African Scientist Vol. 24, No. 2 June 30, 2023
Printed in Nigeria

1595-6881/2023 $80.00 + 0.00

https://africanscientistjournal.org

AFS2023033/24214

Effect of Ethanolic Extract of *Zingiber Officinale* Rhizome on Blood Glucose Level in Glucose-induced Hyperglycaemic Wistar Rats

Israel O. Efejene[1], Osuvwe C. Orororo[2]*, Othuke B. Odeghe[2], and Efetoboh Ejevwo[3]

[1]Deparment of Pharmacology, College of Medical and Health Sciences, Novena University, Ogume, Delta State, Nigeria
[2]Department of Medical Biochemistry, Faculty of Basic Medical Sciences, Delta State University, Abraka, Delta State, Nigeria
[3]Department of Pharmacy, School of Health and Applied Sciences, Institut Superieur Bilingue Libre Du Togo (IBLT)

*Corresponding author Email: osuvwec@yahoo.com, Tel: +234 (0) 806 230 6783

(Received June 10, 2023; Accepted in revised form June 14, 2023)

ABSTRACT: This study determined the effects of *Zinger officinale* Rhizome ethanolic extract on blood glucose levels in hyperglycemic Wistar rats. Twenty five adult male Wistar (150±8 g) with an average blood sugar level of 145 mg/dL were used for the study. They are divided into five treatment groups: Group A (Glucose Control – 1 g/kg bwt), Group B (*Zinger officinale* Rhizome extract low dose - ZOREL – 100 mg/kg bwt), Group C (*Zinger officinale* Rhizome extract medium dose -ZOREM – 250 mg/kg bwt), and Group D (*Zinger officinale* Rhizome extract high dose – ZOREH – 500 mg/kg bwt). Rats in groups B through D also received glucose (as in Group A) to cause hyperglycemia. The extracts were administered within an interval of 1-2 h for a period of ten days. Oral glucose tolerance and fasting blood glucose levels were assessed. Plasma glucose levels increased as a result of experimentally creating hyperglycemia by ingesting glucose orally. However, when the extract was given to the rats, their blood glucose levels significantly dropped. Rats administered ZOREH (Group D) on a 360-minute schedule showed the greatest decrease. At 370 minute into the experiment, ZOREL induced a reduction in blood glucose levels of 17.039%, whereas ZOREM and ZOREH generated reductions of 18.03% and 16.07% respectively. Similarly, rats given the extract (Groups B-D) had considerably lower fasting blood 5 to 10 days of glucose induction indicating that the extract enhanced the utilization of glucose. The findings suggest that ingesting *Zingiber officinale* rhizome extract in sufficient amounts can stabilize blood sugar levels in hyperglycemic rats.

Keywords: Diabetes, *Zinger officinale*, Glucose, Antioxidant

Introduction

One of the main fuels used by the body is glucose. It is a monosaccharide sugar that is high in energy and is converted within cells into adenosine triphosphate (ATP), the cellular energy currency. The breakdown of proteins, lipids, and carbohydrates into glucose, which is then used as the main metabolic fuel, makes glucose essential to energy consumption. As a significant precursor, it is also used to create a variety of other carbohydrates, including glycolipids, glycogen, ribose and deoxyribose, proteoglycans, galactose and glycoproteins (Diakos *et al*., 2023). The majority of cells in the body can utilise alternative fuels, like lipids, and all cells need to produce energy. However, glucose is the main source of energy for neurons (nerve cells). This is why maintaining blood glucose levels is crucial for the nervous system to function properly. Hypoglycemia and hyperglycemia, which occur when glucose levels are either low or too high, can cause a number of diseases, including diabetes and neurological issues (Sharma *et al*., 2017).

Type I diabetes mellitus (T1DM) and Type II diabetes mellitus (T2DM) are two kinds of diabetes, a chronic condition marked by hyperglycemia. Because the pancreas' β-cells are destroyed in T1DM, the circulation receives less insulin. Patients will be entirely reliant on the administration of exogenous insulin to survive. The

majority of diabetes patients (85%) have T2DM, which causes peripheral insulin resistance and lowers the insulin sensitivity of the liver, adipose tissues, and skeletal muscles (Forbes *et al*., 2013). With a projection that the prevalence of diabetes in the world is expected to double to about 366 million in the year 2030 due to demographic changes in people older than 65 years and most importantly, adaptation of sedentary lifestyle by the people in urban areas of the world, factors like aging, obesity, physical inactivity, population growth, and urbanization can gradually lead to steady increase in the number of patients with diabetes (Li *et al*., 2017). Diabetic ketoacidosis, coma caused by extremely high blood sugar, vascular complications caused by damaged blood vessels from high glucose levels, macrovascular and microvascular abnormalities are just a few of the immediate deadly complications that result from untreated diabetes. Retinopathy, neuropathy, and other consequences are caused by microvascular complications, whereas cardiovascular complications are caused by macrovascular complications. According to Forbes *et al*. (2013), lower-limb amputations, depression, sexual dysfunction, and dementia are additional effects of chronic diabetes diseases.

There are numerous types of anti-diabetic drugs available in the market for corrective action, including dipeptidyl peptidase-4 inhibitors, biguanides, a-glucosidase inhibitors, insulin analogues, sulphonylureas, thiazolidiones, etc. (Li *et al*., 2017). Each type of drug has a unique mechanism for reducing this elevated glucose level. However, the long-term use and side effects of the available hypoglycemic drugs have created a large demand for effective, low-side-effect, and cost-effective treatments for diabetes. However, numerous secondary consequences of diabetes, such as heart disease, neuropathy, and hypertension, continue to be severe problems in diabetic patients even with insulin therapy (Jafri *et al*., 2010). Additionally, there is proof that hyperglycemia causes an excess of oxygen free radicals, which damages cells and causes oxidative stress. Diabetes problems have been linked to this oxidative stress (Papachristoforou *et al*., 2020). Additionally, anti-oxidants that are organically generated seem to be more effective at lowering the negative effects of diabetes in diabetic people. Ginger stands out among plants that naturally contain antioxidants for its special anti-inflammatory and antioxidant effects (Mbaveng & Kuete, 2017). With variable degrees of efficacy, medicinal plants have been used to treat a variety of illnesses; they also contain vital nutrients and bioactive substances (Sharma *et al*., 2017; Orororo *et al*., 2018; Ekakitie *et al*., 2021; Efekemo *et al*., 2022).

One of the most popular spices consumed worldwide is Zingiber officinale, also known as ginger, which is a member of the Zingiberaceae family (Mbaveng and Kuete, 2017; Anh *et al*., 2020). According to Shahrajaban *et al*. (2019), ginger has been used in traditional medicine for thousands of years to treat a variety of ailments, including nausea, pain, arthritis, cramps, sore throats, and muscular aches. Pharmacological research on ginger has revealed a variety of effects, including antioxidative (Yeh *et al*., 2014; Hosseinzadeh *et al*., 2017; Diakos *et al*., 2023); anti-inflammatory (Abdi *et al*., 2021; Mahluji *et al*., 2023); anti-cancer (Habib *et al*., 2008); anti-ulcer (Minaiyan *et al*., 2006), and hypoglycemic effect (Arablou *et al*., 2014; Okafor and Okafor, 2022). According to studies by Choudhury *et al*. (2018), Chang and Peng (2019), and others, ginger also has hepatoprotective properties. Monoterpenes and sesquiterpenes are present in the dried extract of ginger. According to Liu *et al*. (2019), the primary substances responsible for ginger's bioactivities are shogaols, gingerols, zingerone, and zingiberene. These bioactive ginger components have been demonstrated to have antidiabetic effects that are considered to improve insulin secretion.

Currently, there is encouraging proof of ginger extract's health benefits, which appear to be effective in reducing blood glucose levels. In streptozotocin (STZ)—diabetic rats—ethanolic ginger extract (200 mg/Kg body weight) showed a substantial antihyperglycemic impact for 20 days (Huang *et al*., 2019). In alloxan-induced diabetic mice, ginger (500 mg/Kg body weight) therapy on day eight significantly decreased blood glucose levels compared to day one (Jafri *et al*., 2010). Recent publications on human investigations, however, have revealed contradictory findings with regard to blood glucose regulation. The consumption of a ginger supplement (four capsules) at a dosage of 3 g per day for seven weeks did not substantially affect blood glucose levels in the ginger group compared to the placebo group, according to a study by Karimi *et al*. (2015). Additionally, in a different trial, the non-diabetic adult ginger group's fasting blood glucose was dramatically lowered by up to 20% after ingesting a ginger capsule (1000 mg daily) for 10 weeks (Imani *et al*., 2015). In contrast, the Bordia *et al*. study (2017) found that nondiabetic participants who consumed 5 g of ginger powder (4 g per day) over the course of three months had no effect on their postprandial and fasting blood glucose levels. There is a need for more research on how garlic affects blood glucose levels. Thus, in order to determine the effects of *Zinger officinale* Rhizome ethanolic extract on blood glucose levels in hyperglycemic Wistar rats, this study was set up.

Material and methods

Materials: The materials used in this study include, adult male rats, rubber cages with iron netting, Saw dust (litter), Animal feed (growers mash) and water, laboratory coat and gloves, measuring cylinder and plastic

specimen bottle, dessicator, syringes, sample bottles, feeding trough, wire net cage, needles and syringes (2 ml, 5 ml), face masks, measuring cylinder, analytical grade of ethanol and filter paper (Whatman no. 1.25 mm).
Plant materials: Fresh leaves of *Zinger officinal rhizome* was purchased from Abraka community main market of Ethiope East LGA of Delta State, same was prepared and taken for authentication in the Department of Pharmacognosy and Traditional Medicine, University of Benin, Edo State. After authentication, a herbarium specimen (1208/03/04) was stored. The plants were thereafter taken to the Pharmaceutical Chemistry Department, Faculty of Pharmacy Delta State University, Abraka, for extraction process.
Preparation of plant extract: The method of Ilkhanizadeh *et al*. (2017) was used for the extraction of plant crude. The zinger officinal rhizome were harvested, cleaned, cut into smaller pieces, dried at room temperature by air-drying, and ground using a blender. In an airtight conical flask with daily shaking for 72 h at room temperature, 200 g of plant powder was measured and soaked in 400 ml of ethanol. The mixture was then filtered through Whatman No. 1 filter paper and the filtrate was collected into airtight bottles. Under lowered pressure and at a low room temperature, the rotary evaporator (MS 50 Hz) was used to extract the ethanol from the filtrate. This was the crude extract. Until they were used, the extracts were kept in a refrigerator at 4 °C.
Animals: Twenty adult male Wistar rats were utilized in the investigation, each weighing between 150 and 180 g and having a normal blood glucose level of 145 mg/dL. Before the trial began, the animals were granted two weeks of acclimation. Following this period of acclimatization, blood was drawn from the rats' tail veins and blood glucose levels were measured using a glucometer. All animal experiments were conducted in accordance with the Institutional Animal Ethics Committee's (IAEC) regulations (IBLT023/22). For the duration of the experiment, they were given a regular laboratory meal (growers mash) and unlimited access to water.
Experimental design: The rats were randomized into 5 groups of 5 rats each and treated as shown in the table below:

Table 1: Experimental design

Groups	Designation	Treatment
A	Glucose Control	Glucose (1 g/kg bw)
B	Glucose and *Zinger officinale* Rhizome extract low dose (ZOREL)	100 mg/kg bwt of *Zinger officinale* Rhizome extract
C	Glucose and *Zinger officinale* Rhizome extract medium dose (ZOREM)	250 mg/kg bwt of *Zinger officinale* Rhizome extract
D	Glucose and *Zinger officinale* Rhizome extract high dose (ZOREH)	500 mg/kg bwt of *Zinger officinale* Rhizome extract

Rats in groups B through D also received glucose (as in Group A) to cause hyperglycemia. Blood was obtained from the tail vein of the rats and using a glucometer, blood glucose levels were tested to establish the presence of hyperglycemia. The extracts were administered daily within an interval of 1-2 h after glucose induction for a period of ten days.
Oral glucose tolerance test (OGTT): The tail vein was pricked at times of 0, 30, 60, 90, 150, and 270 min to measure the serum blood glucose level (Islam *et al*., 2009). The initial glucose level was determined using a glucometer (Biosystems). Then at 0, 30, 60, 90, 150, and 270 min following glucose induction and administration of extracts, the serum glucose of blood drawn from a tail vein was evaluated using a glucometer.
Measurement of fasting blood glucose: The fasting blood glucose levels were determined on day 0, 5, and 10. Blood samples were collected from the rat tail vein (after an overnight fast), and measured using a Glucometer according to the manufacturer's instructions.
Data analysis: Data were expressed as mean ± standard error of mean (SEM). Statistical comparisons were performed by one-way ANOVA followed by Dunnett's Multiple Comparison Test and the values were considered statistically significant when $p < 0.05$. Computation was done with the aid of Statistical Package for Social Sciences (SPSS), software, Version 21.

Results

Oral glucose tolerance test (OGTT): The results of OGTT in hyperglycaemic rats treated with *Zingiber Officinale* rhizome extract are shown in Table 1.
Experimental induction of hyperglycemia by oral ingestion of glucose resulted in increase in plasma glucose levels. However, administration of the extract to the rats caused significant decrease in glucose levels. Most significant reduction was observed in rats given ZOREH (Group D) on 360 min. ZOREL caused 17.039%

reduction in blood glucose level at 370 min compared to the start of the experiment, while ZOREM and ZOREH decreased blood glucose level by 16.07% and 18.03% respectively.
Thus, the administration of *Zingiber Officinale* Rhizome extract to hyperglycaemic rats reduced blood glucose significantly ($p < 0.05$) in therapeutic animals by improving the utilization of oral glucose after 180 and 360 min and a percentage inhibitory effect of 16.07% (ZOREM), 17.04% (ZOREL) and 18.03% (ZOREH).

Table 1: OGTT in hyperglycaemic rats treated with *Zingiber officinale* rhizome extract

Groups	Blood glucose level (mg/dl)				
	0 min	**60 min**	**180 min**	**360 min**	**% diff**
Glucose	77.00±3.44[a]	103.25±4.63[a]	106.00±4.42[a]	104.75±4.05[a]	0
ZOREL (100 mg/kg)	82.75±3.30[a]	101.50±4.66[a]	101.25±5.20[a]	89.50±4.79[b]	17.039
ZOREM (250 mg/kg)	81.25±6.51[a]	124.50±14.72[b]	104.25±3.73[a]	90.25±3.04[b]	16.07
ZOREH (500 mg/kg)	81.50±3.07[a]	120.50±10.19[b]	98.00±6.12[b]	88.75±5.02[b]	18.03

Data are expressed as mean ± SEM. (n=4). ZOREL = Zinger Officinal Rhizome extract low dose, ZOREM = Zinger Officinal Rhizome extract medium dose, ZOREH = Zinger Officinal Rhizome extract high dose. Values on the same column with different superscripts differ significantly ($p < 0.05$).

The percentage change in OGTT of hyperglycaemic rats treated with *Zingiber Officinale* Rhizome extract is shown in Table 2. Administration of various doses of the extract to hyperglycaemic rats showed a significant reduction of blood glucose significantly ($p < 0.05$) in the percentage change of glucose after 60 to 360mins of ZOREL 11.86%, ZOREM 24.48% and ZOREH 24.90%.

Table 2: Percentage change in OGTT of hyperglycaemic rats treated with *Zingiber Officinale* Rhizome extract

Groups	Blood glucose level (mg/dl)			
	0 to 60mins	**60 to 180mins**	**180 to 360mins**	**60 to 360mins**
GLUCOSE	34.73±7.29	3.32±6.49	1.02±3.01	2.42±7.75
ZOREL (100 mg/kg)	23.92±10.81	-0.30±1.48	-11.59±1.61	-11.86±2.03
ZOREM (250 mg/kg)	52.86±10.26	-13.26±9.00	-13.41±.22	-24.90±7.76
ZOREH (500 mg/kg)	49.65±17.43	-16.77±9.19	-9.32±1.00	-24.48±8.49

Data are expressed as mean ± SEM. (n=4). ZOREL = Zinger Officinal Rhizome extract low dose, ZOREM = Zinger Officinal Rhizome extract medium dose, ZOREH = Zinger Officinal Rhizome extract high dose.

Fasting Blood Glucose Level

The results of fasting blood glucose levels in hyperglycaemic rats treated with *Zingiber Officinale* Rhizome extract are shown in Table 3 while the percentage change in fasting blood glucose is presented in Table 4. There was a significant increase in fasting blood glucose following administration of glucose to the rats in all the groups, however, rats administered the extract (Groups B-D) had significantly reduced fasting blood glucose measured on the 5th and 10th days of the experiment. The result indicate that the extract improved the utilization of glucose in the rats given the extract with a percentage effect of -38.57% (ZOREL), -56.85% (ZOREH) and -85.39% (ZOREM).

Table 3: Fasting blood glucose levels in hyperglycaemic rats treated with *Zingiber Officinale* Rhizome extract

Groups	Fasting Blood Glucose level (mg/dl)			
	Before induction	**After induction**	**Day 5**	**Day 10**
Glucose	86.25±6.96[a]	309.25±17.66[a]	284.00±21.30[a]	254.00±15.52[a]
ZOREL (100 mg/kg)	95.75±4.58[b]	296.50±31.46[b]	265.00±33.49[b]	215.50±25.83[b]
ZOREM (250 mg/kg)	84.50±5.63[c]	307.75±28.44[c]	274.50±28.01[b]	196.25±18.26[c]
ZOREH (500 mg/kg)	85.00±4.24[c]	304.50±48.38[c]	253.00±46.04[c]	162.50±21.20[d]

Data are expressed in mean ± SEM. (n=4). ZOREL = Zinger Officinal Rhizome extract low dose, ZOREM = Zinger Officinal Rhizome extract medium dose, ZOREH = Zinger Officinal Rhizome extract high dose. Values on the same column with different superscripts differ significantly ($p < 0.05$).

Table 4: Percentage change in Fasting blood glucose levels in hyperglycaemic rats treated with *Zingiber officinale* Rhizome extract

Groups	Percentage Change in Fasting Blood Glucose level (mg/dl)			
	Before induction	**After induction**	**Day 5**	**Day 10**
Glucose	71.57±3.77	-9.78±6.22	-11.72±4.59	-22.25±6.10
ZOREL (100 mg/kg)	66.53±4.19	-12.63±2.26	-23.00±3.72	-38.57±5.28
ZOREM (250 mg/kg)	72.28±1.02	-12.72±5.77	-39.81±4.33	-56.85±2.85
ZOREH (500 mg/kg)	69.99±4.42	-21.63±2.71	-52.84±7.55	-85.39±6.05

Data are expressed in mean ± SEM. (n=4). ZOREL = Zinger officinal rhizome extract low dose, ZOREM = Zinger officinal rhizome extract medium dose, ZOREH = Zinger officinal rhizome extract high dose.

Discussion

This study investigated the impact of an ethanol extract of *Zingiber officinale* rhizome on blood glucose levels in Wistar rats that had been given glucose to induce hyperglycemia. In comparison to conventional medicine, the use of herbal medicine in the treatment and prevention of diseases like diabetes has a long history. Diabetes is one of the biggest public health concerns around the world (Choudhury *et al*., 2018). According to Ozaki *et al*. (1991), ginger is one of the spices with the strongest anti-inflammatory properties, and Bode *et al*. (2001) listed ginger as one of the spices with the strongest anti-tumor properties.

According to the study's findings, administering *Zingiber officinale* Rhizome extract to hyperglycemic rats significantly decreased glucose levels in a dose-dependent manner. This may be due to the extract's ability to induce increased utilization of glucose. Previous research by Ojewole (2006) showed the hypoglycemic effects of ginger extract. This study's findings also support those of Taghizadeh *et al*. (2007) and Shanmugam *et al*. (2011), who demonstrated that ginger supplementation has beneficial effects and guards against diabetes-induced abnormalities because of its antioxidant and anti-inflammatory capabilities. The results also align with the submission of Ramudu *et al*. (2011) that ginger supplementation increases the overall antioxidant capacity and decreases lipid and protein oxidation in diabetes and other oxidative stress conditions because of the antioxidants present in it. In this context, Ilkhanizadeh *et al*. (2016) demonstrated how ginger extract improved diabetes-induced heart abnormality in rats due to its antioxidant characteristics.

Ginger extract's hypoglycaemic effects were also attributed by Diakos *et al*. (2023) to its anti-inflammatory and antioxidant capabilities. According to Diakos *et al*. (2023), consumption of ginger aqueous extract enhanced glycemic response in non-diabetic participants in comparison to the control group. Hogaols, gingerols, zingerone, and zingiberene are the main compounds that provide ginger its biological effects (Butt and Sultan, 2011; Mbaveng and Kuete, 2017; Liu *et al*., 2019). These bioactive ginger components have been demonstrated to have anti-diabetic activities that are believed to improve insulin secretion (Arablou *et al*., 2014; Nam *et al*., 2020). Thus increased insulin secretion may have caused the reduced glucose levels observed in rats treated with the extract in this study. Additionally, 6-gingerol (present in ginger) has been shown to enhance the pancreatic beta cell's glucose-stimulated insulin-secretion pathway that is mediated by glucagon-like peptide-1 (GLP-1) (Samad *et al*., 2017; Jafarnejad *et al*., 2017; Mbaveng and Kuete, 2017) even though according to Okafor and Okafor (2022), the exact mechanism of the antioxidative and hypoglycemic properties is still being investigated.

The findings of this study are contrary to the study of Mahluji *et al*. (2013) that found no significant change in blood glucose levels following treatment with the spice, but agrees with the studes by Hosseinzadeh *et al*. (2017) and Phool *et al*., (2022) who demonstrated *Zingiber officinale* Rhizomes' protective effect against experimentally induced ulcers in diabetic rats, which they attributed to the extract's anti-oxidant characteristics due to the presence of flavonoids and other polyphenolic components.

Conclusion

Our findings are consistent with those that have already been published and demonstrate the antihyperglycemic action of *Zingiber officinale* rhizome extract. Therefore, even though specific mechanisms of action need more research, administering *Zingiber officinale* Rhizome extract to diabetic rats might reduce hyperglycemia. In

conclusion, our study reveals that a rhizome extract from the ginger plant, *Zingiber officinale*, may be able to stabilize blood glucose levels in hyperglycemic rats.

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