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Ziziphus mauritiana Supplement Improved Spatial Working and Recognition Memory in Swiss Albino Mice

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Abstract

Recognition memory, particularly in the context of spatial tasks, relies on the integration of spatial working memory and long-term memory, with successful performance linked to specific brain activations, such as in the inferior frontal gyrus and hippocampus. *Ziziphus mauritiana* (*Z. mauritiana)* is a plant whose bark and leaves exhibit significant antioxidant, anti-inflammatory, antimicrobial and enzyme inhibitory activities. This study aimed to evaluate the effect of *Z. mauritiana* supplementation on spatial working and recognition memory in Swiss albino mice. Twenty (20) mice weighing between 24 – 30 grams were used for the study. They were divided into five groups of four mice each (N=4). Group I served as control and received 10 ml/kg distilled water; groups II, III, IV and V were given 2 mg/kg glibenclamide, 25 mg/kg, 50 mg/kg and 100 mg/kg of *Z. mauritiana* for 14 days respectively. Y maze and novel object recognition task were used to assess spatial working, long-term and recognition memories respectively. We observed no significant ($p > 0.05$) improvement in spatial working memory in all the *Z. mauritiana* supplemented groups when compared with the control group. Long-term and recognition memories showed significant ($p < 0.05$) improvement after 14 days of 50 mg/kg of *Z. mauritiana* administration compared to day 0 of the same group. Thus, *Z. mauritiana* supplement have no effect on spatial working memory while at 50 mg/kg improved long-term and recognition memories of Swiss albino mice.

Keywords: *Dementia, long-term memory, spatial working memory, Ziziphus mauritiana*

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1. Introduction

Cognitive impairments, particularly in spatial working and recognition memory, are hallmark symptoms of several neurodegenerative disorders, including Alzheimer's disease and dementia. These deficits significantly impact the quality of life and pose challenges to effective therapeutic management (Jorm, 2018). Spatial working memory (SWM) and recognition memory (RM) are fundamental cognitive processes essential for everyday functioning. Deficits in these memory domains are often observed in various neurodegenerative conditions, including Alzheimer's disease and age-related cognitive decline (Jorm, 2018). In animal models, impairments in SWM and RM are often used to simulate cognitive deficits, providing insights into potential therapeutic interventions (Li et al., 2022).

Recently, the exploration of natural remedies and plant-derived supplements has gained considerable attention due to their multifaceted pharmacological properties, including neuroprotection and cognitive enhancement (Singh et al., 2020). Cognitive issues stemming from high glucose levels pose a major problem within diabetes management, as diverse mechanisms are at play in this mental decline (Xu et al., 2024). Sustained high levels of glucose disrupt neuronal glucose processing and intensify oxidative stress, notably impacting the hippocampus, a critical region for memory development and learning activities (Aderinto et al., 2023). Research findings reveal that hyperglycemia triggers (Abbatecola et al., 2024) neuroinflammation and cerebrovascular impairment, which additionally detract from cognitive functions by lessening cerebral blood flow and oxygen supply. In experimental animal models, cognitive impairments have been correlated with compromised insulin signaling and neuroplasticity, thereby elucidating the significance of insulin resistance in the trajectory of cognitive decline (Ansari et al., 2023). Moreover, systematic reviews indicate that efficacious glycemic management can alleviate cognitive impairment, underscoring the criticality of regulating blood glucose levels to sustain cognitive health in individuals with diabetes (Lin et al., 2023). Altogether, the detailed relationship among hyperglycemia, oxidative stress, and neuroinflammation accentuates the multifarious characteristics of cognitive decline in diabetes

Ziziphus mauritiana, commonly known as jujube, is a traditional medicinal plant widely recognized for its therapeutic potential. Its seeds and fruits are rich in phytochemicals such as alkaloids, flavonoids, saponins, and phenolic compounds, which have demonstrated anti-inflammatory, antioxidant, and neuroprotective properties in various preclinical studies (Mehta et al., 2019; Sharma et al., 2021). These bioactive compounds have been reported to mitigate oxidative stress, reduce neuroinflammation, and improve synaptic plasticity, making *Ziziphus mauritiana* a promising candidate for cognitive health (Bhatia et al., 2021). While the hypoglycemic and anti-inflammatory effects of *Ziziphus mauritiana* have been extensively studied, its potential role in modulating cognitive functions remains relatively unexplored (Sharma et al., 2021). Given the intricate relationship between oxidative stress, inflammation, and cognitive decline, this study investigates whether *Ziziphus mauritiana* supplementation can enhance spatial working and recognition memory in Swiss albino mice.

Swiss albino mice are commonly used in neurobehavioral studies due to their well-characterized brain functions and predictable responses to cognitive tests (Tan et al., 2019). By utilizing this model, we aim to elucidate the neurocognitive benefits of *Ziziphus mauritiana* supplementation, thereby contributing to the growing body of evidence supporting its therapeutic potential.

This study hypothesizes that *Ziziphus mauritiana* supplementation improves spatial working memory and recognition memory through its antioxidative and neuroprotective mechanisms. The findings could pave the way for developing novel plant-based supplements aimed at preventing or managing cognitive decline in neurodegenerative diseases.

2. Materials and Methods

2.1 Animals and Preparation of *Ziziphus mauritiana*

A total of twenty (20) Swiss albino mice weighing (24 – 30) grams were housed in plastic cages under standard laboratory conditions with free access to food and water for two weeks to acclimatize with the laboratory environment before commencement of the experiments. Ethical clearance was obtained from the Research Ethics Committee (SAZU/FBMS/REC/VOL.I/23). The animals were handled by principles guiding the use and handling of experimental animals by the London Declaration of September 1977. All drugs and reagents were obtained commercially and were of analytical grades.

Fresh ripen fruits of *Z. mauritiana* was obtained from Azare market, Katagum Local Government Area, Bauchi State, Nigeria. The specimen was identified and authenticated the Herbarium Unit of Department of Biological Sciences, Sa'adu Zungur University, Bauchi State. A voucher number (*1466*) was allocated. The fruits were first washed and dried for one week. The dried fruits were grounded and sieved through a mesh to obtain a fine powder.

A digital glucometer (Accu-Chek Advantage, Roche Diagnostic, Germany) was used for the determination of the blood glucose levels of the animals.

2.2 Estimation of blood Glucose level

Blood glucose levels were checked to establish that the animals were normal. The blood sample was obtained by sequential snipping of the tail (Fluttert *et al*., 2000). Animals were fasted for about 12 hours (overnight) before the determination of blood glucose level (Sun *et al*., 2016). A digital glucometer was used to measure the blood glucose level (Beach and Turner, 1958) and results were recorded in mg/dL.

2.3 Animal grouping

The animals were divided into four groups of five mice each and fed with the appropriate combination of thoroughly mixed vital feed and *Z. mauritiana* for 14 days. The study comprised of four groups of five (5) Swiss albino mice (N = 5) as follows;

Group I received distilled water 10 ml/kg
Group II received glibenclamide 2 mg/kg
Group III received *Z. mauritiana* supplement 25 mg/kg
Group IV received *Z. mauritiana* supplement 50 mg/kg
Group V received *Z. mauritiana* supplement 100 mg/kg

2.4 Experimental procedures

Y-maze test (Spontaneous alternation version)

In this version each mouse is placed in the Y-maze for 6-8 minutes and the number of arms entered as well as the sequence of entries is recorded and a score is calculated to determine the alternation rate. An alternation is defined as entry into all three arms consecutively. For instance, if an animal makes the following arm entries: A, C, B, C, A, B, C, A, C, A, B, C, A; the animal has made 13 arm entries 8 of which are correct alternations. The number of maximum spontaneous alternations is then the total number of arms entered minus two, and the percentage alternation is calculated as (actual alternations/maximum alternations x 100). A high alternation rate is indicative of sustained spatial working memory as the animals must remember which arm was entered last to not re-enter it

Novel object recognition task

The Novel Object Recognition Task is an open-field evaluation of rats' innate propensity to study a novel object rather than the one they are familiar with. The decision to examine the novel object and the decision to resume exploration after an object has been moved demonstrated the use of memory and learning processes (recognition) in experimental animals (Antunes and Biala, 2012). This task consists of two phases separated by 24 hours. The test was conducted between 0700 and 0900 hours after induction before the commencement of *Z. mauritiana* administration.

(Retention interval): The sample phase and the test phase. The rats were shown two identical objects during the sample phase. These items were positioned 15 cm from each neighboring wall in the corners of an arena. Between the sample and test phases, each rat was put in the center of the arena and given 5 minutes to examine the items. To get rid of smell clues, alcohol was used to disinfect all the items. Then, during the test phase, one of the objects was switched, and the rat was given five minutes to investigate the new object. The amount of time spent investigating the two altered objects is compared to the amount of time spent investigating the other object (spatial memory, Ability to identify and discriminate). The rat will spend more time investigating the two objects that were changed compared to the unchanged object if its spatial memory and ability to discriminate and recognize are still functional.

Difference (long-term memory) = Tn – Tf (Tn = time spent exploring the novel object, Tf = time spent exploring the familiar object).

DI = $\frac{Tn-Tf}{Tn+Tf}$

Recognitive index = $\frac{Tn}{Tn+Tf} \times 100$ (Garkuwa *et al*., 2017; Antunes and Biala, 2012; Baxter, 2010; Burke *et al*., 2010)

2.5 Statistical Analysis

Data obtained were expressed as mean ± standard error of mean (SEM). The data were statistically analyzed using repeated measure analysis of variance (ANOVA). *Tukey's* multiple comparison post hoc test was used to see where significance exist. The values of $p < 0.05$ were considered as significant.

3. Results

To determine whether *Z. mauritiana* supplement has effect on the blood glucose levels of normal animals, we checked the blood glucose level before and after 14 days of supplementation with the different doses of *Z. mauritiana* (Table 1) using a digital glucometer and observed no significant ($p < 0.05$) change in the blood glucose level after supplementation compared to the blood glucose level before supplements were given.

Table 1: Effect of *Z. mauritiana* Supplement on Blood Glucose Level of Normoglycemic mice

Group	Supplement	Before Supplementation (mg/dl)	After Supplementation (mg/dl)
I	Normal saline 10 ml/kg	108.00 ± 5.74	104.50 ± 3.12
II	Glibenclamide 2 mg/kg	114.25 ± 8.11	107.00 ± 2.38
III	*Z. mauritiana* 25 mg/kg	154.25 ± 12.08	147.50 ± 11.36
IV	*Z. mauritiana* 50 mg/kg	130.50 ± 5.74	129.50 ± 9.28
V	*Z. mauritiana* 100 mg/kg	155.75 ± 11.87	130.25 ± 9.38

Values were expressed as mean ± SEM. *Z. mauritiana*: *Ziziphus mauritiana*

Also, to determine the effect of *Z. mauritiana* supplement on spatial working memory, we used spontaneous alternation version in Y maze paradigm as shown in Table 2 below. We observed an improvement in the percentage alternation on day 14 of group IV (*Z. mauritiana* 50 mg/kg) compared to day 0 of the same group. No statistical difference was observed between the different groups after 14 days of *Z. mauritiana* administration which means the spatial working memory of the animals were not improved.

Table 2: Effect of *Z. mauritiana* Supplement on Spatial Working Memory of Swiss albino mice

Group	Supplement	Percentage alternation (%) Day 0	Percentage alternation (%) Day 14
I	Normal saline 10 ml/kg	60.50 ± 4.52	74.50 ± 3.07
II	Glibenclamide 2 mg/kg	64.75 ± 4.33	69.00 ± 4.30
III	*Z. mauritiana* 25 mg/kg	69.25 ± 7.11	59.25 ± 4.35
IV	*Z. mauritiana* 50 mg/kg	60.00 ± 6.78	72.50 ± 5.68*
V	*Z. mauritiana* 100 mg/kg	64.50 ± 3.93	60.50 ± 5.33

Values with * superscript are statistically significant ($p < 0.05$) when compared to the control group. *Z. mauritiana*: *Ziziphus mauritian*

To determine the effect of *Z. mauritiana* supplement on memory (long-term, discrimination and recognition indices), we used novel object recognition tasks. The test was done before and after the 14-day supplementation. We observed an improvement in both long-term memory and discriminative index in group IV on day 14 (*Z. mauritiana* 50 mg/kg) compared to day 0 of the same group (table 3 and 4).

Table 3: Effect of *Z. mauritiana* Supplement on Social Memory (long-term and Discriminative index) in Swiss albino mice.

Group	Supplement (%)	Difference Day 0	Difference Day 14	DI Day 0	DI Day 14
I	Normal saline 10 ml/kg	5.02 ± 2.13	3.48 ± 1.10	0.04 ± 0.02	0.03 ± 0.01
II	Glibenclamide 2 mg/kg	4.00 ± 1.78	9.00 ± 6.12[a]	0.03 ± 0.01	0.07 ± 0.04
III	*Z. mauritiana* 25 mg/kg	20.75 ± 2.75	4.50 ± 0.65	0.14 ± 0.02	0.04 ± 0.01
IV	*Z. mauritiana* 50 mg/kg	-6.00 ± 8.04	7.50 ± 4.35[*]	-0.06 ± 0.08	0.06 ± 0.03[*]
V	*Z. mauritiana* 100 mg/kg	1.75 ± 2.84	10.25 ± 6.97[*#]	0.01 ± 0.02	0.07 ± 0.05[*#]

Values having * superscripts are statistically significant ($p < 0.05$) when compared to control. *Z. mauritiana*: *Ziziphus mauritiana*; DI: Discrimination index; RI: Recognitive index group.

Table 4: Effect of *Z. mauritiana* Supplement on Social Memory (Recognitive index) in Swiss albino mice.

Group	Supplement	RI (%) Day 0	RI (%) Day 14
I	Normal saline 10 ml/kg	51.79 ± 0.83	51.36 ± 0.43
II	Glibenclamide 2 mg/kg	51.60 ± 0.69	53.33 ± 2.11
III	*Z. mauritiana* 25 mg/kg	56.94 ± 0.86	52.06 ± 0.30
IV	*Z. mauritiana* 50 mg/kg	46.85 ± 3.99	53.02 ± 1.68[*]
V	*Z. mauritiana* 100 mg/kg	50.71 ± 1.10	53.62 ± 2.67

Values having * superscripts are statistically significant ($p < 0.05$) when compared to control. *Z. mauritiana*: *Ziziphus mauritiana*; RI: Recognitive index group.

4. Discussion

The present study found that *Ziziphus mauritiana* supplementation did not significantly alter blood glucose levels in normal animals after 14 days of administration. This suggests that the hypoglycemic effects of *Z. mauritiana* may be condition-dependent, primarily benefiting individuals with impaired glucose metabolism rather than normoglycemic subjects. The observed lack of effect in normal animals could be attributed to well-maintained glucose homeostasis, where insulin and glucagon dynamically regulate blood sugar levels, thereby minimizing fluctuations (Adewole et al., 2020). Previous studies have demonstrated that plant-based hypoglycemic agents tend to exert their effects more prominently in diabetic or insulin-resistant models. For instance, Khan et al. (2019) reported that bioactive compounds in medicinal plants often act by enhancing insulin sensitivity, reducing oxidative stress, or promoting pancreatic β-cell regeneration, mechanisms that may not be prominent in normoglycemic conditions. Moreover, the hypoglycemic activity of *Z. mauritiana* could be mediated through its polyphenolic content, which is known to modulate glucose uptake and metabolism by targeting AMPK (AMP-activated protein kinase) pathways in hyperglycemic models (Rahman et al., 2021). Another possible explanation for the lack of significant glucose reduction is the duration of treatment and dosage. Cichon et al. (2020) demonstrated that certain plant extracts require prolonged administration, typically exceeding four weeks, to produce metabolic effects. Additionally, the administered doses may not have been sufficient to induce measurable changes in normoglycemic animals. Future studies should consider employing diabetic models, longer treatment durations, and higher doses to better characterize the hypoglycemic potential of *Z. mauritiana*.

The Y-maze spontaneous alternation test was utilized to assess spatial working memory. While *Z. mauritiana* supplementation at 50 mg/kg (Group IV) showed an improvement in percentage alternation on day 14 compared to baseline (day 0), no statistically significant differences were observed between the treatment groups after 14 days. This finding suggests that *Z. mauritiana* may exert mild cognitive-enhancing effects, but these effects were not robust enough to be statistically significant. The observed improvement in within-group performance may be indicative of potential neuroprotective and memory-enhancing effects through its antioxidant and anti-inflammatory properties. Previous studies have shown that plant-derived flavonoids and alkaloids contribute to synaptic plasticity and neuroprotection, which are critical for memory formation and retrieval (Rahman et al., 2021). However, the absence of significant between-group differences suggests that the improvement may be either dose-dependent or require longer administration periods to manifest in a meaningful way. Another explanation could be that plant-based cognitive enhancers often produce more pronounced effects in aged or cognitively impaired models rather than in young, healthy subjects. Studies have indicated that polyphenols exhibit stronger effects in models of oxidative stress-induced cognitive dysfunction rather than in normal physiological conditions (Khan et al., 2020). Consequently, future investigations should explore the efficacy of *Z. mauritiana* in aging models, neurodegenerative conditions, or animals with induced cognitive deficits.

The novel object recognition test was used to evaluate long-term memory and object discrimination ability following *Z. mauritiana* supplementation. The results revealed a significant improvement in both long-term memory and discrimination index in Group IV (50 mg/kg) on day 14 compared to baseline, suggesting a potential cognitive-enhancing effect. The observed enhancement in object recognition memory is particularly relevant, as this task is highly sensitive to hippocampal function and dependent on the integrity of synaptic plasticity and cholinergic neurotransmission. Several bioactive compounds in *Z. mauritiana*, including flavonoids and alkaloids, have been implicated in enhancing acetylcholine levels, reducing oxidative stress, and modulating neuroinflammatory pathways, all of which are essential for memory consolidation (Rahman et al., 2021). One possible explanation for the selective improvement in recognition memory but not spatial working memory is that the hippocampus and prefrontal cortex mediate different cognitive processes. Recognition memory relies more on hippocampal-dependent mechanisms, whereas spatial working memory involves prefrontal cortex activity and is more sensitive to executive function deficits (Khan et al., 2020). The results suggest that *Z. mauritiana* may preferentially target hippocampal synaptic plasticity, leading to improvements in long-term recognition memory rather than executive function-related tasks. The neurobiological mechanism underlying these improvements remains unclear. However, studies have proposed that plant-derived polyphenols may enhance BDNF (Brain-Derived Neurotrophic Factor) signaling, which is crucial for synaptic strength, neuronal survival, and cognitive resilience (Cichon et al., 2020). Future studies should investigate whether *Z. mauritiana* supplementation modulates BDNF expression, cholinergic activity, or oxidative stress markers to elucidate its mode of action.

5. Conclusion

In summary, the findings suggest that *Z. mauritiana* supplementation did not significantly alter blood glucose levels in normal animals, indicating a condition-dependent hypoglycemic effect that may be more relevant in hyperglycemic states. In terms of cognitive function, no statistically significant improvement in spatial working memory was observed; however, long-term memory and discriminative index were enhanced in the 50 mg/kg treatment group, suggesting a possible selective effect on hippocampus-dependent memory processes. These results highlight the potential dose-dependent and time-dependent effects of *Z. mauritiana*, emphasizing the need for further studies using diabetic models, higher doses, and longer supplementation periods. Additionally, investigating aged or neurodegenerative models may provide further insights into the plant's cognitive-enhancing properties. Future research should also focus on molecular mechanisms, particularly BDNF signaling, cholinergic modulation, and antioxidant pathways, to better understand the neuroprotective potential of *Z. mauritiana*.

Declarations

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Consent for publication

All authors have read and approved the final draft of the manuscript

Availability of data and material

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests

Authors' contributions

BI and UAG conceptualized the design of the study. BI, AH, HM, YT conducted the research under the supervision of BI, MB, AHG and UAG. UAG, BI prepared the first draft of the manuscript. All authors helped in the data collection and analysis. BI and UAG did the interpretation of the results. All authors read and approved the final manuscript.

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