



# The methanolic extract of *Zingiber officinale* causes hypoglycemia and proinflammatory response in the rat pancreas

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## ABSTRACT

**Introduction:** *Zingiber officinale* (Ginger) is a commonly used plant for food and herbal treatment of different ailments. There is proof of ginger's antioxidative and hypoglycemic activity, but the mechanism of action is yet to be understood, especially in a non-disease model. The present study assessed the effects of the methanolic extract of *Zingiber officinale* (MEZO) on blood glucose, pancreatic antioxidant levels, and histopathological changes.

**Methods:** Fifteen (15) female Wistar rats with an average weight of 147 g were randomly divided into three (3) groups (A-C). Group A was given no treatment and served as the control group. Groups B and C received only oral administration of 400 mg/kg and 800mg/kg of MEZO, respectively. MEZO was administered once a day for 21 days. The animals were euthanized by cervical dislocation for blood collection and retrieval of pancreatic tissue for oxidative stress and histopathological assessment.

**Results:** The serum glucose level was significantly decreased in group C compared to the control ( $P=0.012$ ). There were no significant changes in the levels of Superoxide dismutase (SOD), Glutathione (GSH), and Catalase (CAT) in all the MEZO groups compared to the control ( $P>0.05$ ). Pancreatic histology showed signs of acute pancreatitis, with dense aggregates of polymorphonuclear inflammatory cells infiltrating the surrounding stroma.

**Conclusion:** A high-dose ginger extract induces hypoglycemia, but a proinflammatory response is elicited in the pancreas at a lower dose. Thus, ginger extracts should be consumed with caution.

## Keywords:

Ginger

Pancreas

Hypoglycemia

Antioxidants

Inflammation

## Introduction

The pancreas is a vital organ with both endocrine and exocrine properties; pancreatic enzymes and hormones

are actively involved in the body's digestion and metabolism of different essential compounds (McGuckin et al., 2020). Therefore, disruptions or changes in the

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activities of the pancreas alter normal physiological processes, which are linked to the onset of metabolic diseases (Abd El-Haleem & Mohamed, 2011). Diabetes is one of the essential pancreas-related metabolic disorders characterized by various physiological alterations, including hyperglycemia. It is associated with long-term microvascular and macrovascular complications such as blindness, kidney failure, lower limb amputations, myocardial infarction, and stroke (Ekoé, 2019).

Studies assessing the therapeutic effects of some important medicinal plants have increased over the last decade (Tripathi et al., 2018) diabetes mellitus, cancer, kidney dysfunctions, and cardiovascular abnormalities. In addition, an alarming increase in the incidence of diabetes and its complications has threatened the economies of several nations, particularly developing countries. Inflamed by an expeditious urbanization, nutritional modifications, and increasingly stationary lifestyles, the diabetic upsurge has flurried up in parallel with the worldwide ascent in cardiovascular diseases (CVDs). Medicinal plants have been used to treat different ailments with varying degrees of success and possess essential nutrients and bioactive compounds (Sharma et al., 2017). One such crucial medicinal plant is *Zingiber officinale* (commonly called ginger). Ginger belongs to the *Zingiberaceae* family and is one of the most consumed spices globally (Mbaveng & Kuete, 2017). Ginger is used in ancient folk medicine to mitigate various disorders, including vomiting, pain, arthritis, cramps, sore throats, rheumatism, and muscular aches (Shahrajan et al., 2019). Pharmacological studies on ginger have reported numerous effects, including antioxidative (Hosseinzadeh et al., 2017; Yeh et al., 2014) followed by incubation with IL-1 $\beta$  (10 ng/mL, gonado-protective (Ataman & Ojukwu, 2014), anti-inflammatory, anti-cancer (Habib et al., 2008), anti-ulcer (Minaiyan et al., 2006), and hypoglycemic effect (Arablou et al., 2014). However, the mechanism of action behind these effects is not clearly established. In this study, we reported the histopathological mechanism behind the effects of the methanolic extract of *Zingiber officinale* (MEZO) on the blood glucose and pancreatic antioxidant levels in a non-disease animal model.

## Materials and Methods

### Study setting

This experimental study was carried out in the research

laboratory of the Department of Anatomy, Nnamdi Azikiwe University, and lasted for about three months.

### Plant collection, identification, and extraction

The aerial parts of the *Zingiber officinale* plant were harvested from the premises of the College of Health Science Nnamdi Azikiwe University, Nnewi, Nigeria. The botanical identification and authentication were carried out in the Department of Pharmacognosy and Traditional Medicine, Nnamdi Azikiwe University, with identification number PCG/474/A/024. The plant calyces were shade-dried and ground. One thousand grams of the powdered plant sample was used for methanolic extraction as described in a previous study (Okafor et al., 2014), generating a methanolic solution of the powdered sample. The methanol used for the phytochemical extraction was removed from the filtrate (extract) by evaporating the methanol under a vacuum in the rotary evaporator (rotavapor) to avoid the influence of methanol in the study outcome. The extract was stored in the refrigerator at 4°C until use. The extract was made up to solution at varying doses per mL on each administration day and given according to body weight and group treatment doses.

### Animal procurement, Care, and Handling

Fifteen (15) female Wistar rats were procured from the animal house of the College of Health Sciences, Nnamdi Azikiwe University, Okofia Nnewi Campus, and acclimatized for two (2) weeks (to exclude any intercurrent infection) under standard housing conditions (ventilated room with 12/12-hour light/dark cycle at 24  $\pm$  2°C). The rats were fed *ad libitum* with water and standard rat chow throughout the experimental period. The health status of the animals was monitored throughout the experiment according to the Federation of European Laboratory Animal Science Associations (FELASA) guidelines (Guillen, 2012).

### Experimental design

Fifteen (15) rats with an average weight of 147 g were randomly divided into three (3) groups (A-C). Group A was given no treatment and served as the control group. Groups B and C received oral administration of 400mg/kg and 800mg/kg of methanolic extract of *Zingiber officinale* (MEZO), respectively. The extract was administered once a day for 21 days. The dose and duration

of MEZO used in this present study were determined in line with previous studies, which have found some notable effects on the body tissues with ginger extract administration (Okafor et al., 2020a; 2020b).

#### *Animal Sacrifice and Sample Collection*

The animals fasted overnight on the last day of MEZO administration. They were anesthetized using chloroform and euthanized by cervical dislocation for blood collection according to the National Academies' Guide for the Care and Use of Laboratory Animals (2011). Afterward, the pancreatic tissues were harvested, weighed, and divided into two parts. One part was fixed in a 10% formal saline for histological processing, while the second part was homogenized for use in oxidant status determination.

#### *Blood glucose determination*

Two milliliters of blood were drawn using a 21-23 gauge needle from the lateral tail vein after at least 8 hours of fasting before day 1 and after day 21 of MEZO administration to determine the blood glucose level. Serum for analysis was obtained by high-speed centrifugation of the blood samples after standing it for about 15 minutes in a plain tube. The blood glucose level was determined by the enzymatic colorimetric method with commercial kits (Pars Azmun Co., Tehran, Iran) on an automatic analyzer (Abbott, model Alcyon 300, Abbott Park, IL).

#### *Antioxidants Quantification*

The oxidant status was determined in the pancreatic tissue by quantifying the Superoxide Dismutase (SOD), Glutathione (GSH), and Catalase (CAT) levels in the pancreatic tissue samples using the tissue homogenate as described in a previous study (Okafor & Gbotolorun, 2018).

#### *Tissue Processing*

The pancreatic tissue samples were trimmed to about 3mm x 3mm thick for easy study of sections under the microscope and fixed in 10% formalin. After fixation, dehydration of the fixed tissues was done in ascending grades of alcohol - 50%, 70%, 95%, and 100% - and the dehydrated tissues were cleared in xylene. The tissue samples were sectioned with a rotary microtome, stained with hematoxylin and eosin (H&E), and mount-

ed in DPX for viewing under a light microscope. Photomicrographs of these sections were obtained using the Leica DM 750 digital photomicroscope.

#### *Ethical Statement*

This study received ethical approval from the Research Ethics Committee of the Anatomy Department, Faculty of Basic Medical Sciences, Nnamdi Azikiwe University, Nnewi Campus (AREC/2019-015). The experimental procedures of this study complied with ARRIVE guidelines (Kilkenny et al., 2010), and National Institutes of Health (NIH) guidelines for the care and use of laboratory animals (2011). The health status of the animals was monitored throughout the experiment according to the Federation of European Laboratory Animal Science Associations (FELASA) guidelines (Guillen, 2012). No informed consent was required for this study.

#### *Statistical Analysis*

The data were analyzed using IBM statistical package for social science (SPSS) for Windows, version 23 (IBM Corporation, Armonk, New York, USA). One-way analysis of variance (ANOVA) with a post hoc LSD test was used to test for significance in changes seen in the variables across and within groups. The statistical significance level was set at  $P < 0.05$ , and the study results were presented using tables and figures. All data were expressed as mean  $\pm$  SEM.

## **Results**

#### *The effect of ginger on the serum glucose level*

The serum glucose level was significantly decreased in group C compared to the control group ( $p = 0.012$ ). There is no significant change in the serum glucose level of group B animals compared to the control group (Table 1).

#### *The effect of MEZO on the antioxidant levels in the pancreas*

There is no significant change in the levels of SOD, GSH, and CAT across all the test groups compared to the control group ( $P > 0.05$ ) (Table 2).

#### *Histopathological studies*

Figure 1 (A-C) represents the histological section of the rat pancreas at different doses of MEZO. The animals in the control group and the animals that received

**TABLE 1:** The serum glucose level of the Wistar rats before and after the administration of MEZO

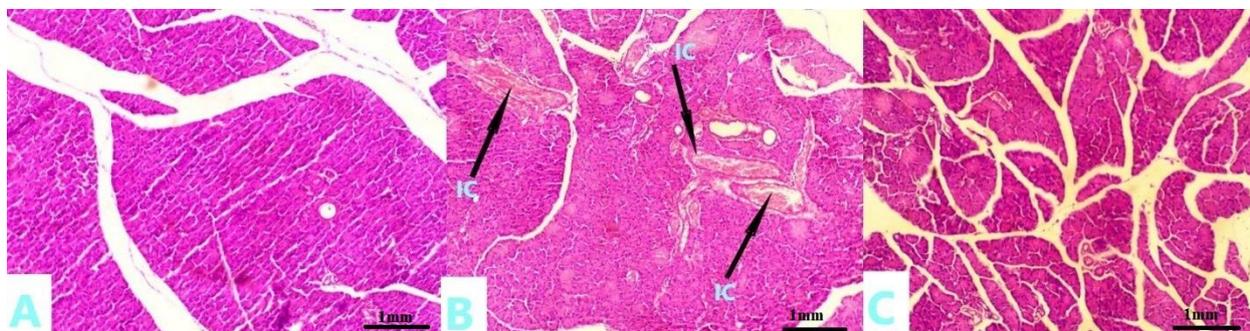
Groups	Serum Glucose Level (mmol/L) (before MEZO intake)	Serum Glucose Level (mmol/L) (after MEZO intake)	p-value
A (Control)	4.05±0.27	3.89±0.21	0.55
B (400 mg/kg MEZO)	3.35±0.30	3.25±0.10	0.087
C (800 mg/kg MEZO)	2.90±0.17	1.82±0.5	0.012*

Data were analyzed using paired t-test. Values were expressed as mean ± Standard error of the mean, and data were considered significant at \* $P < 0.05$ . \* means significant compared to the control group (group A). MEZO means methanolic extract of *Zingiber officinale*.

**TABLE 2:** The oxidant status of the Wistar rat pancreas after administration of MEZO.

Antioxidants	Groups	Mean ± SEM	p-value
SOD ( $\mu\text{mol/ml/min/mg pro}$ )	A (Control)	7.75±3.05	0.694
	B (400 mg/kg MEZO)	11.45±2.95	
	C (800 mg/kg MEZO)	8.15±3.45	
GSH ( $\mu\text{mol/ml/mg pro}$ )	A (Control)	37.17±9.98	0.618
	B (400 mg/kg MEZO)	20.61±14.89	
	C (800 mg/kg MEZO)	31.61±7.36	
CAT ( $\mu\text{mol/ml/min/mg pro}$ )	A (Control)	83.63±8.79	0.084
	B (400 mg/kg MEZO)	32.35±2.90	
	C (800 mg/kg MEZO)	49.87±15.37	

Data were analyzed using a One-way Analysis of Variance (ANOVA). Values were expressed as mean ± Standard error of the mean, and data were considered significant at \* $P < 0.05$ . MEZO means methanolic extract of *Zingiber officinale*.



**FIGURE 1.** Plate A represents the control group that received no treatment for 21 days. Plate B received 400 mg/kg MEZO for 21 days, while Plate C received 800 mg/kg MEZO for 21 days. Staining for all sections was done using H&E, and photomicrography was taken at x200. IC – Inflammatory cells.

800 mg/kg MEZO both showed normocellular islet cells surrounded by normal-appearing exocrine acini (1A and 1C). However, acute pancreatitis and infiltration of surrounding stroma by dense aggregates of polymorphonuclear inflammatory cells were observed in animals treated with 400 mg/kg MEZO (plate B).

## Discussion

Ginger is a well-known culinary condiment widely consumed for its medicinal properties (Mbaveng & Kuete, 2017). Numerous essential phytochemicals and

nutrients have been isolated from ginger, some of which have been proven to have different beneficial therapeutic effects (Jolad et al., 2004; Lantz et al., 2007). Experimental studies have demonstrated the protective effects of ginger against different diseases, including diabetes (Abdulrazaq et al., 2012), cancer (Shukla & Singh, 2007), oxidative damage, and inflammation (Mashhadi et al., 2013). This present study assessed the effects of ginger on the serum glucose level, pancreatic antioxidants, and pancreatic histopathology of Wistar rats.

In this study, evidence shows that low and high-dose

MEZO caused no significant variation in the level of antioxidants in the pancreas, as no changes were seen in the GSH, SOD, and CAT levels when the MEZO-treated groups were compared to the control (Table 2). Depletion of intracellular antioxidants exposes the tissue to ROS-induced toxicity and lipid peroxidation (Khansari et al., 2009). The unchanged levels of tissue antioxidants show oxidative normalcy in tissues, indicating that ginger is relatively safe for chronic consumption. In a study by Hosseinzadeh et al. (2017), the ginger extract showed protective effects against Interleukin-1 $\beta$ -induced oxidative stress in cultured human chondrocytes. There may be different mechanisms of action of ginger in different human tissues; hence oxidative status in the pancreas does not mean the same for another tissue. Again, the level of safety seen may depend on the dosage of ginger administered to achieve the needed therapeutic threshold.

Compared to the untreated group, the glucose level in the serum was significantly lowered in animals that received 800 mg/kg MEZO ( $p=0.012$ ), demonstrating the hypoglycemic properties of ginger. This finding seems to justify its use as an antidiabetic remedy in herbal medicine. Similar to our findings, Arablou and colleagues (2014) reported that the administration of 1600 mg/kg of ginger for 12 weeks caused a significant decrease in fasting blood glucose and improved insulin sensitivity. While some studies have observed no significant change in the blood glucose level following treatment with ginger (Mahluji et al., 2013), a meta-analysis of nine randomized control trials showed that ginger supplementation significantly reduces the fasting blood glucose (Jafarnejad et al., 2017).

Our histopathological analysis showed normal pancreatic exocrine acini in all experimental animals except in group B, where infiltration of dense aggregates of polymorphonuclear inflammatory cells was seen in the surrounding stromal cells. As seen in group B, inflammatory cell infiltration is a sign of acute pancreatitis and may occur in response to infection, trauma, or toxins, mediated by inflammatory cytokines (Imani & Ainehchi, 2014). However, our study did not qualify or quantify the inflammatory markers that are implicated in the pancreatic inflammation seen. This result is unexpected and different from the earlier findings, which reported a normal pancreatic histoarchitecture following the administration of 500 mg/kg and 1000 mg/kg

of aqueous extracts of ginger (Al-Qudah et al., 2016). Again, a 100mg/kg dose of the ginger extract showed anti-inflammatory activity by suppressing TNF-alpha, a proinflammatory marker in an ethnione-induced hematoma (Habib et al., 2008). Our finding suggests that MEZO demonstrates proinflammatory effects at a lower dose in the pancreas, but this effect is lost when administering a higher dose. This conclusion is best seen as a hypothesis that will need further experimentation to be validated. More so, this unexpected finding could have been by chance alone and may be unrelated to ginger administration, as there is no study in a non-disease model where ginger exhibited proinflammatory responses in the pancreas.

Overall, this study showed that when administered at a higher dose of 800 mg/kg, ginger exhibits a hypoglycemic effect without any significant oxidative and histological changes in the pancreas. Our study also showed that ginger might possess some proinflammatory properties as the tissue section of animals treated with 400 mg/kg MEZO showed signs of inflammatory-induced acute pancreatitis.

## Conclusion

The ginger extract induced hypoglycemic and proinflammatory effects at a higher and lower dose, respectively but showed no significant effect on the oxidative profile in this study. Thus, ginger as an antihyperglycemic herbal medicine should be used with caution. It is essential to elucidate the severity of the proinflammatory effect of ginger extract observed in this study. Further investigation should be focused on the underlying mechanisms and the inflammatory markers implicated for possible isolation of potentially bioactive compounds that modulate the effect. There is a need for a controlled clinical trial on ginger herbal medicine to ascertain the overall severity of effects on all body issues before wide usage.

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## Conflict of Interest

The authors have no conflict of interest to declare.

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