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Effect of *Curcuma longa* Supplement on Cognitive Performance in Swiss Albino Mice

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Abstract

Dementia is an age-related mental disorder and a characteristic symptom of various neurodegenerative disorders. Hyperglycemia affects areas of the brain crucial for learning and memory processes, potentially leading to cognitive impairments in individuals with diabetes. *Curcuma longa (C. longa)* contains many pharmacological and chemically important compounds with many beneficial effects. This study aimed to evaluate the effect of *Curcuma longa* on cognitive function in Swiss albino mice. A total of sixteen (16) mice of both sexes weighing between 24 – 30 grams were used for the study. The mice were divided into four groups of four mice each (N=4). Group I served as control and received 10 ml/kg distilled water; groups II, III and IV were given 5%, 10% and 20 % of *Curcuma longa* 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 that the 5% *C. longa* (77.60 ± 10.15%) group showed significant ($p < 0.05$) improvement in percentage alternation compared to the control group (64.40 ± 5.99%). We also found out that the 5% *C. longa* supplemented group showed a significant ($p < 0.05$) increase in both long-term memory (-14.08 ± 3.26) and discriminative index (-0.26 ± 0.07) when compared to control group (-31.55 ± 2.65) and (-0.33 ± 0.07) respectively. Thus, *C. longa* supplement at 5% improves spatial working memory, long-term memory and discriminative index of Swiss albino mice.

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1.0 Introduction

The sensory processor allows us to perceive external stimuli while working memory encodes and retrieves information (Shetty, 2014; Voss *et al.*, 2017). However, memory is not infallible; it can be influenced by various factors. New stimuli may receive less attention during encoding, leading to incomplete storage (Ainsworth and Lowe, 2012). Without memory, language development, relationship building, and personal identity would be impossible (Bernecker, 2009). Learning and memory are not limited to humans; animals and even some machines exhibit learning (Čapek and Loidolt, 2021). An immediate responses triggered by single events to cumulative knowledge gained through repeated experiences, learning shapes our lives (Čapek and Loidolt, 2021). Research across fields like educational

psychology, neuropsychology, and experimental psychology has identified various forms of learning, including habituation, classical conditioning, and operant conditioning (Camina and Güell, 2017; Tyng *et al.,* 2017). Despite these challenges, memory remains a fundamental aspect of our cognitive functioning (Anand and Dhikav, 2012).

Chronic hyperglycemia in individuals with diabetes mellitus is associated with a decline in the formation of spines and the branching of dendrites in brain regions that are involved in memory and learning, such as the prefrontal cortex, hippocampus, and basolateral amygdala (Gupta et al., 2023; Li *et al.,* 2023). The impact of type 2 diabetes mellitus on memory and cognitive function is particularly significant (Voss *et al.,* 2017). Elevated blood glucose levels, even in the absence of diabetes, have a detrimental effect on memory performance and the size and structure of the hippocampus (Flores-Gómez *et al.,* 2019; Gupta *et al.,* 2023). Diabetes also increases the likelihood of developing dementia, including Alzheimer's disease and vascular dementia (Feinkohl *et al.,* 2015). Individuals with prediabetes or type 2 diabetes demonstrate lower cognitive abilities, especially in working memory (Saedi *et al.,* 2016). These findings indicate that chronic hyperglycemia in diabetes has an impact on memory and learning processes, and the management of blood glucose levels may have a positive influence on cognition (Feinkohl *et al.,* 2015; Saedi *et al.,* 2016).

Few researches have been carried out on the potential effects of Curcuma longa, commonly referred to as Turmeric and its primary constituent curcumin in terms of normoglycaemic animals. Several studies have shown that supplementation with curcumin can lead to significant reductions in fasting blood glucose levels and hemoglobin A1C, a marker of long-term regulation of the plasma glucose level (Marton *et al.,* 2021; Ortiz *et al.,* 2022; Pathomwichaiwat *et al.,* 2023). Turmeric's favorable effects on glucose and lipid metabolism are attributed to its anti-inflammatory, antioxidant, and anti-hyperglycemic qualities (Rivera-Mancía *et al.,* 2018). Additionally, curcumin has been shown to improve neuropathic pain and decrease the production of molecules known as advanced glycation end products, which are linked to issues related to diabetes (Ghorbani *et al.,* 2014). Curcumin's anti-inflammatory and antioxidant characteristics are thought to play a major part in its capacity to improve glycemic control and lessen problems associated with diabetes (Zhang *et al.,* 2013; Ghorbani *et al.,* 2014; Pathomwichaiwat *et al.,* 2023). This research aimed to determine the effect of Curcuma longa on cognitive function in normoglycemic mice.

2. 0 Materials and Methods

2.1 Animals and Preparation of *Curcuma longa*

A total of sixteen (16) 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 Ahmadu Bello University Committee on Animal Use and Care (ABUCAUC/051). 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. *C. longa* was obtained from the College of Agriculture Bauchi State and identified by the Department of Forestry and a voucher number *1466* was allocated. The rhizomes of the turmeric were first washed and sliced into pieces and dried. The dried rhizomes were then ground to 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

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 fasting 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 *C. longa* for 14 days. The study comprised of four groups of four (4) Swiss albino mice (N=4) as follows;

Group I received distilled water and vital feed 100% (9.7% moisture, 2 % ash, 9% crude fiber, 10% fat, 20 % crude protein and 49.3% carbohydrate)

Group II received *C. longa* 5% and 95% of vital feed (9.2% moisture, 1.9 % ash, 8.6% crude fiber, 9.5% fat, 19 % crude protein and 46.8% carbohydrate)

Group III received *C. longa* 10% and 90% of vital feed (8.7% moisture, 1.8% ash, 8.1% crude fiber, 9% fat, 18 % crude protein and 44.4% carbohydrate) and

Group IV received *C. longa* 20% and 80% of vital feed (7.8% moisture, 1.6% ash, 7.2% crude fiber, 8% fat, 16 % crude protein and 39.4% carbohydrate).

2.4 Experimental Procedures

Spontaneous alternation in Y-maze

In this version each mouse was placed in the Y-maze for 6-8 min and the number of arms entered as well as the sequence of entries was recorded and a score was

calculated to determine alternation rate. An alternation is defined as entry into all three arms consecutively. 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) (Hughes, 2004).

Novel object recognition task

The Novel Object Recognition Task is an open-field evaluation of mice 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 *C. longa* administration.

(Retention interval): The sample phase and the test phase. The mice 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 mouse 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 mouse 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 mouse 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 = $\frac{Tn}{Tn+Tf} \times 100$ (Baxter, 2010; Burke *et al*., 2010; Antunes and Biala, 2012; Garkuwa *et al*., 2017)

2.5 Statistical Analysis

Data obtained were expressed as mean ± SEM. The data were statistically analyzed using one-way analysis of variance (ANOVA) with Ficher's least significant difference (LSD) *posthoc* test to compare the level of significance. The values of $p < 0.05$ were considered as significant.

3.0 Results and Discussion

We checked the fasting blood glucose level before and after 14 days of supplementation with the different percentages of *C. longa* to see the effect of daily administration on normoglycemic mice (Table 1).

Table 1: Effect of *Curcuma longa* Supplement on Fasting Blood Glucose Level of Normoglycemic Swiss albino mice

Group	Supplementation	Before Supplementation (mg/dL)	After Supplementation (mg/dL)
I	Control	87.64 ± 5.70	114.60 ± 4.52
II	*C. longa* 5%	97.20 ± 10.84	130.60 ± 3.78
III	*C. longa* 10%	97.80 ± 15.76	115.08 ± 9.57
IV	*C. longa* 20%	98.28 ± 7.46	195.84 ± 14.46*

Values with asterisks (*) superscript are statistically significant ($p < 0.05$) when compared to the control group.

Also, to determine the effect of *C. longa* supplement on spatial working memory, we used a spontaneous alternation version using the Y maze paradigm as shown in Table 2 below. We observed an improvement in the percentage alternation in group II (5%) compared to the control.

Table 2: Effect of *Curcuma longa* Supplement on Spatial Working Memory of Swiss albino mice

Group	Supplement (%)	Percentage alternation (%)
I	Control	64.40 ± 5.99
II	*C. longa* 5%	77.60 ± 6.71*
III	*C. longa* 10%	65.40 ± 9.23
IV	*C. longa* 20%	51.60 ± 10.15

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

To determine the effect of *C. longa* supplement on memory (long-term, discrimination and recognition indices), we used novel object recognition tasks before and after the 14-day supplementation. We observed an

improvement in both long-term memory and discriminative index in group II (5%) compared to the control (Table 3).

Table 3: Effect of *Curcuma longa* Supplement on Social Memory in Swiss albino mice.

Group	Supplement (%)	Dif	DI	RI (%)
I	Control	-31.55 ± 2.65	-0.32 ± 0.02	33.64 ± 1.18
II	*C. longa* 5%	-14.08 ± 3.26*	-0.26 ± 0.07*	36.82 ± 3.39
III	*C. longa* 10%	-42.25 ± - 7.07	-0.46 ± 0-07	27.04 ± 3.30
IV	*C. longa* 20%	-38.25 ± 6.78	-0.05 ± 0.10*	25.16 ± 4.99*

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

4.0 Discussion

Researches into the study of diabetes and memory impairment in recent years are gaining more attention mainly focusing on how diabetes mellitus causes memory deficit and the possible ameliorative effects of antioxidants. Only few researchers tried to explore the effect of some of these antioxidants on normoglycemic animals. The pathophysiology of memory has been proposed to include the role played by hyperglycemia, oxidative stress and mitochondrial dysfunction, inflammation, and dyslipidemia. We observed that supplementation with *C. longa* is relatively safe at low percentage intake. This study showed continues increase in blood sugar level with increase in the quantity of usage, an indication of possible risk of hyperglycaemia if used without control or professional advice. At 5%, the supplement improved spatial working memory significantly. This indicates that *C. longa* may be beneficial to both diabetic and non-diabetic animals as previous studies indicated its beneficial role in the mitigation of diabetes-induced memory impairment. This was due its anti-inflammatory, antioxidant and lipid-lowering potentials. Other doses showed no any significant change when compared with the control. Previous studies using curcumin (an active constituent of *C. longa*) in pre-treated rats reported improvement in the impaired spatial working memory in global cerebral ischemia-reperfusion by inhibiting proinflammatory cytokines (Ji *et al*., 2014). Also, a higher dose of curcumin has an interaction with the cholinergic system in the formation of spatial learning in rats, thereby improving spatial learning when pre-injected (Ghadami *et al*., 2012).

The results obtained in this study indicated that supplementation of *C. longa* for fourteen (14) days improved long-term memory in NORT in the 5% group compared to the control. This indicated the potential beneficial effect of *C. longa* in normal animals. Other researches on *C. longa* and diabetes or hyperglycemia mostly used diabetic animals and reported protective effects mostly through its antihyperglycemic, antilipidemic, antioxidant and anti-inflammatory properties (Chuengsamarn *et al*., 2012; Pivari *et al*., 2019; Sharifi-Rad *et al*., 2020; Fuloria *et al*., 2022; Pathomwichaiwat *et al*., 2023). This adds to its vast therapeutic potential if taken with adequate caution. However, with increased concentration (20% supplementation), we found that the long-term memory was affected compared to the control. This further adds to the possible reason why our previous study reported an increase in anxiety-like behavior in 20% of supplemented animals when compared with the control (Garkuwa *et al*., 2021).
Furthermore, the discriminatory index (DI) was assessed using a novel object recognition task (NORT). The discriminatory index is the measure of the ability of the mice to discriminate between two objects presented at different times. The findings of this study showed significant ($p < 0.05$) improvement in the DI when compared to the control group. Also, from the result observed in the treatment group, it is evident that hyperglycemia might impair discrimination ability. Mice that received 20% *C. longa* supplementation showed a significant ($p < 0.05$) decrease in the discriminatory index compared to *C. longa* 5% in the experimental animals. This might be as a result of the increase in blood glucose level which led to increased glucose shunting to the hexosamine pathway, and increased formation of advanced glycation end products (Kang and Yang, 2020; Li *et al*., 2023). It might also be as a result of the formation of reactive oxygen species which is associated with memory impairment or inflammation (Kang and Yang, 2020; Gupta *et al*., 2023).

5.0 Conclusion

These findings suggest that *C. longa* has a dose-dependent effect on cognition and glucose metabolism and that low-dose supplementation may have beneficial effects for both diabetic and non-diabetic individuals. However, high-dose supplementation may pose health risks and should be avoided. Further studies are needed to elucidate the molecular

mechanisms underlying the effects of *C. longa* on memory and learning processes.

Declarations

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Ethics approval and consent to participate
Ethical approval was obtained from the Ahmadu Bello University Committee on Animal Use and Care (ABUCAUC/051). The animals were handled by principles guiding the use and handling of experimental animals by the London Declaration of September 1977.

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.

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Authors' contributions
BI and UAG conceptualized the design of the study. ANB, MS, AT, SRM conducted the research under the supervision of AUK, AAL, AHG and UAG, BI and ANB prepared the first draft of the manuscript. AAL, AHG, MMJ helped in the data collection and analysis. AUK, SRM, ANB did the interpretation of the results. All authors read and approved the final manuscript

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