

Growth and Spatial Memory Responses to *Carica papaya* Leaf Extract in a Diet-Induced Stunting Mouse Model

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Abstract

Stunting is a multifactorial growth disorder that is frequently accompanied by persistent cognitive impairment, driven by nutritional deficiency, oxidative stress, and altered neurodevelopment. This study explored the phytochemical quality and biological response patterns associated with *Carica papaya* leaf extract using a diet-induced stunting mouse model. Papaya leaves were authenticated and extracted with 70% ethanol, followed by phytochemical profiling and quality assessment. Stunted mice were allocated to untreated, zinc-supplemented, and extract-treated groups, while a normal group served as reference. Somatic growth outcomes, including body weight and body length, were monitored alongside behavioral performance assessed through sensorimotor adaptation, spatial learning, and memory retention using the Morris water maze paradigm. Across the observation period, mice receiving *C. papaya* leaf extract displayed consistent catch-up growth trends relative to untreated stunted controls, with growth trajectories directionally similar to those observed in zinc-supplemented animals. In behavioral assessments, extract-treated mice showed observable trends toward improved task adaptation, progressive reductions in escape latency during spatial learning, and preserved performance during memory retention trials. These patterns appeared distinct from the negative control group and broadly aligned with the reference groups, although substantial inter-individual variability was noted. Taken together, the findings describe biologically meaningful response patterns suggesting that *C. papaya* leaf extract may hold potential to support somatic growth recovery and cognitive function in nutritionally compromised conditions. Given the exploratory nature of this study and the absence of inferential statistical testing, the results should be interpreted as descriptive trends that warrant further investigation using larger cohorts and confirmatory analytical designs.

Keywords: *Carica papaya*; cognitive impairment; Morris Water Maze; pepaya leaf extract; stunting.

INTRODUCTION

Stunting remains a significant global health concern, affecting over 140 million children and resulting in long-term physical, cognitive, and socioeconomic consequences (De Sanctis et al., 2021; Harahap et al., 2025). While stunting has traditionally been defined by impaired linear growth due to chronic undernutrition, recent studies have reframed it as a complex, multisystem disorder involving neurodevelopmental deficits, immune dysfunction, and metabolic disturbances (De Sanctis et al., 2021; Kurniadi et al., 2024). Beyond growth failure, stunted children often experience persistent impairments in learning, memory, and executive function, with these outcomes linked to chronic inflammation, oxidative stress, and disrupted neurotrophic signaling (Sun et al., 2022).

Experimental and clinical research highlights the role of early-life protein and micronutrient deficiencies in altering endocrine and metabolic pathways and in impairing hippocampal development and synaptic

plasticity, ultimately affecting cognitive function (Harahap et al., 2025; Sun et al., 2022). Nutritional deprivation during critical periods increases oxidative damage in neural tissues and disrupts neurodevelopmental processes, resulting in lasting cognitive dysfunction. Animal models of diet-induced growth restriction remain essential for elucidating these mechanisms and for testing interventions targeting both growth and neurocognitive outcomes (Fatehfar et al., 2025).

Current interventions focus on nutritional supplementation, including zinc and protein fortification, which improve growth but show inconsistent effects on neurocognitive recovery (Fekete et al., 2023). Zinc, for example, supports cellular proliferation and immune function but only partially addresses the oxidative and inflammatory processes underlying stunting-related cognitive deficits (Sun et al., 2022). This has driven interest in complementary strategies, particularly those leveraging natural products with multifunctional bioactivity. *Carica papaya* L. leaves have gained

attention for their rich phytochemical profile-abundant in phenolics, flavonoids, alkaloids, and terpenoids and their potent antioxidant, antiinflammatory, and cytoprotective properties (Brahim et al., 2025; Choudhary et al., 2025; Lopez et al., 2024). Recent studies demonstrate that papaya leaf extracts modulate oxidative stress pathways and reduce pro-inflammatory responses, supporting metabolic homeostasis in experimental models (Brahim et al., 2025; Choudhary et al., 2025). Notably, papaya-derived phytochemicals have shown neuroprotective potential through antioxidative and anti-inflammatory mechanisms relevant to cognitive function (Sun et al., 2022). Despite these promising findings, the role of *Carica papaya* leaf extract in addressing both growth retardation and cognitive dysfunction in nutritional stunting remains underexplored. There is a need for studies integrating standardized extract quality assessment with comprehensive evaluation of somatic growth and higher order cognitive performance.

This study aimed to evaluate the phytochemical quality and biological effects of *C. papaya* leaf extract on growth recovery and cognitive function using a mouse model of diet induced stunting. A low-protein diet was applied to induce stunting, followed by a comprehensive assessment of somatic growth and neurobehavioral performance. Through this integrated approach, the study seeks to provide a holistic preclinical evaluation of papaya leaf extract as a potential intervention for nutritional stunting.

MATERIALS AND METHODS

Study area

This exploratory preclinical study was conducted in a controlled laboratory environment to ensure consistency in animal handling, dietary intervention, extract preparation, and behavioral assessment. All experimental procedures were carried out in accredited laboratory facilities equipped for small-animal experimentation, phytochemical processing, and neurobehavioral testing. Environmental conditions, including temperature, humidity, and light-dark cycles, were maintained uniformly throughout the study period. Authentication and extraction of *Carica papaya* leaves were performed in a pharmaceutical laboratory under controlled conditions to preserve extract stability and chemical integrity. Cognitive testing using the Morris Water Maze (MWM) was conducted in a dedicated behavioral room with standardized lighting and minimal external disturbance.

Procedures

Plant Material Authentication and Extraction

Fresh leaves of *C. papaya* L. were obtained from a locally cultivated source and authenticated as *C. papaya* L. based on a plant identification certificate (No. 125/HB/7/2025). Botanical identity was verified through

macroscopic and microscopic examination to ensure sample authenticity and to exclude possible adulteration. The collected leaves were thoroughly washed, oven-dried at 50 °C, and ground into a fine powder. Extraction was conducted by maceration using 70% ethanol, selected for its reliable efficiency in extracting phenolic and flavonoid compounds. The powdered material was immersed in the solvent with periodic stirring, followed by filtration and solvent removal under reduced pressure. The resulting extract was dried to a constant weight and stored in airtight containers under controlled conditions until further use. Basic quality parameters, including extraction yield, moisture content, and organoleptic properties, were assessed to ensure batch consistency and extract stability.

Animal Model of Diet-Induced Stunting and Experimental

Male mice aged three weeks and with comparable baseline body weights were acclimatized under standard laboratory conditions with free access to food and water. Stunting was induced through administration of a low-protein diet during a defined induction period, intended to model chronic nutritional insufficiency during early development. Growth retardation was monitored longitudinally by measuring body weight and body length to confirm the establishment of the stunted phenotype. Following the induction phase, animals were randomly allocated into four experimental groups: a normal control group, a stunted negative control group without intervention, a stunted positive control group receiving zinc supplementation, and a stunted treatment group receiving *C. papaya* leaf extract..

The extract and zinc were administered orally during the designated treatment period, while control animals received a standard diet without supplementation. The selected extract dose (100 mg/kg body weight) was based on previous preclinical studies demonstrating biological activity without apparent toxicity and was intended to serve as an initial proof-of-concept rather than a full dose response evaluation. Body weight and body length were recorded at four-week intervals to document growth trajectories while minimizing handling-related stress. This study was designed as an exploratory preclinical investigation aimed at identifying coherent biological response patterns rather than establishing definitive efficacy or mechanistic causality. Accordingly, results were interpreted descriptively, with emphasis placed on longitudinal trends and consistency across growth and behavioral outcomes. Inter-individual variability was anticipated due to differences in metabolic adaptation and developmental sensitivity to nutritional stress and was therefore regarded as an inherent characteristic of the stunting model.

Cognitive Assessment Using Morris Water Maze

Cognitive function was assessed using the Morris Water Maze, a well established behavioral paradigm for

evaluating spatial learning and memory in rodents. The testing protocol comprised three sequential phases: sensorimotor adaptation using a visible platform, spatial learning acquisition using a hidden platform, and spatial memory retention assessed through probe trials. During the sensorimotor phase, escape latency was recorded to confirm intact visual and motor function and to ensure that subsequent task performance was not confounded by non-cognitive impairments. To reduce the influence of anxiety-related behavior, stress reactivity, and inter-individual variability associated with water exposure, all animals underwent standardized pre-handling prior to behavioral testing. The visible-platform phase was specifically incorporated to distinguish sensorimotor adaptation and stress coping from spatial learning processes. Consequently, variations observed during initial trials were interpreted as task familiarization dynamics rather than definitive indicators of cognitive improvement.

The acquisition phase consisted of repeated trials designed to assess learning progression across sessions, while memory retention was evaluated during probe trials by recording the number of crossings over the former platform location. It should be noted that the normal control group was not subjected to a recovery challenge, whereas stunted groups underwent a post insult intervention phase. Therefore, behavioral comparisons were interpreted within the context of recovery-related adaptation rather than absolute performance superiority. All behavioral sessions were video-recorded, and performance measures were evaluated by an observer blinded to group allocation.

Data analysis

Data were summarized descriptively and are presented as mean $\pm$ standard deviation (SD) to illustrate growth trajectories and behavioral performance across experimental groups. Longitudinal changes in body weight, body length, and Morris Water Maze outcomes were examined through visual comparison of temporal trends across observation points. The analysis focused on

identifying coherent and biologically meaningful response patterns across growth and cognitive domains within the experimental framework.

RESULTS AND DISCUSSION

Phytochemical Quality and Extract Characteristics

The ethanolic extraction of *C. papaya* leaves yielded a consistent dry extract with stable physical characteristics, supporting the reproducibility of the extraction procedure. Macroscopic and microscopic authentication confirmed the botanical identity of the plant material prior to extraction. Quality parameters, including extract appearance, yield consistency, and low moisture content, indicated adequate preservation of phytochemical integrity throughout processing. Recent phytochemical profiling studies report that ethanol-based extracts of *C. papaya* leaves are rich in phenolic and flavonoid compounds, including quercetin, kaempferol, caffeic acid, phytol, and related bioactives. These findings are consistent with the extract characteristics observed in the present study and support its suitability for biological evaluation in growth and cognitive models.

Effects of *Carica papaya* Leaf Extract on Growth Recovery in Stunted Mice

Diet induced stunting resulted in markedly reduced body weight and body length in the negative control group throughout the observation period. In contrast, mice receiving *C. papaya* leaf extract exhibited consistent catch-up growth trends in both parameters. Body weight and body length trajectories in the extract-treated group appeared directionally higher than those of untreated stunted controls and followed patterns broadly similar to those observed in the zinc-supplemented group. The normal group maintained the highest growth values across all time points. Variability among individual animals was observed across groups, reflecting heterogeneous growth responses under nutritionally compromised conditions.

Table 1. Body Weight and Body Length Profiles of Mice During Stunting Induction and Treatment Period.

Observation Time	Group	Body Weight (g)	Body Length (cm)
W0 (Baseline)	Positive Control	28.3 $\pm$ 1.5	9.0 $\pm$ 1.0
	Negative Control	27.3 $\pm$ 1.2	9.0 $\pm$ 0.9
	Papaya Extract 100 mg/kg	27.5 $\pm$ 1.4	8.9 $\pm$ 0.8
	Normal	28.0 $\pm$ 1.0	9.1 $\pm$ 0.2
W4	Positive Control	24.7 $\pm$ 1.8	8.7 $\pm$ 0.5
	Negative Control	23.0 $\pm$ 1.2	8.4 $\pm$ 0.4
	Papaya Extract 100 mg/kg	23.3 $\pm$ 1.0	8.5 $\pm$ 0.3
	Normal	29.7 $\pm$ 1.5	9.3 $\pm$ 0.3
W8 (Pre-Treatment)	Positive Control	22.8 $\pm$ 1.3	8.2 $\pm$ 0.3
	Negative Control	21.5 $\pm$ 0.9	8.0 $\pm$ 0.3

Observation Time	Group	Body Weight (g)	Body Length (cm)
W12 (Week 4 of Treatment)	Papaya Extract 100 mg/kg	21.7 ± 1.1	8.0 ± 0.2
	Normal	31.0 ± 1.4	9.4 ± 0.2
	Positive Control	27.3 ± 1.7	8.8 ± 0.4
	Negative Control	23.3 ± 1.0	8.3 ± 0.3
	Papaya Extract 100 mg/kg	26.5 ± 1.6	8.7 ± 0.3
	Normal	32.8 ± 1.2	9.5 ± 0.3
W16 (End of Treatment)	Positive Control	34.0 ± 2.0	9.7 ± 0.3
	Negative Control	25.8 ± 1.0	8.7 ± 0.3
	Papaya Extract 100 mg/kg	31.8 ± 1.5	9.3 ± 0.2
	Normal	36.5 ± 1.0	9.9 ± 0.2

Sensorimotor Adaptation (Initial MWM Exposure)

During the initial sensorimotor adaptation phase of the Morris water maze, all groups demonstrated gradual reductions in escape latency across repeated trials, indicating task familiarization. The extract-treated group showed observable trends toward shorter escape times compared with the negative control group, suggesting

more efficient adaptation to the task environment. Performance patterns in the extract-treated mice appeared directionally aligned with those of the zinc-supplemented and normal groups, although inter-individual variability remained evident. These observations reflect task adaptation dynamics rather than definitive treatment effects.

Table 2. Sensorimotor Performance of Mice During Morris Water Maze Pre-Training.

Phase	Group	Mean (sec)	SD	Interpretation
T0	Positive	14.5	4.8	Typical adaptation
	Negative	22.0	7.5	Slower adaptation
	Papaya Leaf Extract 100 mg/kg	11.8	4.2	Efficient adaptation
	Normal	9.5	3.0	Efficient adaptation
T1	Positive	13.2	4.0	Stable adaptation
	Negative	19.5	6.8	Persistently slow
	Papaya Leaf Extract 100 mg/kg	10.5	3.8	Improved adaptation
	Normal	8.2	2.5	Stable adaptation

Note: The small differences in escape time from T0 to T1 across all groups suggest that the mice adapted well to the task and showed no signs of motor impairment.

Spatial Learning Performance (Acquisition Phase)

Across the acquisition phase, untreated stunted mice exhibited slower and less consistent reductions in escape latency, indicating impaired spatial learning performance. In contrast, mice receiving Carica papaya leaf extract demonstrated progressive reductions in escape latency over training days, forming a clearer

learning trajectory. The observed learning patterns in the extract-treated group appeared directionally similar to those of the zinc-supplemented group and closer to the normal reference group, although variability among subjects was noted. These findings describe observable learning trends rather than statistically confirmed differences.

Table 3. Acquisition Trial Performance (Spatial Learning Ability).

Phase	Group	Mean (sec)	SD	Interpretation
T0	Positive	50.0	9.0	Slow adaptation
	Negative	42.0	10.5	Delayed adaptation
	Papaya Leaf Extract 100 mg/kg	33.5	8.0	More efficient adaptation
	Normal	28.0	7.0	Moderate adaptation

Phase	Group	Mean (sec)	SD	Interpretation
T1	Positive	38.5	9.5	Improved adaptation
	Negative	34.0	8.5	Persistently delayed
	Papaya Leaf Extract 100 mg/kg	22.0	6.0	Improved performance
	Normal	15.5	5.0	Rapid adaptation

Note: The group receiving papaya leaf extract demonstrated a steady improvement in escape latency, reflecting better spatial learning over the course of the trials.

Spatial Memory Retention (Probe Trial)

In the probe trial, negative control mice showed lower platform crossings, consistent with weaker spatial memory retention. Extract-treated mice demonstrated higher platform-crossing frequencies relative to untreated stunted controls, suggesting preserved memory-related

performance patterns. The distribution of crossings in the extract-treated group appeared broadly comparable to those of the zinc-supplemented and normal groups, with noticeable inter-individual variation. These observations describe memory retention trends without implying inferential significance.

Table 4. Probe Trial Performance (Spatial Memory Retention).

Phase	Group	Mean Crossings (x)	SD	Interpretation
T0 (Baseline Memory)	Positive Control	4.0	2.5	Weak; variable
	Negative Control	3.8	2.0	Baseline-level
	Papaya Extract 100 mg/kg BW	4.2	1.5	Stable
	Normal	4.5	1.8	Consistent
T1 (Memory Retention)	Positive Control	4.8	2.0	Moderate, improving
	Negative Control	3.0	1.5	Declining performance
	Papaya Extract 100 mg/kg BW	4.6	1.2	Stable, preserved
	Normal	5.0	1.3	Consistent, preserved

Note: The papaya extract group maintained stable platform crossing counts, consistent with a potential protective trend in spatial memory retention.

Discussion

Nutritional stunting represents a multifactorial condition in which growth retardation and neurocognitive impairment arise from prolonged deficiencies in protein and essential micronutrients during critical developmental periods (Allgäuer et al., 2023; Mattei & Pietrobelli, 2019). In the present exploratory model, growth restriction induced by a low-protein diet was accompanied by behavioral patterns consistent with impaired learning and memory, reflecting the close physiological interconnection between somatic growth and brain development. These observations align with current conceptual frameworks that describe stunting not solely as a disorder of linear growth, but as a systemic condition involving metabolic, inflammatory, and neurodevelopmental dysregulation (Mattei & Pietrobelli, 2019; Urquiza-Martínez et al., 2024)

The growth recovery patterns observed following administration of *C. papaya* leaf extract may be biologically contextualized through the phytochemical composition of papaya leaves. Ethanol-based extracts of *C. papaya* are known to contain phenolic and flavonoid compounds with antioxidant and cytoprotective properties. In nutritionally compromised states, oxidative stress contributes to impaired cellular proliferation, altered endocrine signaling, and reduced tissue repair

capacity (Ciancarelli et al., 2022; Godos et al., 2020; González-Burgos et al., 2021).

Phytochemicals with redox-modulating activity may therefore support physiological environments more conducive to growth normalization without acting as direct growth-promoting agents (Jeon et al., 2025; Sharma et al., 2022). This interpretation remains consistent with the descriptive nature of the present findings and avoids attribution of direct causality. Beyond somatic outcomes, spatial learning and memory performance are closely linked to hippocampal integrity and synaptic plasticity, both of which are vulnerable to early-life nutritional deficits. (Abey et al., 2019; Allgäuer et al., 2023; Fadó et al., 2022; Mattei & Pietrobelli, 2019; Urquiza-Martínez et al., 2024)

Chronic protein insufficiency has been shown to disrupt neurotrophic signaling, reduce dendritic complexity, and exacerbate neuroinflammatory processes (Abey et al., 2019; Mattei & Pietrobelli, 2019). The behavioral patterns observed in extract-treated mice may reflect indirect neuroprotective support through attenuation of oxidative and inflammatory stressors rather than direct cognitive enhancement (Kong et al., 2021; Sharma et al., 2022).

Such a mechanism is consistent with existing preclinical literature reporting neuroprotective effects of

papaya-derived bioactives in models of oxidative and inflammatory brain injury (Jeon et al., 2025; Koul et al., 2022). The comparison between extract-treated and zinc-supplemented groups highlights an important conceptual distinction. Zinc supplementation primarily addresses micronutrient insufficiency and supports cellular proliferation and immune competence, yet may not fully target the oxidative and inflammatory dimensions of stunting-related neurocognitive dysfunction (Ciancarelli et al., 2024).

In contrast, phytochemical-rich extracts may exert broader biological modulation across multiple pathways (Kong et al., 2021; Kurniadi et al., 2025). The parallel performance patterns observed between these interventions suggest that phytochemical-based strategies could complement, rather than replace, conventional nutritional approaches. This interpretation is framed cautiously and reflects convergence of response patterns rather than equivalence of efficacy. It is important to acknowledge that inter-individual variability remained evident across all experimental groups, particularly in behavioral outcomes. Such variability is characteristic of exploratory animal studies and underscores the complexity of modeling nutritional stunting, where developmental timing, metabolic adaptation, and stress responsivity may differ among subjects (Mattei & Pietrobelli, 2019; Urquiza-Martínez et al., 2024).

Accordingly, the present study was not designed to establish definitive efficacy, dose–response relationships, or mechanistic causality. Several limitations should be considered when interpreting these findings. The absence of inferential statistical testing restricts conclusions to observed biological trends. In addition, biochemical markers of oxidative stress, inflammation, or neurotrophic signaling were not directly assessed, limiting mechanistic inference. Future studies incorporating molecular endpoints, histological analysis of neural tissue, and expanded dosing regimens would strengthen the translational relevance of papaya leaf extract as a candidate intervention (Jeon et al., 2025; Koul et al., 2022; Sharma et al., 2022).

In summary, this exploratory preclinical study provides descriptive evidence that *C. papaya* leaf extract is associated with coherent growth and behavioral response patterns in a mouse model of diet-induced stunting. The findings support the biological plausibility of phytochemical-based modulation of growth and neurocognitive outcomes in nutritionally compromised states and justify further hypothesis-driven investigations integrating mechanistic and translational endpoints (Jeon et al., 2025; Kong et al., 2021; Sharma et al., 2022; Urquiza-Martínez et al., 2024).

CONCLUSIONS

These effects are likely related to the antioxidant and neuroprotective phytochemicals present in *C. papaya*

leaves, which may mitigate oxidative stress and support neurodevelopmental processes impaired by early life undernutrition. The comparable performance of extract treated and zinc supplemented groups suggests that phytochemical based interventions may complement conventional nutritional strategies. Although exploratory in nature, the consistency of observed biological improvements supports further investigation of *C. papaya* leaf extract as a natural product candidate for addressing growth and cognitive deficits associated with nutritional stunting.

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