

# *Curcuma Longa* (Turmeric) Supplements Improved Fasting Blood Glucose Level and Anxiety-Like Behavior in Diabetic Wistar Rats

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## Abstract

*Turmeric is a spice derived from the rhizomes of *Curcuma longa* (C. longa) which is a member of the ginger family (Zingiberaceae). *Curcuma longa* is widely used for food spices, preservatives, and coloring agents. Anxiety disorders are the most frequently occurring mental disorders, they encompass a group of conditions that share extreme or pathological anxiety as the principal disturbance of mood or emotional tone. This study aimed to evaluate the effect of C. longa supplements on fasting blood glucose levels and anxiety-like behavior in diabetic Wistar rats. Twenty (20) rats were randomly assigned into five (5) groups of four each (N=4). Group I served as control and received distilled water (1 ml/kg), groups II, III, IV and V were diabetic and received glibenclamide (1mg/kg), and C. longa supplements at 2.5%, 5% and 10% respectively. Diabetes was induced using intraperitoneal injection of freshly dissolved alloxan monohydrate (150 mg/kg). All administrations were made for 21 days. Fasting blood glucose levels and anxiety-like behavior were determined using a digital glucometer and elevated plus*

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maze test respectively. Based on the results obtained from this study, there was significant ( $p < 0.05$ ) improvement in fasting blood glucose levels across all supplemented doses of *C. longa* (2.5%, 5% and 10% at  $9.33 \pm 0.46$  mmol/L,  $11.20 \pm 0.68$  mmol/L and  $11.00 \pm 0.40$  mmol/L respectively) compared to control group ( $18.13 \pm 1.28$  mmol/L). Time spent in the opened arm was also increased significantly ( $p < 0.05$ ) in 5% ( $18.25 \pm 1.18$  s) and 10% ( $19.25 \pm 1.49$  s) groups after 21 days of supplementation compared to before the commencement of supplementation ( $9.75 \pm 1.11$  s and  $10.25 \pm 1.49$  s respectively). These findings suggested that the *C. longa* supplement improved fasting blood glucose and anxiety-like behavior in diabetic Wistar rats.

**Keywords:** Anxiety, *Curcuma longa*, Diabetes mellitus, Fasting blood glucose.

## INTRODUCTION

Diabetes mellitus remains one of the leading causes of morbidity and mortality globally (Liu *et al.*, 2022). This is in addition to the financial burden it places on individuals and governments. The incidence and mortality due to diabetes continue to rise among both developed and developing nations despite many breakthrough researches (Animaw and Seyoum, 2017). Despite the availability of many medications to treat diabetes mellitus, still, the growing incidence and prevalence of this modern pandemic is yet to be checked (Abouzid *et al.*, 2022). These highlight the increasing burden of diabetes worldwide and the need for effective prevention and treatment strategies (Khan *et al.*, 2020; Lin *et al.*, 2020). Furthermore, currently available anti-diabetic drugs have several adverse effects, so there is increased demand for herbal/natural products that are supposed to have no or fewer side effects. Also, following the recommendation of the World Health Organization (WHO, 2022) expert committee on diabetes mellitus on the beneficial uses of medicinal plants in the treatment of diabetes mellitus, research on medicinal plants has gained momentum (Kooti *et al.*, 2016; Thorsen and Pouliot, 2016). Hyperglycaemia and insulin resistance in type 2 diabetes also increase the production of reactive oxygen species (ROS) which exacerbates the complications of type 2 diabetes (Giacco and Brownlee, 2010; Oguntibeju, 2019; Pasupuleti *et al.*, 2020).

Anxiety-related disorder is commonly observed in individuals diagnosed with diabetes. Numerous investigations have explored the correlation between diabetes and anxiety, particularly in patients with type 2 diabetes mellitus (T2DM) (Edwards and Mezuk, 2012; Chaturvedi *et al.*, 2019; Nigussie *et al.*, 2023). A high prevalence of stress and anxiety-related behavior among patients with T2DM was reported, indicating the necessity for the evaluation and control of stress and anxiety in these individuals (García-Lara *et al.*, 2022; McCoy and Theeke, 2019; Paudel *et al.*, 2023). Impairment or alterations in the noradrenergic locus coeruleus (LC), dysregulation of the serotonergic system, particularly the 5-HT<sub>1A</sub> receptors in the dorsal periaqueductal gray (dPAG), reduced leptin levels and leptin receptor expression in the prefrontal cortex (PFC) have been implicated in anxiety-like behavior in diabetic rats (Breton-Provencher *et al.*, 2021; Samuels and Szabadi, 2008; Taylor and Westlund, 2017). Oxidative stress and inflammation have been reported in diabetic patients. Both oxidative stress and inflammation play a role in the pathogenesis of anxiety-like behavior (Oguntibeju, 2019; Réus *et al.*, 2019).

*Curcuma longa*, commonly known as turmeric (kurkur in Hausa), is a spice with a long history of use in traditional medicine (Hatcher *et al.*, 2008). Its active component, curcumin, has been extensively studied for its potential therapeutic effects in various conditions (Sharifi-Rad *et al.*, 2020). Turmeric is a well-known condiment in the world. It is a prime ingredient in curry powder (Hewlings and Kalman, 2017). Turmeric is extensively used in medicinal systems and also as a home remedy for various ailments (Fuloria *et al.*, 2022). Traditional medicine is one of the richest medicinal systems in the world (Thorsen and Pouliot, 2016; Yuan *et al.*, 2016).

Turmeric has many medical properties with a wide spectrum of actions such as anti-inflammatory, anti-fungal, anti-mutagenic, and anti-carcinogenic (Ahmad *et al.*, 2020; El-Saadony *et al.*, 2022). *Curcuma longa* has been previously studied in the form of rhizome extract; it can be efficacious in reducing several parameters in DM patients (Chuengsamarn *et al.*, 2012; Pivari *et al.*, 2019). Also, *C. longa* rhizome extract caused a decrease in fasting blood glucose levels and glycated hemoglobin in humans (Pathomwichaiwat *et al.*, 2023). However, only a few researches focus on its influence on anxiety-like behavior in diabetic rats. Therefore, this research work investigated the effect of *C. longa* supplements on fasting blood glucose levels and anxiety-like behavior in diabetic Wistar rats.



Figure 1. *Curcuma longa* (turmeric) powder (Garkuwa *et al.*, 2018)

## **MATERIALS AND METHOD**

### **Chemicals and Supplements Collection and Preparation**

All chemicals and reagents used in this study were obtained commercially and were of analytical grade. *Curcuma 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 sliced into pieces and dried. The dried rhizomes were then ground to a fine powder. Alloxan was purchased from (Sigma Chemical Company St. Louis U.S.A.). A digital glucometer (Accu-Chek Advantage, Roche Diagnostic, Germany).

### **Study Animals and Ethical Approval**

Male and female Wistar rats weighing about 160 – 200 grams were purchased from the Department of Pharmacology and Therapeutics, Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria, Kaduna State. The animals were housed in well-ventilated cages in the animal house of the Department of Physiology, Bauchi State University Gadau. The rats were allowed to acclimatize for two weeks before the experiment and had free access to food and clean water. The animals were handled by principles guiding the use and handling of experimental animals by the London Declaration of September 1977. Ethical approval was obtained from the Bauchi State University Gadau Committee on Animal Use and Care (BASUG/FBMS/REC/VOL.2/23).

### **Induction of Diabetes**

The animals were fasted for 12 – 16 hours before the induction of diabetes. Diabetes was induced by a single intraperitoneal injection of alloxan monohydrate (150 mg/kg) dissolved

in 0.9% cold normal saline (Katsumata *et al.*, 1993). The rats were kept for the next 24 hours on a 5% glucose solution in their cages to prevent hypoglycemia (Dhandapani *et al.*, 2002). Rats with fasting blood glucose levels of 16 mmol/L were selected for the study (De Magalhães *et al.*, 2019).

### **Experimental Design**

Twenty (20) rats were used and were grouped into Five (5) groups of Four (4) rats each. The supplementation was administered to the animals for three weeks (21 days).

Group I: diabetic + distilled water (1 ml/kg)

Group II: diabetic + glibenclamide (1 mg/kg)

Group III: diabetic + 2.5% *C. longa*

Group IV: diabetic + 5% *C. longa*

Group V: diabetic + 10% *C. longa*

### **Estimation of Blood Glucose Level**

Fasting blood glucose was estimated before and after the commencement of *C. longa* supplementation (days 0 and 21). 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 expressed in mmol/L (Katsumata *et al.*, 1993).

### **Elevated plus Maze (EPM) for Anxiety Assessment**

Anxiety-like behavior was determined before and after the commencement of *C. longa* supplementation (days 0 and 21). The EPM was used to test exploratory and anxiety-like behavior. The elevated plus-maze test was conducted as described by Komada *et al.* (2008). The elevated plus-maze consists of two open arms (28 × 5 cm) and two closed arms (30 × 5 cm) with a 15-cm high wall. The arms and central square were made of wooden plates elevated 51 cm above the floor. Notably, the arms of the same type are located opposite from each other. Each rat was placed in the central square of the maze (5 × 5), facing one of the closed arms. Then, the behavior of the mouse including time spent in the open and closed arm was recorded and analyzed during a 5 min test period.

### **Statistical Analysis**

Data obtained were expressed as mean ± SEM. One-way analysis of variance (ANOVA) was used to compare between groups. Dunnett *post hoc* test was employed to determine the level of significance. While paired t-test was used to compare groups (days 0 and 21) using a statistical package for social sciences (SPSS). The values of  $p < 0.05$  were considered as significant.

## **RESULTS**

To determine if *C. longa* supplementation for 21 days affected fasting blood glucose levels in diabetic rats, we checked the blood glucose level after diabetes induction (before commencement of supplementation (day 0)). It was found that after *C. longa* supplementation for 21 days at 2.5%, 5%, and 10%, FBG was significantly ( $p < 0.05$ ) reduced when compared with the control group as detailed in Table 1.

Table 1. Effect of *Curcuma longa* Supplement on Fasting Blood Glucose (FBG) Level in Diabetic Wistar Rats.

Group	Treatment	Day 0 (before treatment) (mmol/L)	Day 21 (after treatment) (mmol/L)
I	DW (1 ml/kg)	22.15 ± 0.77	18.13 ± 1.28
II	Glib (1 mg/kg)	21.80 ± 0.70	9.28 ± 1.06*#
III	<i>C. longa</i> 2.5%	24.23 ± 1.16	9.33 ± 0.46*#
IV	<i>C. longa</i> 5%	19.48 ± 1.27	11.20 ± 0.68*#
V	<i>C. longa</i> 10%	24.20 ± 1.19	11.00 ± 0.40*#

Values having superscripts are statistically ( $p < 0.05$ ) significant. \* = compared with group I (between groups) and # = compared with day 0 (before supplementation). DW = distilled water; Glib = glibenclamide

To determine if time spent in different arms was affected by 21 days of supplementation with *C. longa*, anxiety-like behavior was determined using EPM before (after diabetes was induced) and after *C. longa* supplementation. After 21 days of administration, it was observed that time spent in the open arm was increased significantly ( $p < 0.05$ ) when compared with day 0 (before commencement of supplementation after diabetes was induced) in groups IV and V as detailed in Table 2.

Table 2: Effect of *Curcuma longa* Supplement on Time Spent in Closed and Opened Arms in Diabetic Wistar Rats

Group	Treatment	Closed Arm Day 0 (s)	Closed Arm Day 21 (s)	Opened Arm Day 0 (s)	Opened Arm Day 21 (s)
I	DW (1 ml/kg)	265.00 ± 13.39	276.25 ± 10.28	37.00 ± 1.22	17.75 ± 1.89
II	Glib (1 mg/kg)	265.50 ± 7.01	216.00 ± 7.22#	17.50 ± 1.04	46.25 ± 3.25
III	<i>C. longa</i> 2.5%	230.25 ± 1.70	284.75 ± 5.41#	67.00 ± 5.70	7.75 ± 1.11*#
IV	<i>C. longa</i> 5%	283.75 ± 8.72	271.75 ± 8.05	9.75 ± 1.11	18.25 ± 1.18#
V	<i>C. longa</i> 10%	287.75 ± 7.31	273.75 ± 16.75	10.25 ± 1.49	19.25 ± 1.49#

Values having superscripts are statistically ( $p < 0.05$ ) significant. \* = compared with group I (between groups) and # = compared with day 0 (before supplementation). DW = distilled water; Glib = glibenclamide

We also used the number of arms entry into both closed and open arms before and after supplementation to see whether *C. longa* supplementation for 21 days would have affected it. It was observed that the number of entry for both closed and opened arms were not affected significantly ( $p > 0.05$ ) as seen in Table 3.

Table 3. Effect of *Curcuma longa* Supplement on Number of Arms Entered in Diabetic Wistar Rats

Group	Treatment	Closed Arm Day 0	Closed Arm Day 21	Opened Arm Day 0	Opened Arm Day 21
I	DW (1 ml/kg)	1.33 ± 0.24	1.25 ± 0.25	2.00 ± 0.29	0.50 ± 0.29
II	Glib (1 mg/kg)	1.75 ± 0.25	4.00 ± 0.41*#	2.25 ± 0.75	3.25 ± 0.75*
III	<i>C. longa</i> 2.5%	1.25 ± 0.25	2.25 ± 0.95	1.25 ± 0.58	1.00 ± 0.58
IV	<i>C. longa</i> 5%	1.25 ± 0.25	1.00 ± 0.00	1.00 ± 0.00	0.00 ± 0.00
V	<i>C. longa</i> 10%	2.75 ± 0.63	2.50 ± 0.87	2.25 ± 1.44	2.25 ± 1.44*

Values having superscripts are statistically ( $p < 0.05$ ) significant. \* = compared with group I (between groups) and # = compared with day 0 (before supplementation). DW = distilled water; Glib = glibenclamide

## DISCUSSION

Anxiety-like behavior and depression are common comorbidities in diabetes, and addressing mental health is important for the proper management and prognosis of the disease (Bădescu *et al.*, 2016). Studies have shown that people with diabetes are more likely to have depression than those without diabetes (Chaturvedi *et al.*, 2019). The prevalence of depressive disorder in diabetic patients is high. Oxidative stress plays a role in the development of anxiety and depressive disorders in diabetes (Réus *et al.*, 2019; Bampi *et al.*, 2020). The management of diabetes becomes challenging when combined with mental health conditions, and patients who struggle with mental health concerns may have difficulty managing their diabetes (Akhaury and Chaware, 2022; Barbosa *et al.*, 2022). Limited research focuses on mental disorders in diabetic experimental animals. In this study, we determined the effect of 21 days of *C. longa* supplementation on fasting blood glucose levels and anxiety-like disorders in diabetic Wistar rats.

From the findings of this study, FBG level was reduced significantly ( $p < 0.05$ ) after supplementation for 21 days across 2.5%, 5% and 10% when compared with the control groups. Previous studies demonstrated the beneficial role of *C. longa* among diabetic animals. It was shown to improve glucose metabolism (Uchio *et al.*, 2022), reduce fasting blood glucose levels (Pathomwichaiwat *et al.*, 2023), glycaemic control and reduce the formation of advanced glycation end products among type-2 diabetic individuals (Abbas *et al.*, 2022). Hyperglycemia has been the major driver of oxidative stress, inflammation and dyslipidemia (Hasheminasabgorji and Jha, 2021; Tangvarasittichai, 2015). These have all been linked to the pathogenesis of many neuropsychiatric disorders among diabetic patients. Managing the blood glucose level could be beneficial and reduce the occurrence of many other complications associated with diabetes.

The elevated plus maze is an open-field test that examines anxiety-like behavior in experimental animals (Komada *et al.*, 2008). In this study we observed a significant ( $p < 0.05$ ) increase in the time spent in the opened arm after 21 days of supplementation in both 5% and 10% groups compared to day 0 (after diabetes induction and before commencement of supplementation). This indicated a reduction in anxiety in the group that was supplemented with 5% and 10%. There was no significant difference in the number of arms entered between days 0 and 21 as seen in Table 3. The results may be attributed to the antihyperglycaemic property of *C. longa*, its antioxidant and anti-inflammatory properties. Poor glycaemic control, oxidative stress, dyslipidemia and inflammation have been linked to anxiety-like behavior and *C. longa* might have acted through its effect on blood glucose levels, antioxidant enzyme activities, inflammation and dyslipidemia (Ahmad *et al.*, 2020; Sharifi-Rad *et al.*, 2020; Ovaditya *et al.*, 2022; Pathomwichaiwat *et al.*, 2023). These findings disagree with our previous findings where a high percentage (20% *C. longa* supplementation) increases anxiety-like behavior in normoglycaemic animals (Garkuwa *et al.*, 2021).

## CONCLUSION

In conclusion, this study demonstrated that *C. longa* supplements improved fasting blood glucose levels and anxiety-like behavior in diabetic Wistar rats. *Curcuma longa* may offer a promising natural alternative for managing diabetes and anxiety-related disorders. However, further research is needed to elucidate the mechanisms of action and optimize the dosage and treatment regimen of *C. longa* for human application.

## Conflict Interests

The authors declare no competing interests.

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