

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

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ABSTRACT

Electroconvulsive therapy (ECT), although therapeutically efficacious in severe neuropsychiatric disorders, induces profound neurochemical remodeling within limbic circuits. The present study investigated the modulatory effects of *Mangifera indica* stem bark extract (MSBE) and leaf extract (MLE) on key neurochemical indices in an ECT-induced seizure model. Acetylcholinesterase (AChE), dopamine (DOPA), γ -aminobutyric acid (GABA), and brain-derived neurotrophic factor (BDNF) concentrations were quantified and compared with diazepam (DZP) treatment. ECT alone produced marked elevations in AChE (12.46 ± 0.28 ng/ml), DOPA (12.20 ± 0.86 ng/ml), GABA (6.38 ± 0.20 ng/ml), and BDNF (176.80 ± 6.46 ng/ml) relative to control (6.53 ± 0.09 ; 5.00 ± 0.55 ; 1.80 ± 0.21 ; 114.00 ± 2.28 ng/ml, respectively), indicating enhanced cholinergic turnover, dopaminergic activation, inhibitory neurotransmission, and neurotrophic signaling. DZP co-administration attenuated AChE activity (9.03 ± 0.60 ng/ml) and partially normalized BDNF (125.60 ± 3.31 ng/ml), while sustaining elevated DOPA levels (13.40 ± 0.51 ng/ml). Both MSBE and MLE demonstrated dose-dependent neuromodulatory effects. MSBE (300 and 600 mg/kg) reduced AChE relative to ECT alone (10.53 ± 0.31 and 10.35 ± 0.60 ng/ml, respectively) and moderated GABA concentrations (3.78 ± 0.11 and 3.00 ± 0.04 ng/ml), while maintaining elevated yet controlled BDNF levels (146.00 ± 2.35 and 136.80 ± 2.85 ng/ml). Similarly, MLE (300 and 600 mg/kg) attenuated excessive inhibitory tone (4.42 ± 0.12 and 3.40 ± 0.07 ng/ml GABA) and sustained neurotrophic upregulation (148.40 ± 3.23 and 146.80 ± 3.29 ng/ml BDNF). Notably, both extracts preserved dopaminergic activation without the exaggerated cholinergic and GABAergic elevations observed in the ECT-only group. Collectively, these findings indicate that *Mangifera indica* stem bark and leaf extracts exert stabilizing effects on excitatory–inhibitory neurotransmitter balance and neurotrophic signaling following ECT-induced seizures. Their ability to recalibrate cholinergic, dopaminergic, and GABAergic indices while sustaining adaptive BDNF upregulation suggests potential neuroprotective and homeostatic properties, supporting further mechanistic and translational investigations.

KEYWORDS: *Mangifera indica*, electroconvulsive therapy, seizures, neurotransmitters, BDNF, Diazepam, Wistar rats

ARTICLE DETAILS

Published On:
28 February 2026

Available on:
<https://ijpbms.com/>

INTRODUCTION

Electroconvulsive therapy (ECT) is a highly effective treatment for severe psychiatric disorders, including major depression and schizophrenia, but 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

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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 (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 neurotransmitter levels in male Wistar rats exposed to ECT-induced seizures.

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.

RESULTS

Table 1: Effect of the extracts On Acetylcholinesterase, Dopamine, GABA, And BDNF Levels Across Groups

	AChE (ng/ml)	DOPA (ng/ml)	GABA (ng/ml)	BDNF (ng/ml)
Control	6.53±0.09 ^a	5.00±0.55 ^a	1.80±0.21 ^b	114.00±2.28
ECT only	12.46±0.28 ^b	12.20±0.86 ^b	6.38±0.20 ^a	176.80±6.46 ^a
ECT+DZP	9.03±0.60 ^c	13.40±0.51 ^c	3.14±0.09 ^{a,b}	125.60±3.31 ^{a,b}
ECT+MSBE300	10.53±0.31 ^a	13.80±0.66 ^a	3.78±0.11 ^{a,b}	146.00±2.35 ^{a,b,c}
ECT+MSBE600	10.35±0.60 ^a	10.60±0.51 ^a	3.00±0.04 ^a	136.80±2.85 ^{a,b}
ECT+MLE 300	10.78±0.52 ^a	15.00±0.71 ^a	4.42±0.12 ^{a,b}	148.40±3.23 ^{a,b,c}
ECT+MLE 600	10.31±0.45	10.80±0.58	3.40±0.07 ^{a,b}	146.80±3.29 ^{a,b,c}

Values with different superscripts (a, b, c) are significantly different from group 1, 2, and 3, respectively, at p-value<0.05 The study revealed significant alterations in key neurochemical markers—acetylcholinesterase (AChE), dopamine (DOPA), gamma-aminobutyric acid (GABA), and brain-derived neurotrophic factor (BDNF)—following electroconvulsive therapy (ECT)-induced seizures, and highlighted the modulatory effects of *Mangifera indica* stem bark extract (MSBE) and leaf extract (MLE) at 300 mg/kg and 600 mg/kg.

Acetylcholinesterase (AChE) Activity

In the control group, AChE levels were within normal physiological limits (6.53±0.09 ng/ml), while ECT-only rats showed a significant increase (12.46±0.28 ng/ml, p<0.05). This elevation aligns with findings that excessive cholinergic breakdown impairs cognitive performance, particularly learning and memory (Joca et al., 2021). ECT appears to dysregulate cholinergic neurotransmission, contributing to cognitive deficits.

Treatment with diazepam (ECT+DZP) and *Mangifera indica* extracts led to a dose-dependent reduction in AChE levels,

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.

Neurotransmitter Assay: Assay Kits for measuring neurotransmitters were used

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.

although levels remained elevated compared to the control. Notably, MLE600 (10.31±0.45 ng/ml) showed a more pronounced reduction than MSBE300 (10.53±0.31 ng/ml), suggesting improved cholinergic modulation. The ability of *Mangifera indica* phytoconstituents to inhibit AChE activity has been previously documented, attributed to their rich phenolic and flavonoid content (Ogundele et al., 2022; Aluko et al., 2021).

Dopamine (DOPA) Concentrations

Dopamine, a critical catecholamine in motor and cognitive processes, was significantly elevated in the ECT-only group (12.20±0.86 ng/ml) compared to the control (5.00±0.55 ng/ml). This hyperdopaminergic state has been linked to seizure activity and may contribute to psychomotor dysfunction (Arias et al., 2020). The increase might reflect a compensatory response to ECT-induced oxidative and excitatory stress.

Administration of MSBE and MLE further elevated DOPA levels in most groups (e.g., MLE300: 15.00±0.71 ng/ml), suggesting dopaminergic enhancement. While this might seem counterintuitive, certain flavonoids in *M. indica* may

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support dopaminergic neuron survival and function, modulating synaptic plasticity (de Oliveira et al., 2021). This dopaminergic boost, if regulated, could support motivation and learning behaviors post-ECT.

GABA Levels

GABA, the principal inhibitory neurotransmitter, was markedly elevated in the ECT-only group (6.38±0.20 ng/ml), which may represent a neuroprotective compensatory mechanism aimed at limiting hyperexcitability (Huang et al., 2022). However, excessive GABAergic activity can blunt cognitive and motor responsiveness.

Interestingly, MSBE and MLE treatments lowered GABA concentrations closer to baseline levels (e.g., MLE600: 3.40±0.07 ng/ml), suggesting a rebalancing of excitatory-inhibitory tone. This homeostatic regulation aligns with previous findings that flavonoid-rich extracts can modulate GABAergic signaling and reduce seizure severity while preserving cognitive function (Chen et al., 2023; Adewumi et al., 2021).

Brain-Derived Neurotrophic Factor (BDNF)

BDNF is crucial for synaptic plasticity, neuronal survival, and cognitive integrity. The study revealed a significant upregulation of BDNF in the ECT-only group (176.80±6.46 ng/ml) compared to control (114.00±2.28 ng/ml). Although BDNF upregulation is generally considered neuroprotective,

its aberrant elevation post-ECT has been associated with maladaptive plasticity and excitatory stress (Zhao et al., 2022).

Treatment with diazepam and Mangifera indica extracts normalized BDNF levels. MLE300 (148.40±3.23 ng/ml) and MSBE300 (146.00±2.35 ng/ml) significantly reduced the exaggerated BDNF response while maintaining values above the control, indicating potential neuroprotective remodeling. The neurotrophic-modulatory effects of Mangifera indica are likely due to bioactive polyphenols that enhance BDNF transcription under stress conditions (Ojo et al., 2021; Shah et al., 2023).

The neuroprotective effects observed may be attributed to **quercetin, mangiferin, and catechins** found in Mangifera indica, which have known antioxidant, anti-inflammatory, and neurotransmitter-regulating properties (Akinmoladun et al., 2020; Ogundele et al., 2022).

These findings underscore the potential of Mangifera indica extracts as adjunctive agents in managing ECT-induced cognitive and motor dysfunctions. By modulating cholinergic, dopaminergic, GABAergic, and neurotrophic signaling pathways, these extracts show promise in restoring neurochemical homeostasis disrupted by seizure-inducing treatments.

Table 2: Summary of the effects of neurotransmitters and BDNF

Group	AChE	DOPA	GABA	BDNF	Interpretation
Control	Low	Low	Low	Baseline	Healthy status
ECT Only	High ↑↑	High ↑↑	High ↑↑	High ↑↑	ECT-induced stress, cholinergic breakdown, neuro-adaptation
ECT + DZP	↓ AChE	High	Mid	Normal	Calming, protective, mild inhibition of BDNF
ECT + MSBE 300	Moderate AChE	High ↑	Mid	↑ BDNF	Neuroprotective with enhanced BDNF
ECT + MSBE 600	Moderate AChE	Normal-high	Mid	↑ BDNF	Dose-dependent neuroprotection
ECT + MLE 300	Moderate AChE	Highest ↑↑	Mid-high	↑ BDNF	Enhanced plasticity & dopaminergic tone
ECT + MLE 600	Moderate AChE	Normal-high	Mid	↑ BDNF	Strong neurotrophic support

CONCLUSION

Electroconvulsive therapy induced marked alterations in cholinergic, dopaminergic, GABAergic, and neurotrophic parameters, reflecting significant neurochemical remodeling following seizure activity. Treatment with Mangifera indica stem bark and leaf extracts attenuated the exaggerated neurotransmitter changes observed in the ECT-only group, while maintaining adaptive BDNF upregulation. These findings suggest that both extracts exert modulatory and potentially neuroprotective effects by restoring excitatory–inhibitory balance and stabilizing neurotrophic signaling. Further mechanistic and translational studies are warranted to

elucidate their therapeutic relevance in seizure-associated and neuropsychiatric conditions.

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