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Neuropharmacological activity of Hydroethanol Leaf Extract of Carica papaya Linn in Swiss Albino Mice

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ABSTRACT

Background: One of new medicinal plants that have gained popularity in neurological disorders is *Carica papaya*. In Nigeria, the leaf extract of *C. papaya,* either as water decoction or soaked in ethanol, is claimed to be effective in convulsions, sleep disturbances and other neurological conditions. This study investigated the anticonvulsant, anxiolytic, antidepressant, muscle relaxant and sedative activities of the hydroethanol leaf extract of *Carica papaya* (HELC).

Methods: Different groups of mice received HECL (100 or 200 mg/kg, *p.o.)*, diazepam (3 mg/kg, *i.m.*) or phenobarbitone (40 mg/kg, *i.p.*) 30 min. before seizure induction with strychnine (4 mg/kg, *i.m.*) or picrotoxin (4 mg/kg, *i.p.*), and seizure latency and duration were measured. For each of Y-maze, chimney, traction, forced swimming and thiopentone-induced sleeping time or forced swimming tests, mice received oral HECL (100 and 200 mg/kg, *p.o.*) or diazepam (1 mg/kg, *i.p.*) 30 min. before subjecting them to the test. Data were analysed via one-way ANOVA, with significance at $P < 0.05$.

Results: HECL significantly and dose-dependently increased latency to strychnine- and picrotoxin-induced seizures, with the 200 mg/kg dose achieving efficacy comparable to diazepam ($P < 0.05$). HECL, like diazepam caused significant effect on Y-maze performance and chimney tests, whereas there were significant effects in the traction and forced swimming tests. Moreover, HECL did not cause a potentiation of thiopentone-induced sleeping time compared to control.

Conclusion: Hydroethanol leaf extract of *C. papaya* demonstrated promise as a potent anticonvulsant at GABAergic and glycinergic inhibitory pathways. By the prolongation of seizure onset, with corresponding reduction in seizure duration, as well as its lack of sedative effect it suggests favorable neurosafety potential. Its effect on muscle tone was minimal on general locomotor; with indication for possible antidepressant effect. These support the traditional use and highlighting its potential as a novel neuroprotective agent.

INTRODUCTION

Due to challenges of accessibility, rising costs, and untoward effects of many conventional medications used for neurological ailments, such as convulsive illnesses, sleep disorders, depressive illness and musculoskeletal disorders, the use of medicinal plant extracts currently has significant acceptability, worldwide. Neurological disorders are a leading cause of disability and mortality worldwide, affecting 349 million Disability-Adjusted Life Years and over 10 million deaths.[1] These disorders, including epilepsy, anxiety, cognitive, sleep–wake disturbances, and neuromuscular disorders, contribute markedly to the quality of life, productivity, and health system costs.[2]

The pathophysiology of these disorders is multifactorial, involving oxidative stress, neuroinflammation, excitotoxicity, synaptic dysfunction, mitochondrial impairment, and altered neurotransmitter systems, including GABAergic, glutamatergic, serotonergic, and dopaminergic pathways.[3] A study by Schallert in 2006 noted that contemporary preclinical research increasingly relies on integrated neurobehavioral test batteries that can

probe multiple functional domains in the same experimental framework.[4] Epilepsy is increasingly recognized not merely as a channelopathy but as part of a broader neurodegenerative continuum in which recurrent seizures exacerbate neuronal loss, cognitive decline, and behavioural disturbances.[5] Previous studies have demonstrated that the heterogeneous mechanisms of Seizure pathophysiology involve deficient inhibitory neurotransmission via γ-aminobutyric acid (GABA) and glycine pathways, as well as excessive excitatory drive through glutamatergic signaling.[6,7] Preclinical evaluation of neuroprotection includes several models to demonstrate its mechanistic heterogeneity: seizure models, e.g., strychnine-induced and picrotoxin seizure models (for neuroinhibitory pathways like glycine and GABA, respectively), chimney tests (for motor coordination and muscle tone impairments), Y-maze (for spatial working memory, and anxiolytic activities), Thiopentone-induced sleeping time (for CNS depression).[8,9] Anxiety disorders were among the leading mental and physical illnesses in terms of "years lived with disability" (YLD), affecting 61.5 million.[10] The pathophysiology of anxiety is a result of the disruption of monoamine pathways.[11] Studies have demonstrated the Y-maze model for evaluating prefrontal cortex function, memory, exploratory drive, and anxiety-related avoidance behavior, making the Y-maze relevant to conditions such as Alzheimer's disease, Parkinson's disease, frontotemporal dementia, and post-traumatic stress disorder (PTSD).[12] Furthermore, because anxiety can modulate exploratory behavior in the maze, the test indirectly provides insights into anxiolytic or anxiogenic drug effects, bridging cognitive and affective neuroscience [13]

In addition, altered sleep regulation is also a hallmark of mood disorders, chronic fatigue syndrome, and certain neurodegenerative diseases, highlighting the cross-domain utility of thiopentone-induced sleeping time. This test provides a pharmacodynamic probe into GABA receptor-mediated neurotransmission and sleep modulation and sedative hypnotic potential and drug–drug interactions within the CNS depressant class. Such data are relevant to the management of insomnia, preoperative sedation, and seizure disorders, where sedation can modulate anxiety and seizure thresholds.[14]

Neuromuscular disorders are among the common neurological disorders. Spasticity is the upper motor neuron condition that causes hypertonicity and uncontrollable jerks in the muscles, probably as a result of neuronal inhibition of postsynaptic gamma-aminobutyric acid neurons. It is used to treat painful musculoskeletal conditions like acute low back pain and muscle strains are attributed to muscle spasm.[15] Preclinical tests, like the chimney test, which measures motor initiation, proprioceptive feedback, and muscle endurance, while the traction test emphasizes sustained muscle contraction and inter-limb coordination. Both are sensitive to sedative–muscle relaxant agents, neuromuscular blocking drugs, and compounds affecting central motor control. Notably, motor deficits in these tests can also reflect extrapyramidal side effects, making them valuable for screening CNS-active agents for safety profiles.[16]

However, the forced swim tests are a common antidepressant property of compounds that act through peripheral pathways lacking extrapyramidal pathways. This model has been linked to antidepressant compounds that act on serotonergic and noradrenergic pathways.[17] The clinical application of AEDs is often limited by sedative, cognitive, and motor side effects, poor tolerability, and incomplete mechanistic coverage of the diverse neurobiological pathways underlying hyperexcitability.[7,10] These limitations highlight the urgent need for novel bioactive compounds from medicinal plants, capable of modulating multiple inhibitory neurotransmission systems while maintaining an acceptable safety profile.

Carica papaya Linn. (Caricaceae) is widely cultivated across tropical and subtropical regions, including Africa and Asia. Studies have identified the potential therapeutics of its phytochemicals, such as alkaloids, flavonoids, phenolic acids, and proteolytic enzymes like papain, in exerting neuro-modulatory, haematological, antiaging, antioxidant, and anti-inflammatory effects, hepatoprotection, and cardioprotection [18-22]

Although the antiepileptic effect of C. papaya has been documented, its potential neurosedative mechanism in controlled experimental models is still vague. This hypothesizes that HECL may possess multi-target CNS therapeutic properties, including modulating both glycinergic and GABAergic inhibitory systems, thereby demonstrating a broad-spectrum neuroprotective effect. These findings aim to provide a mechanistic and pharmacological foundation for the traditional use of *C. papaya* in seizure management and inform its potential progression toward preclinical development as a multi-target CNS therapeutic agent.

MATERIALS AND METHODS

Plant material

Fresh leaves of *Carica papaya* were collected in February 2023 from the botanical garden of Lagos State University College of Medicine, Ikeja, Lagos State, Nigeria. It was authenticated and stored in the University Herbarium by Dr. George Nodza of the Department of Botany, Faculty of Science,

University of Lagos, and given the identification number: LUH 9852.

Extract preparation

The fresh leaves of *C. papaya* were washed with clean running tap water and oven-dried for about 72 hours at 40°C. The dried leaves were ground into a fine powder of which 100g of leaves were macerated for 4 hours at 70°C using a heating mantle in 4.0 liters of 50:50 distilled water and ethanol. This resulted in a thick, brownish, concentrated solution. After allowing the solution to settle, it was filtered with filter paper. The filtrate was evaporated to dryness in an oven set at 40°C, stored in the refrigerator, and dissolved in distilled water before each use.

Laboratory Animals

Young adult Swiss albino mice of both sexes weighing 20 - 25 g were used for the experiment. They were obtained and kept in the Laboratory Animal House of the Lagos State University College of Medicine, Ikeja, Lagos, Nigeria. The animals were maintained under standard environmental conditions, fed with standard rodent feeds and given water *ad libitum.* Animals were acclimatized for 14 days before the experiment. All animals were kept at room temperature in a cross-ventilated room without illumination at night.

All animal procedures adhered to the Animal Research Reporting of *In Vivo* Experiments (ARRIVE) guidelines to ensure ethical and transparent reporting of animal research[23] and institutional ethical approval given be Animal Research Ethical Committee of LASUCOM (Ref No: AREC/2022/087).

Anticonvulsant Study

Acute Chemical Convulsant Test

Strychnine-Induced Seizure Test

Mice of either sex (8 per group, 4/sex) were distributed randomly between the control and test groups. The control mice were administered with strychnine (4 mg/kg, *i.m*.) 30 min after 0.1ml, *p.o.* normal saline; positive control mice received strychnine 30 min. after pentobarbitone sodium (40 mg/kg, *i.p*). Two extract-treated test groups received 100 and 200 mg/kg doses of the oral HECL, respectively, 30 minutes prior to strychnine. The onset of tonic hindlimb extension seizure was recorded in each case. Mice that did not convulse 30 minutes after strychnine administration were considered to be protected.[24]

Picrotoxin-induced seizure test

Mice of either sex (8 per group, 4/sex) were distributed randomly between the control and test groups. The control mice were administered with picrotoxin (4 mg/kg, *i.m*.) 30 min after 0.1ml, *p.o.* normal saline; positive control mice received picrotoxin 30 min. after pentobarbitone sodium (40 mg/kg, *i.p*). Two test groups received 100 and 200 mg/kg doses of the oral HECL, respectively, 30 minutes prior to picrotoxin. Onset to clonic-tonic seizure and duration were recorded in each case. Mice that did not convulse 30 minutes after strychnine administration were considered to be protected.[25]

Anxiolytic Activity

Y-Maze test

This was done according to modified methods of Adeyemi and Colleagues.[24] Different groups of mice received distilled water (10 ml/kg, *p.o*.), HECL (100 and 200 mg/kg, *p.o*.), or diazepam (1 mg/kg, *i.m*.) for 30 minutes before being carefully placed in the center of a Y-shaped wooden cage (Y-maze; YM; 70 cm x 15 cm x 12 cm) with one of the three arms closed. For five minutes, the total amount of time a mouse spent in open arm in relation to the total five minutes in both arms was recorded.[11]

Forced Swim Test

A 1000 ml beaker (height: 19.3 cm, diameter: 13.1 cm) was used in place of vertical plexiglass cylinder used by Porsolt *et al*. (1978).[26] It was filled with tap water at 23 ±1 °C, and the depth was adjusted according to each mouse's erect height, preventing it from touching the bottom of the beaker with its hind limb. Each mouse was placed in the water-filled beaker and observed for 30 minutes. The time taken for the mouse to remain afloat in the water, in an upright position, making only slight movements to keep its head above the water was recorded as the latency time. After 30 minutes, the mouse was removed from the water and wiped with clean dry towel until dry. Each mouse was also closely monitored during recovery.[9]

Musculoskeletal Relaxant Study

Chimney test

The Pyrex glass tube (30 cm long x 3.0 cm diameter at 20 cm from base) was initially kept in a horizontal position. A mouse with its head forward was introduced near the end tube, near the mark. The tube is shifted to a vertical position when the mouse reaches the other end of the tube. The time it took the mouse to climb backwards out of the cylinder at the top was recorded. The mice that successfully reached the mark within 30 s were selected for further testing. The test was repeated with screened animals 30 min. after the administration of distilled water (10 ml/kg, *p.o*.), HECL (100 and 200 mg/kg, *p.o*), diazepam (1mg/kg, *i.p*) to different groups.[27]

Traction test

The fore paws of a mouse were placed on a small twisted wire loop rigidly supported above the laboratory bench top. Normal mice grasped the wire with the fore-paws and when allowed to hang free, placed at least one hind foot on the wire within 5 s. Inability to place at least one hind foot marked failure in the traction test. Previously screened mice were used for the test after the administration of distilled water (10 ml/kg, *p.o*.), HECL (100 and 200 mg/kg, *p.o*), diazepam (1mg/kg, *i.p*) to different groups.[27]

Other Central Nervous System Activities

Thiopentone induced sleeping time test

Thiopentone sodium (40 mg/kg, *i.p*.). was administered to three groups of mice 30 min. after normal saline (10 ml/kg, *i.p*.), or HECL (100 and 200 mg/kg, *p.o*.). Onset of sleep was considered when mice accepted the decubitodorsal position for three consecutive trials. Conversely the duration was completed when the mice did not accept the decubitodorsal position for three consecutive trials.[24]

Statistical Analysis

The data were expressed as mean ± SEM. The mean of each treated group was compared for significance at $P < 0.05$, using the one-way analysis of variance (ANOVA), followed by Tukey *post hoc* for multiple group comparison to analyze the parameters. The GraphPad Prism 8.0.2 software was used for all statistical analyses and graphical illustrations.

RESULTS

Effect of HECL on Strychnine-induced seizures

Administration of HECL significantly prolonged the latency to strychnine-induced seizures in mice in this strychnine seizure model. When compared with the control group, HECL at 100 mg/kg showed a moderate, but significant increase in seizure latency ($p < 0.05$), while at 200 mg/kg, HECL elicited a further, statistically significant prolongation ($p < 0.05$ vs. Control). The standard anticonvulsant drugs, diazepam (3 mg/kg, *i.m*.) and phenobarbitone (40 mg/kg, *i.p*.) markedly increased seizure latency as regards to the Control-treated group. Tuckey *Post hoc* analysis revealed that HECL 100 mg/kg exhibited a significantly lower anticonvulsant effect compared with diazepam ($p < 0.05$), whereas HECL 200 mg/kg did not significantly differ from diazepam, but remained significantly less potent than phenobarbitone (Figure 1).

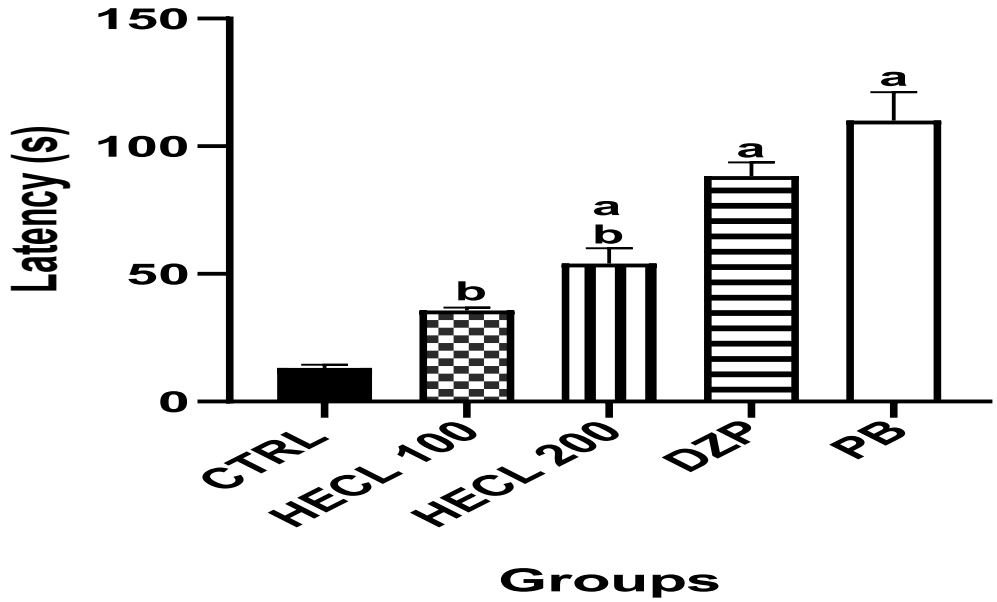

Figure 1: Effect of hydro-ethanol leaf extract of C. papaya on anxiety on the latency to strychnine-induced seizures in mice. Data were expressed as Mean ± S.E.M. $^{a}p<0.05$ vs Control-treated group; $^{b}p < 0.05$ vs Diazepam-treated group (one-way ANOVA followed by Dunnett's post hoc test). CTRL: Control, HECL 100: Hydroethanol extract of *Carica papaya* (100 mg/kg), HECL 200: Hydroethanol extract of *C. papaya* (200 mg/kg), DZP: Diazepam (3 mg/kg), PB: Phenobarbitone (40 mg/kg)

Effect of HECL on Picrotoxin-induced Seizures

Exposure to picrotoxin induced seizures more rapidly in control mice, with onset occurring in less than 8 minutes on average. Treatment with both doses of HECL produced a significant dose-dependent delay in seizure initiation. At 100 mg/kg,

HECL extended latency by nearly two-fold compared with control, while 200 mg/kg produced an almost three-fold increase. The effect of HECL at the higher dose was comparable to that of diazepam, which yielded the longest latency values among all groups. Phenobarbitone also significantly prolonged latency, although its effect was intermediate between diazepam and HECL 200 mg/kg. Statistical analysis confirmed that both HECL doses and the reference drugs significantly differed from control animals ($p < 0.05$). Furthermore, HECL at 100 mg/kg was less effective than diazepam ($p < 0.05$), whereas HECL at 200 mg/kg showed no significant difference from diazepam (Figure 2)

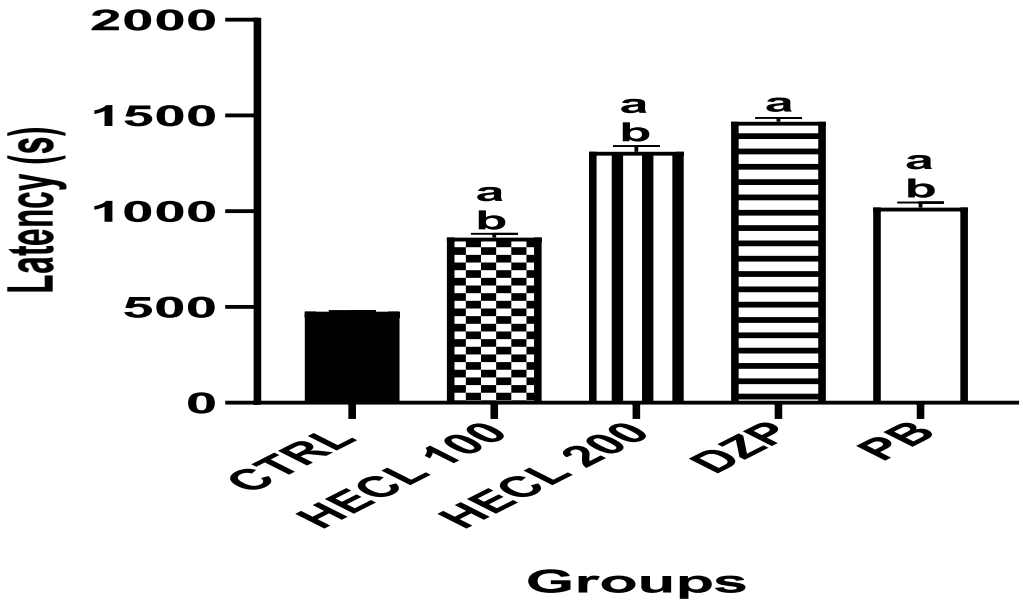

Figure 2: Effect of hydro-ethanol leaf extract of C. papaya on anxiety on latency to Picrotoxin-induced seizures in mice. Data were expressed as Mean ± S.E.M. $^{a}p<0.05$ vs Control-treated group; $^{b}p < 0.05$ vs Diazepam-treated group (one-way ANOVA followed by Dunnett's post hoc test). CTRL: Control, HECL 100: Hydroethanol extract of *Carica papaya* (100 mg/kg), HECL 200: Hydroethanol extract of *C. papaya* (200 mg/kg), DZP: Diazepam (3 mg/kg), PB: Phenobarbitone (40 mg/kg)

Effect of HECL on Y Maze

Both doses of the extract, like diazepam, caused significant ($p < 0.05$) increases in time spent in the open arms of the Y maze. Control mice spent most of the time in the closed arms of the Y maze (Table 1).

Table 1: Effect of hydro-ethanol leaf extract of *C. papaya* on anxiety in the Y maze test

Treatment (Dose)	Time spent in open arms as a function of total time spent in open and closed arms within 5 mins
CTRL	1.22 ± 0.03
HECL (100)	3.47 ± 0.06[a]
HECL (200)	4.08 ± 0.07[a]
DZP	4.48 ± 0.13[a]

Data were expressed as Mean ± S.E.M. *$^{a}P > 0.05$;* significant difference from control*; $P < 0.05$* (one-way ANOVA followed by Dunnett's post hoc test). CTRL: Control, HECL (100): Hydroethanol extract of *Carica papaya* (100 mg/kg), HECL (200): Hydroethanol extract of *C. papaya* (200 mg/kg), DZP: Diazepam (3 mg/kg).

Effect of HECL on Forced Swimming Test

The groups treated with control, 100 and 200 mg/kg of *C. papaya* showed equivalent latency of swimming with values of 15 mins, while mice administered diazepam exhibited a reduced latency value of 13.5 mins (Table 2).

Table 2: Effect of hydro-ethanol leaf extract of *C. papaya* on Forced Swimming test

Treatment (Dose)	Latency within 30 mins
CTRL	>30
HECL (100)	>30
HECL (200)	> 30
DZP	13.5

Data was expressed as Mean (one-way ANOVA followed by Dunnett's post hoc test). CTRL: Control, HECL (100): Hydroethanol extract of *Carica papaya* (100 mg/kg), HECL (200): Hydroethanol extract of *C. papaya* (200 mg/kg), DZP: Diazepam (3 mg/kg).

Effect of HECL on Musculoskeletal Relaxant Study

Chimney Test

In comparison to the control, the extracts 100 and 200 mg/kg and diazepam caused a significant increase in the proportion of mice unable to climb with a backward movement. However, the two doses of the extract caused a significant ($P < 0.05$) reduction in the proportion of mice unable to climb with a backward movement compared with diazepam (Table 3)**.**

Traction Test

Neither the two doses of the extract nor the control treatment group caused any mouse to exhibit significant muscle incoordination that affected climbing in the traction test. On the contrary, diazepam caused significant muscle incoordination, thereby preventing 40% of mice from showing muscle relaxation control enough to prevent them from climbing in the Traction test (Table 3)**.**

Table 3: Effect of hydro-ethanol leaf extract of *C. papaya* on muscle relaxation (Chimney and Traction test)

Treatment (Dose)	Percentage of showing muscle incoordination	
	Chimney test	Traction test
CTRL	**3.6**	**0**
HECL (100)	**7.6**^{abc}	**0** ^{c}
HECL (200)	**9.4** ^{ac}	**0** ^{c}
DZP	**15.6** ^{a}	**40** ^{a}

Data was expressed as Mean (one-way ANOVA followed by Dunnett's post hoc test). ^{a} *p < 0.001,* significantly different from control, 100 mg/kg, ^{b} *p < 0.*001 being significantly than 200 mg/kg, ^{c} *p < 0.001,* significantly different from diazepam. CTRL: Control, HECL (100): Hydroethanol extract of *Carica papaya* (100 mg/kg), HECL (200): Hydroethanol extract of *C. papaya* (200 mg/kg), DZP: Diazepam (3 mg/kg).

Effect of HECL on Thiopentone-induced sleeping time

The control (CTRL) group showed a baseline latency to Thiopentone-induced sleep in mice. Treatment with HECL at 100 mg/kg significantly reduced latency to ($p < 0.05$ vs. CTRL), while HECL at 200 mg/kg further decreased latency to approximately 4 seconds ($p < 0.05$ vs. CTRL and $p < 0.05$ vs. DZP). Diazepam, used as a positive control, reduced latency to approximately 7 seconds ($p < 0.05$ vs. CTRL) (Figure 3).

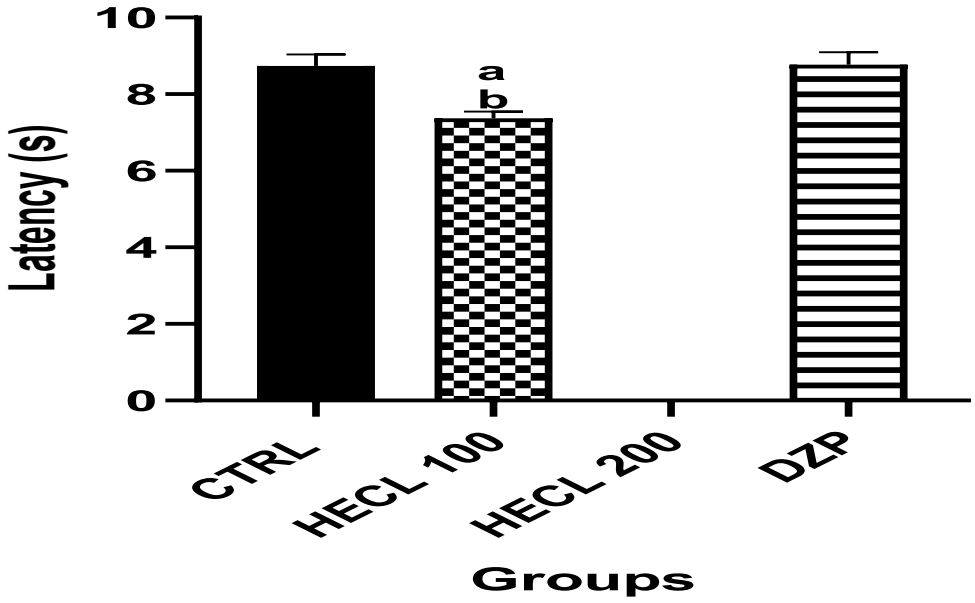

Figure 3. Effect of hydro-ethanol leaf extract of C. papaya on anxiety on latency to Thiopentone-induced sleep in mice. Data is presented as Mean ± S.E.M. Data is presented as Mean ± S.E.M. (n = 5); [a]$p<0.05$ vs control-treated group; [b]$p < 0.05$ vs Diazepam-treated group (one-way ANOVA followed by Dunnett's post hoc test). CTRL: Control, HECL 100: Hydroethanol leaf extract of *Carica papaya* (100 mg/kg, *p.o.*); HECL 200: Hydroethanol leaf extract of *Carica papaya* (200 mg/kg, *p.o*), DZP: Diazepam (3 mg/kg, *i.m.*).

DISCUSSION

The marked anticonvulsant, anxiolytic, antidepressant, and musculoskeletal modulatory effects produced by HECL suggest potential therapeutic applications in seizure disorders, anxiety, depressive illness and neuromuscular dysfunction. HECL demonstrated efficacy against strychnine and picrotoxin-induced acute seizures, indicating a significant anticonvulsant activity. With a comparable effect as diazepam and phenobarbitone in the strychnine-and picrotoxin-induced seizure model, the extract 100 mg/kg produced a significant ($P < 0.05$) dose-dependent prolongation of time before convulsion onset for both models employed. Studies demonstrated that glycine and GABA function as convulsive-inhibitory neurotransmitters in the central nervous system.[25] Strychnine, a strong convulsant of the spinal cord, selectively inhibits glycine receptors to stimulate the central nervous system's excitatory response. Picrotoxin, however, interferes with $GABA_A$ receptors to cause generalized seizures. These findings suggest that HECL's anticonvulsant effect was most likely brought about by its modulatory activity on glycine and $GABA_A$ receptor sites from the inhibition of strychnine and picrotoxin models, respectively.[28]

The chimney test is highly sensitive to central motor incoordination and axial muscle tone changes that depend on cerebellar–brainstem integration and spinal inhibitory reflexes; small increases in failure rates often reflect centrally mediated myorelaxation/ataxia rather than peripheral neuromuscular block. By contrast, the traction test is relatively more sensitive to grip strength and segmental reflex integrity and thus detects stronger sedation, cerebellar dysfunction, or impairment of motor unit recruitment.[29] The study showed modest chimney impairment, absent traction impairment, thereby indicating that HECL could cause mild, centrally mediated muscle relaxation/coordination deficits without compromising forelimb strength or spinal monosynaptic reflex performance. Diazepam robust effects in both assays are classic for benzodiazepine-like $GABA_A$ potentiation, strong enough to depress both cerebellar coordination and segmental motor output.[30] Moreover, significant protection against strychnine-induced seizures strongly suggests a capacity to enhance or sustain glycinergic inhibitory tone. Such facilitation would plausibly account for the mild but measurable impairment in complex axial movements detected in the chimney test, while leaving simpler grip-based performance, as in the traction test, largely unaffected. This selective influence on motor control reflects a profile more aligned with subtle modulation than with global neuromuscular suppression.[29]

Bioactive constituents abundant in *C. papaya*, including flavonoids such as apigenin, chrysin, and quercetin glycosides, as well as alkaloids and phenolic compounds have been reported to act as

non-benzodiazepine- GABAergic pathway.[31] The combination of spinal glycinergic reinforcement and tempered GABA potentiation thus provides a coherent mechanistic explanation for muscle relaxant profile caused by HECL, characterized by improved motor inhibition and reduced hypertonicity while preserving overall motor strength and coordination to a greater extent than conventional sedative-hypnotics. This dual-modality interaction places HECL in a unique pharmacological class, with potential applications in conditions where targeted myorelaxation is desired without significant sedation or motor impairment.[32] HECL delayed strychnine- and picrotoxin-induced seizures and modestly potentiates thiopentone hypnosis, suggesting glycinergic/GABAergic facilitation without gross motor suppression.[33]

The total amount of time that mice spent in the open arms in the Y-Maze was not significantly changed by the extract. This effect was found to be less severe than that of diazepam. This finding implies that the extract possessed minimal anxiolytic activity without altering locomotor and sedative effects as parallel to Kebebew *et al*.[34]

Given that the open arms of the Y-maze represent aversive, anxiogenic environments for rodents due to their elevated and unprotected nature, increased time spent in these zones is interpreted as reduced anxiety levels, aligning with established behavioral paradigms for anxiolytic assessment.[35]

The observed dose-response pattern strengthens the pharmacological plausibility of HECL anxiolytic potential, suggesting that its bioactive phytoconstituents may modulate central neurotransmission in pathways implicated in anxiety regulation. Flavonoids such as quercetin, kaempferol, and apigenin, reported in *C. papaya* leaves, are known to exert anxiolytic effects via positive allosteric modulation of the GABA receptor complex, particularly at non-benzodiazepine binding sites, thereby enhancing inhibitory tone without the profound sedative or myorelaxant effects associated with classical benzodiazepines.[31,36]

When contrasted with diazepam, HECL demonstrated comparable efficacy at the higher dose, though likely via mechanisms with a more favorable side-effect profile.

The anxiolytic profile of *C. papaya* thus positions it as a promising candidate for further development, particularly for patients who require anxiolysis without cognitive or psychomotor compromise.[37]

The Forced Swimming Test (FST) paradigm revealed that control mice and the *Carica papaya* groups exhibited a latency to immobility greater than the 30 min. observational threshold. This suggests that the bioactive compounds in HECL exert a modulatory influence without impairing locomotor or psychomotor performance.[38]

By contrast, the sustained swimming activity in both control and HECL-treated mice indicates that the extract did not induce central nervous system depression sufficient to compromise motor drive or swimming motivation within the testing window. This is notable because phytochemicals with sedative or myorelaxant effects, such as certain alkaloids or flavonoids with strong GABAergic activity, might be expected to mimic the diazepam profile. The absence of such an effect suggests that at the doses tested, the hydroethanolic extract of HECL either lacks potent CNS-depressant constituents or that its bioactive compounds exert a modulatory influence without impairing locomotor or psychomotor performance.[34]

CONCLUSION

Hydroethanol leaf extract of *C. papaya* demonstrated potent inhibitory activity on the postsynaptic pathway, particularly the GABAergic and glycinergic inhibitory pathways. The prolongation of seizure onset, with corresponding reduction in seizure duration, as well as its lack of sedative effect, indicates favorable neurosafety potential. Its muscle relaxant effect is also demonstrated in the traction test and the positive forced swimming tests outcome suggests a potential antidepressant effect without affecting general locomotor and extrapyramidal pathways. All of these activities by the extract support the traditional use and highlight its potential as a novel neuroprotective agent.

Declaration of Interest

The authors do not have any declaration of interest in this study

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