seizures cause synaptic reorganization, such as mossy fiber sprouting, leading to inappropriate neural connections [19].

3. **Neuroinflammation**

- Epilepsy triggers glial cell activation and increases pro-inflammatory cytokines, worsening neuronal damage and cognitive dysfunction [20].
- Blood-brain barrier (BBB) disruption due to inflammation allows toxic mediators to enter the brain, further impairing cognition [21].

4. **Neurotransmitter Imbalance**

- Imbalance between excitatory (glutamate) and inhibitory (GABA) neurotransmitters disrupts memory-related circuits [22].
- Alterations in NMDA and AMPA receptor expression impact synaptic plasticity and memory formation in epileptic conditions [23].

5. **Cognitive Impairments and Seizure Frequency**

- Frequent and prolonged seizures correlate with greater memory dysfunction and cognitive decline [24].

KINDLING MODEL AS A RESEARCH TOOL

Overview of the Kindling Model

The kindling model is a widely used preclinical tool for studying epilepsy and associated cognitive impairments. Developed in the 1960s, it involves repeated stimulation to induce seizures and replicate epilepsy-related memory dysfunction.

1. **Methodology**

- Seizures are induced in rodents via repeated electrical stimulation of the amygdala or hippocampus, leading to progressive seizure severity [25].
- Over time, animals exhibit spontaneous seizures, mimicking human epilepsy's chronic state [26].

2. **Application to Memory Research**

- Cognitive performance is assessed through behavioral tests like the Morris water maze and novel object recognition [27].
- The model helps investigate neurotransmitter changes, synaptic plasticity, and neuroinflammation in epilepsy-related memory dysfunction [28].

3. **Advantages and Limitations**

- Advantages: Controlled seizure induction, gradual epilepsy progression, and relevance to human temporal lobe epilepsy [29].
- Limitations: Does not fully replicate human epilepsy's complexity and cognitive variations [30].

MATERIAL AND METHODS

Animal

We purchased 24 male Wistar rats, each weighed around 200 to 250 grams, through the Central Animal House of the Bhopal Memorial Hospital. The rats were put inside of typical laboratory environment at a temperature of 22 ± 2°C including a 12-hour light/dark cycle. They got unrestricted consumption of meals and drinks as well. The experimental subjects had been accustomed for one week prior to the start of the trial. Institutional animal ethics committee gave its approval to all operations (Reference No: IAEC/research/23/2024).

Expeimental design

Four groups were randomly selected from among the rats:

1. **Control group (n = 6)**: No treatment, no kindling.
2. **Kindling group (n = 6)**: Seizures induced by the kindling protocol, no treatment.
3. **Kindling + *Nigella sativum* group (n = 6)**: Seizures induced by kindling, followed by treatment with *Nigella sativum* extract.
4. ***Nigella sativum* group (n = 6)**: No seizures, treated with *Nigella sativum* extract.

Kindling induction

Racine's description of the igniting process was followed (1972). To put it simply, ketamine In order to put the experimental subjects to sleep, intraperitoneal (i.p.) injections of xylazine (10 mg per kilogram of body and (75 mg per kilogram of body) were administered. The right hippocampal region was implanted

with a bipolar electrode (-3.5 mm for AP, ±2.5 mm for ML, and -3.0 mm for DV). Electric stimulation of the hippocampus (0.5 mA, 1-second duration, 20 Hz) was used to produce seizures once every 48 hours unless the mice had stage 5 convulsions (Racine's scale). Until stage 5 convulsions were regularly seen for at least three sessions in a row, the kindling process was continued.

***Nigella sativum* extract preparation**

We bought Nigella sativum seeds via a nearby herbal shop. The seeds were ground and macerated for 48 hours with 70% ethanol to create a powdered extract. A concentrated extract was then obtained by evaporating the ethanol at lower pressure. One day following the initial kindling session, the extract was diluted in regular saline and taken orally for 14 days at a dosage of 100 mg per kilogram.

Behavioral testing

To assess the cognitive function of the rats, the following behavioral tests were performed:

- **MWM, or Morris Water Maze Test:** The MWM test was used for assessing memory for location. Over the course of five days, the animals were taught to find a submerged platform. The distance traveled and the latency to locate the platform were noted.
- **Novel Object Recognition (NOR)**: This test measured the rats' preference for a new item over a known one in order to evaluate short-term memory. The amount of time spent examining the new and well-known items was noted.

Biochemical assays

The rats were put to death under anesthesia following the behavioral tests, and the tissues of the hippocampus were removed. The biochemical tests listed below were carried out:

- **Malondialdehyde (MDA) Assay**: The thiobarbituric acid reactive substances (TBARS) technique was used to measure MDA levels in order to evaluate lipid peroxidation.
- **Glutathione (GSH) Assay**: GSH levels within the hippocampus were measured in order to assess the antioxidant capability.
- **Acetylcholinesterase (AChE) Activity**: A colorimetric test was used to evaluate AChE activity since the enzyme is essential for memory as well as cognition.

RESULT

Acute oral toxicity study of methanolic extract of *nigella sativa*:

In an acute oral toxicity study, no mortality was observed within 24 hours following the administration of *Nigella sativa* at any of the tested doses. Behavioral assessments conducted during this period indicated that a pronounced sedative effect was noted only in the group receiving a dose of 1000 mg/kg body weight. This sedative effect was not observed at the lower doses administered.

Hindlimb extension (HLE) time and recovery time (RT) in the mes model treated with *nigella sativa*:

In the control group, all animals exhibited hindlimb extension (HLE), resulting in a 0% seizure protection rate (Table 1). The mean time for the onset of hindlimb extension in this group was found to be 3.0 ± 0.57 seconds. However, animals that were administered phenytoin did not show any signs of hindlimb extension, indicating that phenytoin was entirely (100%) effective in protecting against seizures. In comparison to the control group, both groups treated with *Nigella sativa* (400 mg/kg body weight and 600 mg/kg body weight) showed that only 50% of the rats experienced hindlimb extension, suggesting that the plant extract provided partial protection against seizures. There was no significant difference in the hindlimb extension times between the two *Nigella sativa* treated groups (400 mg/kg and 600 mg/kg body weight) when compared to the control group. Furthermore, animals in both *Nigella sativa* treatment groups demonstrated slightly prolonged recovery times relative to the control animals (Table 1).

Table 1: Hind limb extension, seizure protection rate and recovery time in MES model:

Groups	Percentage of animals showing HLE (%)	Seizure protectionrate (%)	HLE in seconds (M±SEM)	RT in seconds (M±SEM)
Control (1% CMC)	100.00%	0.00%	3.0 ± 0.57	189.0 ± 49.2
Phenytoin (300mg/kg)	0.00%	100.00%	0	0
TQ (400 mg/kg)	50.00%	50.00%	2.6 ± 0.33	226.0 ± 47.00
TQ (600 mg/kg)	50.00%	50.00%	4.0 ± 0.00	236.0 ± 28.35

Mortality rate, latency for myoclonic jerks, and generalized seizures in the PTZ model treated with *Nigella sativa*:

1. Mortality:

In the 1% CMC-treated control group, the mortality rate was observed to be 50%. In contrast, all other experimental groups that received treatment showed protective effects, resulting in a mortality rate of 0%.

2. Latency for the Onset of First Clonus:

The effects of sodium valproate and *Nigella sativa* on the latency of myoclonic jerks in a control group. Sodium valproate significantly extended this latency, while *Nigella sativa* at 400 mg/kg showed a delay that was not statistically significant. However, at 600 mg/kg, *Nigella sativa* significantly delayed the onset of the first clonus, indicating protective effects against PTZ-induced seizures. Despite this, sodium valproate remained more effective overall.

3. Latency for the Onset of Generalized Seizures:

a study on the anti-epileptic effects of sodium valproate and *Nigella sativa*. Sodium valproate significantly increased the latency for seizure onset, about 15 times longer than in the control group. While a lower dose of *Nigella sativa* (400 mg/kg) showed no significant effect, a higher dose (600 mg/kg) significantly delayed seizure onset, though still less effectively than sodium valproate. Statistical analysis confirmed the protective effect of the higher *Nigella sativa* dose against PTZ-induced seizures, highlighting its potential in epilepsy treatment.

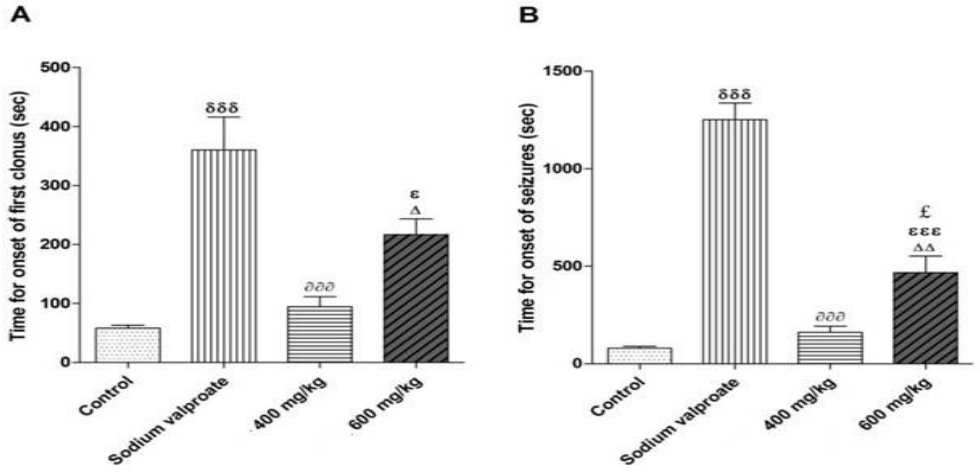

Figure 1: Effect of TQ extract on the latency for the onset of first clonus (A) and seizures (B) in rats. Both doses of TQ extract was effective in increasing the latency forthe onset of clonus and seizures, but the high dose of TQ extract had a significantly better effect comparing to the low dose. p<0.001, p <0.01, £p<0.05

***Electroencephalogram (EEG) studies**:*

Analysis of the Amplitude and Frequency of EEG Signals Recorded from the Rat Brain:

EEG findings in rats treated with PTZ, sodium valproate, and *Nigella sativa* extract. PTZ significantly increased EEG amplitude (from 3.5 μV to 70 μV) and decreased frequency (from 15 Hz to 6 Hz). Sodium valproate significantly reversed these effects, reducing amplitude and increasing frequency. *Nigella sativa* at both 400 mg/kg and 600 mg/kg doses also mitigated PTZ-induced changes, with the higher dose being more effective. While the 400 mg/kg dose had limited impact, the 600 mg/kg dose showed effects comparable to sodium valproate, suggesting *Nigella sativa's* potential as an antiepileptic treatment.

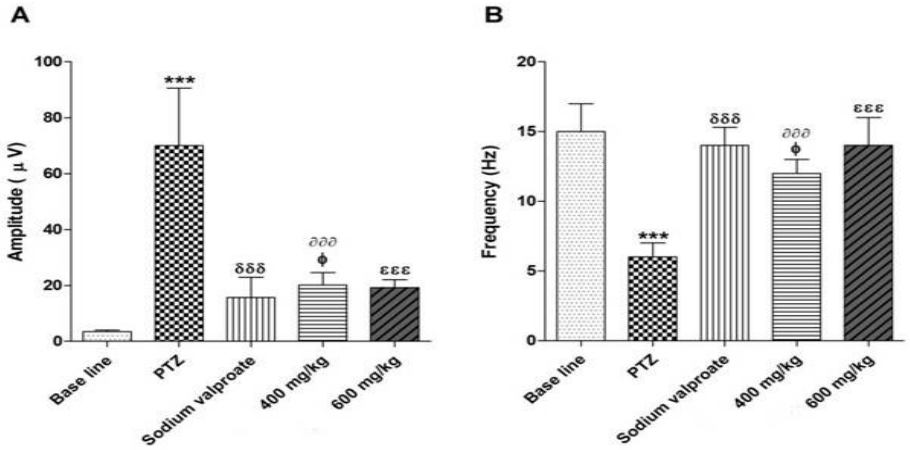

Figure 2 : Effect of TQ extract on EEG amplitude (A) and frequency (B). PTZ significantly elevated the EEG amplitude and decreased the frequency. These changesin the EEG were significantly prevented in rats pre-treated with MQ extracts. The high dose of TQ extract showed a slightly better effect on the EEG compared to thelow dose. $p<0.001$ and $p<0.05$.

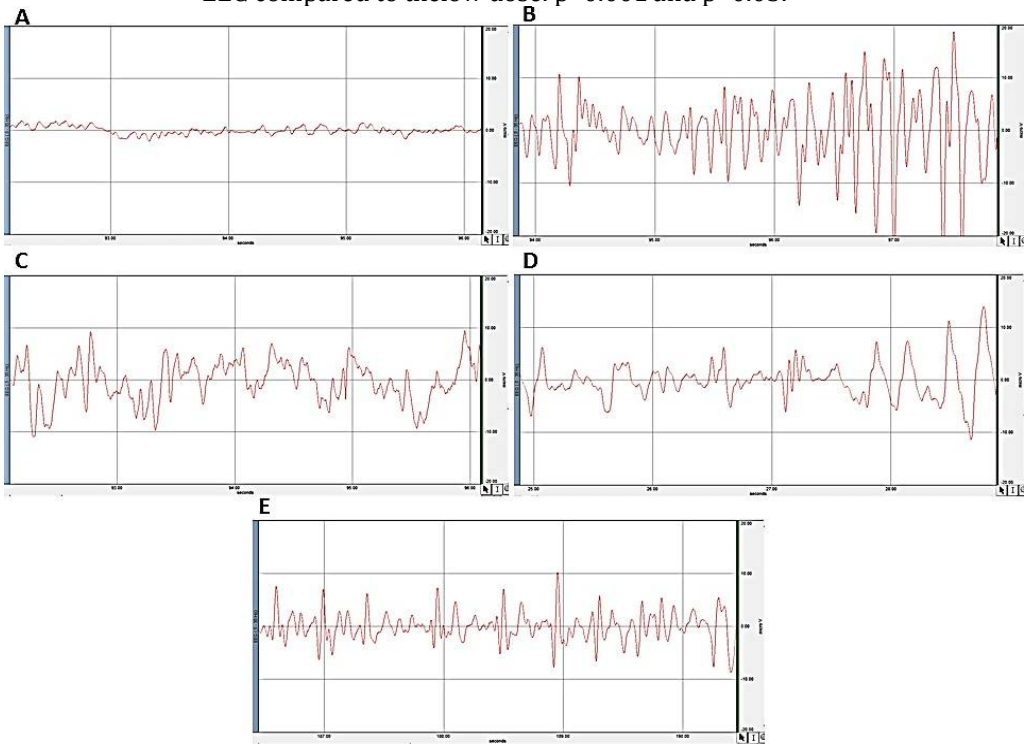

Figure 3 : Representative cortical EEG recording obtained from various groups: Control or base line EEG (A), after PTZ challenge (B),treated with sodium valproate after PTZ challenge (C), treated with TQ 400 mg kg^{-1} (D), treated with TQ 600 mg kg^{-1} after PTZ challenge (E). Note: Both doses of TQ extract significantly decreased the amplitude and increased the frequency of EEG when compared to PTZ challenge.

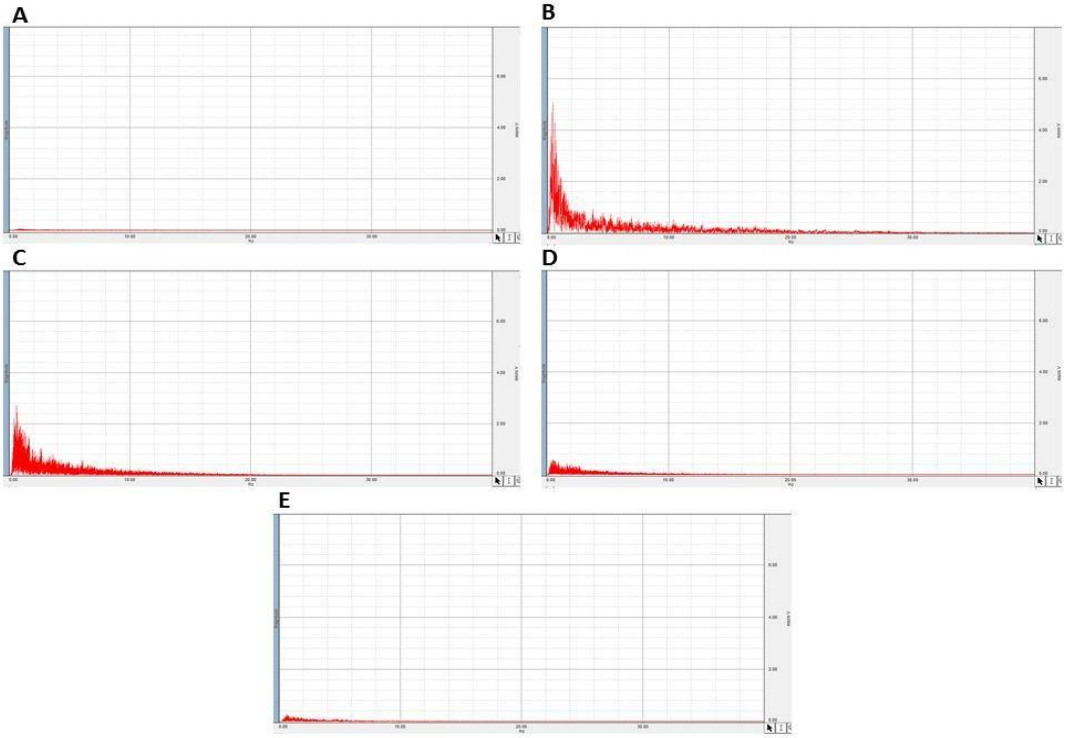

Figure 4: Respective power spectrum analysis from the recorded EEG. Control or base line EEG (A), after PTZ challenge (B), treatedwith sodium valproate after PTZ challenge (C), treated with TQ 400 mg kg-1 (D), treated with TQ 600 mg kg-1 after PTZ challenge (E).

Result of acute oral toxicity study of Nigella sativa (TQ):

- No mortality observed in control and groups treated with 10, 40, 100, and 400 mg/kg body weight.
- Symptoms like somnolence, reduced spontaneous motility, and sleep posture were observed.
- Higher doses (800 and 1000 mg/kg b.w.) caused mortality in three and four rats, respectively.
- **Median lethal dose (LD50) was determined as 800 mg/kg b.w.**

Action of TQ on eeg changes during PTZ kindling:

EEG Recorded at Different Time Points:

- **Day 1:** Baseline EEG recorded across groups.
- **Day 15:** Increased EEG amplitudes observed in PTZ-treated animals.
- **Day 30:** EEG amplitudes further increased, indicating epileptic activity.
- **Findings:**
  - PTZ significantly elevated EEG amplitude.
  - Sodium valproate and TQ pre-treatment significantly reduced EEG amplitude.
  - Higher TQ dose showed a better effect.

Effect of TQ on EEG amplitude in frontal cortex and hippocampus:

- **Day 1:** PTZ-treated group showed a 3-fold increase in EEG amplitude.
- **Day 15:** PTZ-induced seizures caused a 12-fold increase in amplitude.
  - TQ significantly reduced EEG amplitude.
- **Day 30:** PTZ-induced amplitude increased 18-fold.
  - TQ treatment significantly reduced EEG amplitude in a dose-dependent manner.

Effect of TQ on latency for seizure onset upon PTZ challenge:

- Ptz administration progressively reduced seizure latency.
- Groups treated with sodium valproate and TQ showed prolonged latency.
- High-dose TQ was most effective in delaying seizure onset.

Effect of TQ on seizure grade during PTZ kindling:

- PTZ-treated animals (Group III) experienced higher seizure grades.
- Sodium valproate and TQ significantly reduced seizure grades.
- **High-dose TQ was most effective in reducing seizure severity.**

Effect of TQ on neuropathological evaluation (hippocampal CA3 and MPFC regions):

- **Hematoxylin and Eosin Staining:**
    - Group III (untreated PTZ group) showed severe neuronal damage.
    - TQ-treated groups exhibited significantly reduced cell death.
- **Cresyl Violet Staining:**
    - Normal neuronal structure was preserved in TQ-treated groups, especially at high doses.

Effect of TQ on neuronal cell count in MPFC and hippocampal CA3 regions:

- **Neuronal count significantly decreased in PTZ-treated rats.**
- TQ treatment **restored neuronal count**, with the high dose showing the best effect.

Effect of TQ on lipid peroxidation (MDA concentration):

- **MDA levels increased in PTZ-treated animals.**
- TQ significantly reduced MDA concentration, with the **higher dose being most effective.**

Effect of TQ on spatial learning and memory (water maze test):

- PTZ-treated rats took longer to locate the platform.
- TQ-treated rats **showed significant improvement in spatial learning** over successive trials.

Effect of TQ on passive avoidance memory:

1. Entrance Latency Test:

- PTZ-treated rats showed **longer entrance latency**, indicating impaired learning.
- TQ significantly improved learning and memory.

2. Retention Latency Test (24h and 48h):

- **PTZ-treated rats had the shortest retention latency, indicating memory deficits.**
- TQ-treated rats exhibited significantly improved retention, especially at high doses.

DISCUSSION

Antiepileptic Properties of Nigella sativa

Epilepsy, a chronic neurological disorder, is caused by an imbalance between inhibitory and excitatory influences in the brain. The study explored the antiepileptic potential of *Nigella sativa* (N. sativa) using the maximal electroshock (MES) and pentylenetetrazol (PTZ) models. Results showed that N. sativa significantly reduced seizures, with a 50% reduction in hind limb extension (HLE) in MES-induced epileptic rats. The efficacy of N. sativa suggests that its active components may modulate voltage-dependent sodium (Na+) channels and NMDA receptors.

In the PTZ model, N. sativa extract increased seizure latency and decreased seizure severity, with higher doses (600 mg/kg) being more effective. PTZ-induced seizures occur due to impaired GABAA receptor inhibition, and N. sativa demonstrated a mechanism similar to sodium valproate in enhancing GABAA receptor function. The study suggests that N. sativa extract holds promise for epilepsy treatment due to its modulation of ion channels and neurotransmitters.

Antiepileptic Effects of 1-Triacontanol Cerotate (Thymoquinone - TQ)

Thymoquinone (TQ), a bioactive compound isolated from N. sativa, showed superior antiepileptic efficacy in the PTZ-kindling model. Compared to sodium valproate, TQ (80 mg/kg) more effectively reduced epileptiform activity and EEG abnormalities. The compound prolonged seizure onset latency and mitigated seizure severity in PTZ-kindled rats.

The antiepileptic mechanism of TQ involves modulation of neurotransmitter pathways, including inhibition of NMDA receptors, enhancement of GABAergic transmission, and regulation of ion channels. Additionally, TQ restored acetylcholinesterase (AChE) activity in PTZ-kindled rats, balancing excitatory and inhibitory neurotransmission.

Effect of Thymoquinone on Oxidative Stress in Epilepsy

Chronic epilepsy leads to oxidative stress, increasing reactive oxygen species (ROS) and lipid peroxidation in the frontal cortex and hippocampus. This study found that PTZ-kindled rats exhibited elevated oxidative stress markers, which were significantly reduced with TQ treatment. The antioxidant properties of N. sativa, particularly TQ, played a vital role in counteracting oxidative damage.

Impact of Thymoquinone on Memory and Learning

Chronic epilepsy impairs cognitive function, particularly in tasks requiring memory retention. In the passive avoidance test, PTZ-kindled rats showed significant memory deficits, but TQ-treated rats exhibited improved memory retention. Histological analysis revealed hippocampal neuroprotection in TQ-treated rats, suggesting its role in preventing epilepsy-induced cognitive decline.

Thymoquinone and Spatial Memory Improvement

The Morris Water Maze (MWM) test revealed that PTZ-induced epilepsy resulted in significant spatial memory deficits. Rats treated with TQ demonstrated improved learning and memory performance, with

higher doses yielding better outcomes. Histological analysis confirmed that TQ reduced hippocampal neuronal damage, further supporting its neuroprotective role.

CONCLUSION

Study on the neuroprotective effects of *Nigella sativa* and its active component, thymoquinone (TQ), in epilepsy management. It highlights the limitations of conventional antiepileptic drugs (AEDs), which provide symptomatic relief but fail to prevent disease progression and have adverse effects. The study demonstrates that TQ possesses significant anticonvulsant properties in a PTZ-induced epilepsy model, delaying seizure onset, reducing severity, and enhancing GABAergic transmission while inhibiting excitatory pathways.

Additionally, TQ exhibits strong antioxidant properties by reducing oxidative stress markers in the frontal cortex and hippocampus, which are crucial for preventing neuronal apoptosis and synaptic dysfunction. Behavioral assessments show that TQ improves spatial learning and memory retention in epilepsy-affected rats, further supported by histological evidence of reduced hippocampal damage.

The study suggests that *Nigella sativa* could serve as a complementary or alternative approach to epilepsy management, offering dual benefits—seizure control and cognitive protection. Despite promising results, further research is needed to clarify TQ's molecular mechanisms, optimize dosage, and conduct clinical trials to confirm its efficacy and safety. The integration of natural neuroprotective agents like *Nigella sativa* could improve epilepsy treatment outcomes while minimizing side effects associated with conventional drugs.

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