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Dose-dependent Antidiabetic and Antiobesity Potentials of Aqueous Extract of *Zingiber officinale* Linn (Ginger) Rhizomes in Experimental Diabetic Rats: Need for Precaution?

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Received: April 09, 2019; **Published:** May 03, 2019

Abstract

Therapeutic use of Ginger (*Zingiber officinale* Linn) in the treatment of many medical conditions has been reportedly abused as consumption of ginger in whatever form at abnormal quantity poses harmful effects on human health. This experimentally-controlled designed nutritional study aimed to determine the dose-dependent antidiabetic, antiobesity and organoprotective potentials of aqueous ginger extract (AEG) in experimental diabetic rats with the rationale of proffering safety precautions on consumption of ginger for euglycemic control in diabetics. Twenty four (24) diabetes-induced (Alloxan monohydrate solution; 150 mg/dL, intraperitoneally) male Wistar rats each weighing ≥ 200g were randomly categorized into four experimental groups (n = 6, each): Control; 250 mg/kg extract-treated; 500 mg/kg extract-treated and 1000 mg/kg extract- treated. Animals were fed with standard rat feeds and water *ad libitum* while ginger extract was orally administered daily for 28 days according to the experimental design. Body weights were measured twice weekly and recorded while the Fasting blood sugar (FBS) concentrations were determined on days 7, 14, 21 and 28. Oral glucose tolerance test was conducted followed by animals sacrifice for organs (spleen, kidneys, heart, lungs, testes and liver) extractions and respective weight measurement. Data were analyzed using Microsoft Excel and statistical program SPSS version 22.0 while P values < 0.05 were considered significant. In extract-treated groups, the mean body weight gain decreased significantly ($P < 0.05$) inversely proportional to extract dosage compared with the control. No significant change observed in mean organ weight. Glycemic tolerance and FBS concentrations improved significantly proportional to extract dosage. However, higher dose of ginger extract above 500 mg/kg showed insignificant difference on the glycemic tolerance indicating necessity for precaution. *Zingiber officinale* impacts dose-dependent organoprotective, antidiabetic and antiobesity effects in diabetic rats.

Keywords: *Diabetic Rats; Ginger Extract; Glycemic Control and Tolerance; Body and Organ Weights*

Introduction

Ginger is one of the more commonly used spices in the world as herbal remedies for the treatment of many medical ailments. It has been reported to possess anti-obesity, anti-inflammatory and antidiabetic activities [1,2]. In recent time, *Zingiber officinale* has been shown to possess effective glycemic control properties in diabetes mellitus [3,4]. The mechanisms underlying these actions are associated with the inhibition of key enzymes controlling carbohydrate metabolism and increased insulin release/sensitivity, resulting in enhanced glucose uptake in peripheral adipose and skeletal muscle tissues [5]. The use of "natural" or alternative medicines, dietary supplements and herbal remedies has increased markedly over the last few years [6] and such use at abnormal dose or quantity without caution or advice from physicians or nutritionists pose dangers on consumers' health [7]. Previous reviews have emphasized the importance of

careful scientific research in establishing the safety and efficacy of potential therapeutic plant remedies in defining the risks and benefits of herbal remedies [8,9]. To prevent such possible associated health complications resulting from excess consumption of ginger, this experimentally-controlled designed nutritional study focused on establishing the dose-dependent potentials of ginger in glycemic and weight control in diabetic rats through determination of its effects on body and organ weights, glycemic tolerance and profile.

Materials and Methods

Plant materials

The ginger rhizomes used for this study were purchased from a reputable market in Ibadan, Oyo State, Nigeria and was identified and authenticated by the plant botanist in the Department of Botany at the University of Ibadan, Ibadan, Oyo State Nigeria with the voucher number UIH - 22396. Voucher specimen was deposited in the institution herbarium.

Preparation of the Extract

Aqueous ginger extract was freshly prepared from locally available ginger rhizomes. 500g of Ginger roots peeled on crushed ice and cut into small pieces was homogenized in 750 ml cold, sterile 0.9% NaCl solution and 250 ml ice cold water to make the volume 1000 ml using a blender for 12 minutes. The homogenized mixture was then filtered three times through cheese cloth to obtain a filtrate that was centrifuged at 2000 rpm for 10 minutes. The clear supernatant fraction was separated and volume made up to 1000 ml with normal saline. The concentration of this ginger preparation was considered to have 500 mg/ml on the basis of the weight of the starting material. The extract was stored in sample tubes at - 20°C until administered to the experimental rats.

Toxicity test

A stair-case method [10] was used to conduct the acute toxicity test for the extract. Animals were provided orally with increasing doses of 250, 500, 750 and 1000mg/kg body weight of the extract while the toxicity was assessed by mortality and behavioral changes of the rats.

Experimental animals

Healthy male Wistar (*Rattus norvegicus*) rats weighing about ≥ 200g purchased from the disease-free stock of the animal house of Olu Reasearch Farm, Sango-Ota, Ogun State, Nigeria were used for the study. The animals were housed in poly propylene cages, maintained under standard conditions (12:12h light:dark cycle; 25 ± 2°C, relative humidity). They were fed with standard rat pellet diet (Oladokun Feed Ltd. Ibadan, Nigeria) and water *ad libitum*. The Animal Ethical Committee of the institution approved the study protocol.

Induction of diabetes

After 15 hour overnight-fast following the two weeks of acclimatization, twenty four rats were injected by single intraperitoneal injection of 150 mg/kg body weight of freshly prepared 2% Alloxan monohydrate (Sigma chemicals, USA) dissolved in sterile 0.9% normal saline in a standard volumetric flask strapped with foil to prevent alloxan instability. Diabetes was confirmed 4 - 7 days later by use of glucometer (Accuchek-Active Blood Glucose Monitoring System, ACON Laboratories, Inc. San Diego, USA) and compatible strips. Rats with Fasting Blood Glucose (FBG) level > 150 mg/dl were considered diabetic and used for this study since the level of serum glucose considered to be normal in *Rattus norvegicus* ranges from 50 - 135 mg/dL [11]. Diabetes was allowed to stabilize for 5 days before exposure to extract.

Experimental design

Diabetic rats were divided into four groups (n = 6, each): Control (without extract); 250 mg/kg extract-treated; 500 mg/kg extract-treated and 1000 mg/kg extract-treated. Extract-treated grouped rats received oral administration of freshly prepared aqueous extract of ginger daily for 28 days. All rats were fed with standard feed and water freely for the study period. FBG levels of all rats in each group was measured on weekly basis for the study period while the body weights were measured twice weekly and recorded. At the end of 4th week, oral glucose tolerance test was conducted to construct the glycemic response curves followed by animals sacrifice for organs (spleen, kidneys, heart, lungs, testes and liver) extractions and respective weight measurement.

FBG and OGT tests

The Fasting Blood Glucose (FBG) and Oral Glucose Tolerance (OGT) Tests were conducted in all groups. The blood glucose concentrations after overnight fast (using glucometer) were determined weekly in all grouped rats from blood samples collected from the cordal veins by tail snipping method. The glucose tolerance was determined on the 28th day of the study using orally administered D-glucose load of 2g kg^{-1} dissolved in distilled water. Blood glucose concentrations at intervals of 30, 60, 90, 120 and 150 minutes were measured to construct the glycemic profile.

Organ extraction and measurement

Animals were sacrificed on the last day of the study using light anesthesia to extract the internal organs which were measured. The organ weights were measured and recorded as a percentage of final body weight together with the absolute values.

Statistical analysis

The data obtained was computed, analyzed and summarized using appropriate statistical methods and program of Microsoft excel and SPSS v. 22. Results were expressed as mean ± SEM (Standard Error of Mean). Comparison between groups and the significant difference between the control and the treated groups were made using student's t-test and one way analysis of variance (ANOVA). P values < 0.05 were considered significant.

Results

Toxicity evaluation

Administrations of single dose of extract from 250 - 1000 mg/kg body weight *per oris* did not produce any mortality. All the animals used were alive, healthy and active during the observation period of 28 days. Acute toxicity study revealed that extract doses of up to 1 g/kg b.w. *per oris* was the peak dose that produced no signs of toxicity and mortality.

Effect of AEG on body and organ weights

Body weight

The effect of AEG on mean body weight gain is shown in table 1 below. Aqueous extract of ginger caused significant (P < 0.05) reduction in weight gain in all treated groups compared with the control. Comparison between the treated groups revealed that rats treated with 1000 mg/kg of AEG showed significant difference in weight gain compared with those treated with 250 mg/kg. No significant difference in weight gain exists between 500 mg/kg and 1000 mg/kg treated groups. Impact of AEG on body weight gain was dose-dependent.

Parameters	Animal Categories			
	Control (without extract)	250 mg/kg extract-treated	500 mg/kg extract-treated	1000 mg/kg extract-treated
Initial Weight Gain	200. 13 ± 2.17	201. 42 ± 0.01	200. 01 ± 2.20	201. 32 ± 0.21
Final Weight Gain	268.16 ± 5.20	221.34 ± 3.56	215.15 ± 4.20	211.76 ± 5.00
Weight Change (%)	34.00	9.90*	7.04*	5.19**

Table 1: *Effect of AEG on Body Weight (n = 6/group).*

*Values are expressed in mean ± SEM, *Significant (p < 0.05) when compared with control, **Significant (p < 0.05) when compared with 250 mg/kg.*

Organ weight

Figure 1 shows the effect of varying doses of AEG on organs weights. No significant difference was observed in mean organ weights among the treated rats and between the control and the treated rats. The slight reduction in mean size of the testis and liver of the treated rats compared with the control was insignificant (P > 0.05).

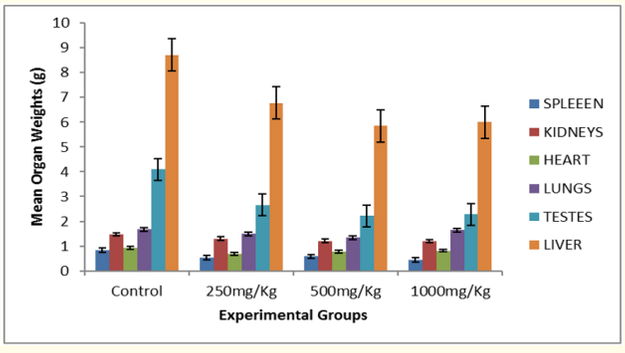

Figure 1: *Effect of Aqueous Extract of Zingiber officinale on organ weights (g) (n = 6/group).*

Glycemic profile and hypoglycemic effect of AEG in diabetic rats

The hypoglycemic activity of AEG on the blood sugar level of diabetic rats is shown in table 2. Acute and chronic treatment with AEG in the doses of 250, 500 and 1000 mg/kg b.w in diabetic rats showed a significant ($P < 0.05$) dose-dependent decrease in the elevated blood glucose level when compared between the treated groups and; between the control and the treated groups.

Experimental Groups	Mean Fasting Blood Glucose Concentrations (mg/dL)				
	Entry (Day 0)	Day 7	Day 14	Day 21	Day 28
Control	180.2 ± 5.6	188.2 ± 4.0	178.4 ± 2.4	170.4 ± 1.0	168.2 ± 1.8
250 mg/kg Extract	181.1 ± 2.5	173.2 ± 5.6	145.8 ± 2.0	130.8 ± 6.6	120.83 ± 2.1
500 mg/kg Extract	180.5 ± 3.4	164.5 ± 2.6	139.2 ± 1.4	119.7 ± 2.8	89.8 ± 8.2
1000 mg/kg Extract	181.2 ± 3.6	150.4 ± 6.2	125.8 ± 2.4	103.7 ± 1.6	90.5 ± 4.2

Table 2*: Effect of AEG on fasting blood (venous) glucose concentration in diabetic rats (n = 6/group).*

*Values are expressed in mean ± SEM, *Significant ($p < 0.05$) when compared with control.*

Effect of AEG on glycemic tolerance in diabetic rats

The glycemic responses to doses of ginger extract given during OGT test are depicted in figure 2 below. Ginger extract confers improved glycemic tolerance in all treated groups over the control. Among the treated groups, rats served with 500 mg/kg and 1000 mg/kg extract, showed better significant tolerance as revealed by their lower incremental areas under the glycemic response curves. However, it was observed that the effect of higher dose of ginger extract above 500 mg/kg showed unremarkable insignificant difference on the glycemic tolerance.

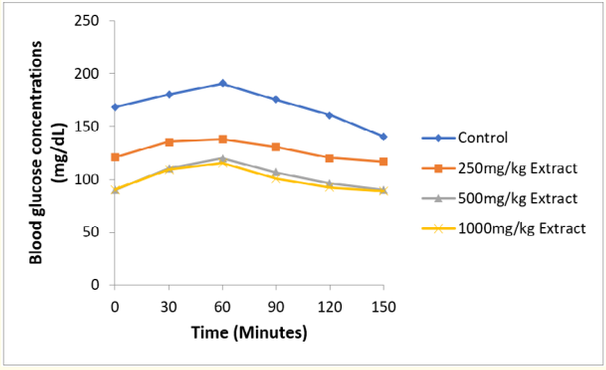

Figure 2: *Effect of Aqueous Extract of Zingiber officinale on Glycemic Tolerance (n = 6/group).*

Discussion

The dose-dependent antidiabetic and antiobesity potentials of ginger (*Zingiber officinale* Linn) in diabetic rats were assessed in this experimentally-controlled nutritional study with the rationale to determine its safety and suitability in glycemic and weight control in diabetic rats. Findings obtained revealed that antidiabetic and antiobesity potentials of ginger are dose-dependent and its impact on organs is beneficial if consumed at non-lethal dose. Toxicity evaluation of ginger consumption in diabetic rats revealed that consumption above 1000 mg/kg body weight per day is detrimental to health while higher dose of ginger extract above 500 mg/kg showed insignificant difference on glycemic tolerance.

Dietary approach to weight reduction has long been scientifically employed. Going by various findings of many research studies carried out, several diets or parts of plants have been recommended for weight reduction without proper monitoring by the nutritionist or physician. Knowing the fact that individuals react in different ways to given diet or phytochemicals, it is paramount therefore that the safety and suitability of any recommended herbs be determined to prevent under- or over usage leading to undesirable effects. In this study, the effect of ginger on body and organ weights of diabetic rats was determined using different dosage regime. Aqueous extract of ginger caused significant reduction in weight gain in all treated groups compared with the control (Table 1). Comparison between the treated groups revealed that rats treated with 500 mg/kg and 1000 mg/kg of AEG showed significant difference in weight gain compared with those treated with 250 mg/kg while such significant difference was unobserved between 500 mg/kg and 1000 mg/kg treated groups. This may imply that optimal benefits of ginger may be derived with 500 mg/kg dosage even though there was a difference in values obtained. Impact of AEG on body weight gain was dose-dependent. Ginger reduces body weight by downregulating the absorption of lipids via inhibiting the fat hydrolysis processes [12]. Organ weight measurement is important to access general toxicity because any change in organ weight is a sensitive indicator of toxicity. In theory, organ weight will be affected by the suppression of body weight as described by Michael [13]. In this study, no comparable significant difference in mean organ weights was observed between treated groups and between control and treated groups. In this study, a slight insignificant reduction in mean size of the testis and the liver of the 1000 mg/kg treated rats was observed compared with the control. This observed change contrasts the finding of a study which revealed that in diabetic rats, ginger extract enhanced male fertility index and sexual organ weight over a 65 day successive treatment [14]. Based on the short duration of this study, it is suggested that long-term effect of ginger using 1000 mg/kg be examined on the organs to ascertain its impact on their physiological functions.

The glycemic profile and tolerance of the experimental rats is shown in table 2 and figure 2 respectively. The hypoglycemic effect of AEG became remarkably appreciated on the 14th day of the study especially in 500 mg/kg and 1000 mg/kg treated rats while the 250 mg/kg treated rats achieved similar value by the 28th day. This supports the fact that the glycemic effect of ginger resulting from the concentrations of the active ingredient is dose-dependent as revealed by this study. By the 28th day of the study, rats treated with 500 mg/kg and 1000 mg/kg extract achieved normoglycemic values indicating the antidiabetic potentiality of ginger in diet. Unless otherwise contraindicated, the use of ginger in diabetic individuals for glycemic control is promising if consumed at a safe and recommended dose. It is therefore necessary to rule out other existing underlined medical problems in such individuals to avert undesirable effect on the overall health. Ginger extract confers improved glycemic tolerance in diabetic rats in a dose-dependent manner.

Conclusion

The results of this study demonstrated the dose-dependent antidiabetic and antiobesity potentials of ginger rhizome. Acute and chronic treatment with AEG in the doses of 250, 500 and 1000 mg/kg b.w in diabetic rats showed a significant dose-dependent decrease in the elevated blood glucose level and weight gain effective for good glycemic control and profile. For safe or desirable effect, use of ginger for whatever medical ailment, should be guided strictly with precautions to prevent ginger toxicity and its associated complications resulting from excess consumptions.

Conflict of Interest

No conflict of interest exists.

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Volume 14 Issue 5 May 2019