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The Effect of Hydromethanolic Extracts of *Mangifera Indica* Stem Bark and Leaf on Seizure Latency and Seizure Duration in Electroconvulsive Therapy-Induced Seizures in Male Wistar Rats

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ABSTRACT

Electroconvulsive therapy (ECT) remains an effective intervention for severe psychiatric disorders but is associated with adverse seizure effectss. Natural products with neuroprotective properties, such as *Mangifera indica*, may offer safer adjunctive benefits. *M. indica* is rich in bioactive compounds with antioxidant, anti-inflammatory, and neuromodulatory properties. Their role in modulating seizure latency and duration in ECT-induced seizures remains underexplored. Male Wistar rats (n = 6/group) were assigned to: Control, ECT only, ECT + diazepam (5 mg/kg), ECT + stem bark extract (MSBE; 300 or 600 mg/kg), or ECT + leaf extract (MLE; 300 or 600 mg/kg). Extracts were administered orally for four weeks. Seizure latency and duration were recorded weekly following ECT induction. ECT-only rats showed reduced seizure latency (week 4: 1.90 ± 0.65 s) and prolonged duration (35.00 ± 0.74 s). Diazepam significantly increased latency (4.40 ± 1.29 s) and reduced duration (16.20 ± 0.70 s). Both MSBE and MLE significantly improved latency (5.60 ± 0.55 s to 6.30 ± 0.57 s) and reduced duration (16.60 ± 0.48 s to 19.60 ± 0.37 s; $p < 0.05$ vs. ECT only), with MSBE 600 mg/kg producing the most pronounced effects. *M. indica* extracts demonstrated significant anticonvulsant activity in ECT-induced seizures, with efficacy comparable to diazepam. The effects may be linked to modulation of neuronal excitability and oxidative stress pathways. These findings suggest that *M. indica* stem bark and leaf extracts possess significant anticonvulsant potential in ECT-induced seizures, likely mediated by modulation of neuronal excitability.

KEYWORDS: *Mangifera indica*, electroconvulsive therapy, seizure latency, seizure duration, anticonvulsant, Electroconvulsive Therapy (ECT).

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INTRODUCTION

Electroconvulsive therapy (ECT) is an effective treatment for psychiatric disorders, such as major depression and schizophrenia. However, it is often associated with significant cognitive impairments such as retrograde amnesia and deficits in learning and memory (Semkovska & McLoughlin, 2022). These adverse effects limit its clinical acceptability, underscoring the need for adjunctive agents to protect or restore cognitive function.

Natural products with antioxidant, anti-inflammatory, and neuroprotective properties are being explored as alternative therapeutic interventions for seizure-related cognitive dysfunction (Bali et al., 2023). *Mangifera indica* (mango), widely known for its ethnomedicinal use, contains bioactive compounds such as mangiferin, quercetin, and gallic acid, which exhibit neuroprotective, anxiolytic, and antioxidant effects (Shah et al., 2022; Akinmoladun et al., 2023). Both the stem bark and leaves of *M. indica* have been implicated in memory enhancement and seizure modulation, though comparative studies in ECT-induced models are limited.

This study investigates the effects of hydromethanolic extracts of *M. indica* stem bark (MSBE) and leaf (MLE) on learning and memory performance in male Wistar rats

exposed to ECT-induced seizures, using the navigational maze and passive avoidance tests.

MATERIALS AND METHODS

Animals

42 adult male Wistar rats (150–200 g) were maintained under standard laboratory conditions with ad libitum access to food and water. All experimental procedures complied with international ethical guidelines for the care and use of laboratory animals.

Experimental Design

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

1. Control – no treatment.
2. ECT only – received ECT without treatment.
3. ECT + DZP – received diazepam (5mg/kg).
4. ECT + MSBE 300 mg/kg.
5. ECT + MSBE 600 mg/kg.
6. ECT + MLE 300 mg/kg.
7. ECT + MLE 600 mg/kg.

Treatments were administered orally once daily for four weeks. ECT was induced using standard transcranial current application twice weekly.

Assessments of Seizure Latency and Duration

- The time interval between the administration of the ECT and the onset of seizure, measured in seconds (s).
- The time interval between the onset of seizure and the termination of seizure, measured in seconds (s).

Statistical Analysis

Data were expressed as mean ± SEM and analyzed using ANOVA followed by Tukey's post hoc test. $p < 0.05$ was considered significant.

RESULTS

The results are organized according to the experimental objectives. All data were analyzed by one-way ANOVA followed by Tukey's post-hoc test, and significance was set at $p < 0.05$.

SEIZURE LATEENCY AND DURATION

Table 1: Effect of the extracts On Seizure Latency

	Duration (sec) week 1	Duration (sec) week 2	Duration (sec) week 3	Duration (sec) week 4
Control	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
ECT Only	1.50±0.50	1.60±0.42	1.80±0.45	1.90±0.65
ECT+DZP	3.10±0.82[a]	3.90±0.82[a]	4.20±0.57[a]	4.40±1.29[a]
ECT+MSBE 300	3.90±0.42[a]	4.80±0.76[a]	5.40±0.42[a]	5.60±0.55[a]
ECT+MSBE 600	4.90±0.42[a]	5.10±0.55[a]	5.90±0.65[a]	6.30±0.57[a]
ECT+MLE 300	4.70±0.76[a]	5.20±0.67[a]	5.50±0.50[a]	5.70±0.45[a]
ECT+MLE 600	4.90±0.55[a]	6.00±0.50[a]	5.80±0.45[a]	6.00±0.61[a]

Values with different superscript 'a' are significantly different from group 2 at p-value<0.05

Table 2: Effect of the extracts On Seizure Duration

	Duration (sec) week 1	Duration (sec) week 2	Duration (sec) week 3	Duration (sec) week 4
Control	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
ECT Only	50.20±7.17	34.30±1.45	35.40±1.05	35.00±0.74
ECT+DZP	34.90±6.34[a]	19.00±0.65[a]	17.60±0.58[a]	16.20±0.70[a]
ECT+MSBE 300	28.20±3.12[a]	27.90±0.37[a]	25.10±0.48[a]	19.60±0.37[a]

ECT+MSBE 600	28.60±2.58[a]	26.60±0.53[a]	22.30±0.46[a]	16.60±0.48[a]
ECT+MLE 300	29.10±2.18[a]	32.20±2.10[a]	24.10±0.58[a]	18.50±0.69[a]
ECT+MLE 600	30.70±2.40[a]	28.90±1.39[a]	23.30±0.51[a]	17.70±0.46[a]

Values with different superscript 'a' are significantly different from group 2 at p-value<0.05

Seizure Latency Test Results

Seizure latency refers to the duration between the administration of an epileptogenic stimulus and the onset of seizure activity. It serves as a crucial indicator of the brain's susceptibility to seizure induction and is inversely related to seizure severity—shorter latencies typically reflect higher neural excitability and lower seizure thresholds (Yuen et al., 2022).

In this study, the control group (non-ECT) showed no seizure activity throughout the four weeks (0.00 ± 0.00 seconds), as expected, indicating the absence of external seizure induction and the intact neurophysiological state of the animals. In contrast, the ECT-only group exhibited significantly shortened seizure latency across all weeks (Week 1: 1.50 ± 0.50 sec; Week 4: 1.90 ± 0.65 sec), highlighting the pro-convulsant and excitotoxic impact of repeated electroconvulsive shocks (Rocchi et al., 2023). These findings align with existing literature demonstrating that repeated ECT reduces seizure threshold over time by enhancing glutamatergic neurotransmission and oxidative stress, thereby promoting hyperexcitability in neuronal circuits (Kumar et al., 2020; Inozemtsev et al., 2021).

The administration of diazepam, a well-established benzodiazepine with anticonvulsant properties, significantly prolonged seizure latency compared to the ECT-only group (Week 4: 4.40 ± 1.29 sec), confirming its effectiveness in raising seizure threshold through potentiation of GABAergic inhibition (Rogawski et al., 2020).

Interestingly, rats treated with **hydromethanolic extracts of *Mangifera indica* stem bark (MSBE)** and **leaf extract (MLE)**, at both 300 mg/kg and 600 mg/kg, demonstrated a dose-dependent and time-dependent increase in seizure latency. Notably, the **MSBE 600 mg/kg** group showed the highest latency by Week 4 (6.30 ± 0.57 sec), followed closely by the **MLE 600 mg/kg** group (6.00 ± 0.61 sec). This prolonged latency indicates a protective, anticonvulsant-like effect of both extracts, suggesting their potential in modulating seizure susceptibility in ECT-induced models.

The observed effects may be attributed to the phytochemical constituents of *Mangifera indica*, particularly **polyphenols, flavonoids, mangiferin**, and **tannins**, which are known to exert **antioxidant, anti-inflammatory**, and **neuroprotective** actions (Akinmoladun et al., 2021; Jaiswal et al., 2023). Mangiferin, a xanthonoid predominantly found in the stem bark and leaves, has been shown to modulate the balance between excitatory and inhibitory neurotransmission by **enhancing GABAergic activity** and **suppressing glutamate-induced excitotoxicity** (Silva et al., 2021).

Furthermore, the extended seizure latency observed in extract-treated groups may also reflect **reduced oxidative stress and improved mitochondrial function**, both of which are critical in maintaining neuronal stability and preventing seizure propagation (Zhang et al., 2023). Chronic ECT has been associated with increased reactive oxygen species (ROS) production and lipid peroxidation, leading to neuronal damage (Ali et al., 2022). The antioxidant defense capacity of *Mangifera indica* extracts could counteract such oxidative insults, thereby stabilizing neuronal membranes and increasing seizure threshold.

Comparatively, while diazepam showed a consistent anticonvulsant effect, the **higher doses of both MSBE and MLE outperformed diazepam** in seizure latency by Week 4. This suggests that the phytochemicals in the plant extracts might exert **multimodal neuroprotective effects**, beyond GABAergic potentiation, possibly involving modulation of ion channels, anti-inflammatory pathways, and neurotrophic signaling cascades (Chauhan et al., 2020; Ojo et al., 2023).

Taken together, these findings support the hypothesis that *Mangifera indica* stem bark and leaf extracts mitigate ECT-induced seizure susceptibility in rats, likely through **antioxidant mechanisms**, **GABAergic modulation**, and **inhibition of excitotoxic pathways**. The dose-dependent efficacy further suggests therapeutic potential, particularly for MSBE at 600 mg/kg.

Seizure Duration Test Results

Electroconvulsive therapy (ECT) is a widely used therapeutic intervention for severe psychiatric disorders, particularly treatment-resistant depression. However, it is associated with adverse neurological outcomes, including prolonged seizure duration and cognitive deficits (Obembe et al., 2022). Seizure duration is a key parameter used to evaluate the severity of ECT-induced convulsions and to assess the anticonvulsant potential of therapeutic agents (Dhir & Naidu, 2007).

In the present study, rats subjected to ECT alone exhibited significantly prolonged seizure durations across the four-week treatment period, with values ranging from **50.20±7.17 seconds in week 1 to 35.00±0.74 seconds in week 4**, indicating sustained excitability of the neuronal circuits following repeated ECT administration. This observation aligns with prior studies suggesting that repeated

electroconvulsive shocks can exacerbate seizure duration by lowering the seizure threshold and enhancing neural excitability (Duman et al., 2023; Sharma et al., 2019).

Administration of **diazepam (ECT+DZP)** markedly reduced the seizure duration across the weeks (**34.90±6.34 to 16.20±0.70 seconds**), consistent with its well-established anticonvulsant and GABA_A receptor potentiating effects (Treiman, 2001). This serves as a pharmacological benchmark to evaluate the efficacy of the plant extracts used in this study.

The groups treated with **hydromethanolic extracts of *Mangifera indica* stem bark extract (MSBE)** and **leaf extract (MLE)** showed a **dose-dependent and time-dependent reduction** in seizure duration when compared with the ECT-only group. Notably, the **ECT+MSBE 600 mg/kg group** exhibited a significant reduction from **28.60±2.58 seconds (week 1)** to **16.60±0.48 seconds (week 4)**, nearly paralleling the effects observed with diazepam. Similarly, **ECT+MLE 600 mg/kg** resulted in a reduction to **17.70±0.46 seconds in week 4**, confirming the anticonvulsant potential of the extract.

These findings support the hypothesis that *Mangifera indica* possesses neuroprotective and anticonvulsant properties. Phytochemical analyses of the plant have revealed the presence of bioactive compounds such as **mangiferin, quercetin, catechins, and gallic acid**, which are known to modulate oxidative stress, inhibit neuronal hyperexcitability, and enhance GABAergic transmission (Pardo-Andreu et al., 2020; Kabir et al., 2023). These mechanisms may underlie the observed reduction in seizure duration in the MSBE and MLE-treated groups.

In particular, **mangiferin**, a prominent xanthonoid in *Mangifera indica*, has been reported to inhibit seizure activity via modulation of GABAergic and glutamatergic neurotransmission, suppression of pro-inflammatory cytokines, and enhancement of antioxidant enzyme activities in the brain (Soman et al., 2021). This supports its potential as a complementary therapy in seizure disorders and in mitigating ECT-induced neurotoxicity.

Furthermore, the extracts' effects on seizure duration suggest a possible **synergistic action between antioxidative and neurotransmitter-modulating mechanisms**, providing sustained neuronal stability across the treatment period. The **dose-dependent reduction in seizure duration** also emphasizes the therapeutic window of *Mangifera indica* extracts, particularly at higher doses, in attenuating ECT-induced hyperexcitability.

In summary, the significant reduction in seizure duration observed in MSBE and MLE-treated groups, especially at **600 mg/kg**, highlights the efficacy of *Mangifera indica* in modulating seizure parameters, possibly via its **antioxidant, anti-inflammatory, and GABAergic enhancing properties**. These findings underscore the potential of this plant as a **neuroprotective agent** in ECT-related seizure models.

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