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Effect of Raw and Cooked Ginger (Zingiber Officinale) Extracts on Serum Insulin in Normal and Diabetic Rats

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Abstract The possible mechanisms of action of the hypoglycemic effect of ginger are yet to be properly defined and this is of paramount importance in the application of the spice in combating the increasing global prevalence of diabetes mellitus. Also these mechanisms need to be explored in cooked ginger extract because this is the form in which the spice is mostly consumed. This study hereby determined the effect of raw and cooked ginger extracts on serum insulin in normal rats, streptozotocin-induced and high-fat diet (HFD)- induced diabetic rats. Rat models of Type 1 diabetes mellitus was induced with intraperitoneal injection (60 mg/kg body weight) of streptozotocin, Sigma, Germany and Type 2 with 12 weeks HFD consumption. This was followed by four weeks daily oral administration (4 ml/kg body weight) of raw and cooked ginger extracts and anti diabetic drugs in separate groups of animals. Serum insulin was determined before and after diabetes induction, and at the second and fourth weeks of extracts' administration using Mercodia Rat Insulin ELISA Assay kit, Sweden. ANOVA and LSD were used to compare mean values. Raw and cooked ginger extracts and glibenclamide increased serum insulin significantly ($p< 0.05$) from 0.050 µg/L in STZ-induced diabetic control to 0.104, 0.122 and 0.303 µg/L respectively but this parameter reduced significantly in HFD-induced diabetic group. Having ascertained that raw and cooked ginger extracts enhanced insulin secretion and reduced hyperinsulinemia in HFD-induced diabetic rats clinical trials with human subjects is hereby recommended.

Keywords: *ginger extracts, serum insulin, diabetic rats*

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1. Introduction

The major metabolic pathways that influence hepatic blood glucose concentration include: digestion and absorption from the gastrointestinal tract; hepatic glucose production via gluconeogenesis and glycogenolysis; and uptake and metabolism of glucose by body tissues and cells, hence, any blood glucose lowering agent must be able to modulate one or more of these pathways in order to exert its effect.

The role of insulin in maintaining glucose homeostasis cannot be overemphasized due to the unrivalled role it performs in enhancing glucose uptake by the body tissues and cells. The β-islet cells of the pancreas are stimulated to release insulin when the blood glucose is raised via the pathways mentioned above and insulin receptors on tissues receive the insulin, The glucose is then released into the cells or tissues for further metabolism. This is commonly occurring in normal physiological states.

Insulin is able to enhance glucose uptake by the muscle and adipose tissues by stimulating the translocation of the glucose transporter GLUT4 from the intracellular sites to the cell surface thus enhancing the transport of glucose into the cell for further metabolism [1]. In a state of insulin deficiency the uptake of glucose by cells is impaired thus leading to excessive accumulation of glucose in the blood (hyperglycemia) and its depletion within the cells.

Insulin inhibits hepatic production of glucose by the liver via the blockage of gluconeogenesis and glycogenolysis.. This is achieved by the influence of insulin on the activities of some metabolic enzymes by phosphorylation [2] and dephosphorylation [3] thus regulating the expression of the genes encoding such enzymes. It is able to inhibit the transcription of the gene encoding fructose-1,6-biphosphatase and glucose-6-phosphatase which are gluconeogenic enzymes but increases the transcription of glycolytic enzymes; glucokinase and pyruvate kinase [4] as well as lipogenic enzymes such as fatty acid synthase and acetyl-CoA carboxylase [5] The role of insulin in the phosphorylation or dephosphorylation of these enzymes may be a possible mechanism for this transcription [6].

More still, insulin enhances glucose coversion to glycogen by activating glycogen synthase via promoting its dephosphorylation through the inhibition of kinases such as Protein kinase A and and protein phosphatase [7] thus enhancing glycogen synthesis.

Insulin resistance results from reduced sensitivity of insulin receptors to insulin. Insulin receptor belongs to receptor tyrosine kinases which consists of insulin-like growth factors (IGF-1) receptor and the insulin receptor-related receptor (IRR).

In insulin resistant state which commonly results from hyperlipidemia and hyper- uricaemia that results from obesity/ chronic high-fat and high fructose-diets respectively, unesterified lipids and uric acid interfere with the insulin receptors-insulin interaction by reducing the affinity of insulin receptors for insulin thus reducing glucose uptake by the body cells consequently leading to hyperglycemia and hyperinsulinemia. Hyperlipidemia has also been reported to increase the expression and activity of protein tyrosine phosphatase-1B (PTP-1B) which forms a physical complex with insulin receptor (IR) and insulin receptor substrate-1 (IRS-1) via dephosphorylation [8,9,10,11]. This results in deactivation of phosphoinositide 3 kinase (PI3K), reduced tyrosine kinase activity and GLUT4 expression thus rendering the insulin receptors in muscles and adipose tissues insensitive to insulin [8,12]. This is commonly occurring in Type 2 diabetes mellitus. In Type 1 diabetes there exists absolute deficiency of insulin which leads to chronic uncontrolled hyperglycemia.

The hypoglycemic effect of raw and cooked ginger extracts have been ascertained in our previous publications [13,14]. For proper application of ginger as an anti diabetic food adjunct the possible mechanisms of action of its hypoglycemic effect need to be clearly understood, hence this study determined the effect of raw and cooked ginger extracts on serum insulin in normal, streptozotocin-induced and high-fat diet-induced diabetic rats.

2. Materials and Method

2.1. Extracts Preparation

Fresh ginger rhizomes (Zingiber *officinale* Roscoe) w as purchased from Bodija market in Ibadan, Nigeria. The method used by Elshater *et al. [15]* with slight modification was used to prepare the raw extract. Ginger rhizome was washed, weighed, peeled, weighed and wet-milled using plate attrition mill (Amuda Plate mill, India). The smooth paste was sieved without addition of water using cheese cloth. The raw extract was stored in plastic jars at 2°C until use.

Cooked ginger was prepared by boiling the raw ginger extract for 1 hour on the medium burner of a 3-burner Haier Thermo cool gas cooker, India. This was allowed to cool and stored in a plastic jar at 2°C until use.

2.2. Streptozotocin-induced Diabetic Group

2.2.1. Collection of Rats

Male albino rats (70) of weight range 155-195 g were purchased from the Experimental Animals Unit of the Department of Veterinary Physiology, University of Ibadan, Ibadan, Nigeria. These were acclimatized for two weeks and were fed rats pellets and tap water ad libitum. These were grouped according to weight in seven plastic cages with 10 rats in each group. The animals were treated in accordance with the research protocol as approved by the UI/UCH Ethical Review Committee (Ethical approval Number –NHREC/05/01/2008a).

2.2.2. Experimental Protocol

The seven groups of rats were designated thus: N1S- normal control group, N1R- normal rats given raw ginger extract (daily single oral dose 4 ml/kg body weight for 4 weeks), N1Co- normal rats given cooked ginger extract, D1S- diabetic control group, D1R- diabetic rats given raw ginger extract, D1Co- diabetic rats given cooked ginger extract and D1D- diabetic rats given glibenclamide (5 mg/kg body weight), The control groups were given distilled water instead of ginger extract.

Diabetes was induced by intra peritoneal injection of streptozotocin (Sigma Aldrich, Germany) at 60 mg/kg body weight and fasting blood glucose (FBG) was monitored until stable hyperglycemia (≥ 170 mg/dl) was confirmed using the Glucometer.

2.3. High Fat Diet (HFD) –induced Diabetic Group

2.3.1. Collection Animals

Male albino rats (70) of weight range 120-160 g were purchased from the Experimental Animals Unit of the Department of Veterinary Physiology, University of Ibadan, and Ibadan, Nigeria. These were acclimatized for two weeks and were fed rat pellets and tap water ad libitum. These were grouped according to weight in seven plastic cages with 10 rats in each group. The animals were treated in accordance with the research protocol as approved by the UI/UCH Ethical Review Committee (Ethical approval Number –NHREC/05/01/2008a).

2.3.2. Formulation of High Fat Diet (HFD)

High fat diet was formulated using the method of Panchal et al., [16] with slight modification. The composition was as follows: 45% normal rat pellets, 30% beef tallow, 20% full cream milk powder and 5% sugar.

2.3.3. Experimentation

The groups of rats as designated treated thus: N2S – rats fed with normal rats pellets for 12 weeks and 2 ml/kg body weight distilled water orally for the following 4 weeks, N2R - rats fed with normal rats pellets and given oral administration of raw ginger extract (2 ml/kg body weight) for 4 weeks, N2Co- rats fed with normal diet and given cooked ginger extract, D2S- rats fed with HFD and given distilled water, D2R- rats fed with HFD and given raw ginger extract, D2Co- rats fed with HFD and given cooked ginger extract and D2D- rats fed with HFD and given Metformin (Hovid Diabetamin, Malaysia) – 200 mg/kg body weight [17],. The dosage of extracts used by Elshater et al [15] (2 ml/kg body weight) was applied.

2.4. Serum Insulin

Blood samples were taken from overnight fasted rats via retro orbital plexus before and after diabetes induction and at the end of the 2nd and 4th weeks of ginger extracts' administration. This was then prepared into serum by centrifuging at 10,000 rpm for 15 minutes at 4°C and

stored at -20°C until analyzed. Serum insulin was determined using Mercodia Rat Insulin ELISA assay kit.. Serum was allowed to thaw and vortexed before analysis. Calibrators and serum (10 µl) was pipetted into wells in the plates in duplicates after which 100 µl of enzyme conjugate solution was added into each well. This was then incubated for 2 hours on a plate shaker (800 rpm) after which washing was done 6 times with 700 µl wash buffer solution. After the final wash the plate was inverted on an absorbent paper. To each well 200 µl of Substrate TMB was added and this was incubated for 15 minutes at 25°C after which 50 µl of Stop solution was added. The optical density was read at 450 nm with ELISA plate reader. The values for the calibrators were used to plot a calibrator curve from which the values for the samples were extrapolated.

2.5. Statistical Analysis

Analysis of Variance was used to compare the groups of data while Least Significant Difference was used to compare mean values of one group and another ($p < 0.05$).

3. Results and Discussion

3.1. Serum Insulin in Normal and STZ-Induced Diabetic Rats

There was no significant difference in the serum insulin of the animals before the induction of diabetes (Table 1) but at 4 weeks of ginger extracts and glibenclamide administration there existed a marked significant($p<0.05$) increase in serum insulin in both normal and diabetic rats (Table 1). In normal rats raw and cooked ginger extracts increased the serum insulin from 0.072 µg/L to 0.95 and 0.103 µg/L respectively while in the diabetic group this parameter was increased from 0.050 in diabetic control group to 0.104 and 1.22 µg/L respectively. The anti diabetic drug (glibenclamide) exerted the highest significant increase ($p<0.05$) from 0.050 to 0.303 µg/L. (Table 1). The effect of this significant increase was reflected in the lowering of fasting blood glucose from 111.90 to 81.60 and 83.60 mg/dl by raw and cooked ginger extracts respectively in normal rats [13]. In the diabetic group the increase in serum insulin consequently lowered the fasting blood glucose from 426.29 mg/dl in the diabetic control to 115.10, 111.30 and 115.90 mg/dl by the taw extract, cooked extracts and glibenclamide respectively [13]. This increase in serum insulin corroborates the findings of Islam and Choi [18] who reported a significant increase in serum insulin by 4 weeks consumption of a diet containing 2% freeze-dried ginger powder in type 2 diabetic rats which was induced by a low dose (40 mg/kg body weight) of streptozotocin and high fat diet. Similarly, Madkur et al, [19] reported an increase in serum insulin from 26.0 µU/L in STZ-induced diabetic control group to 37.0 µU/L in the diabetic group treated with ginger powder given at 200 mg/kg body weight. Glibenclamide was also reported to increase insulin secretion by 174% in streptozotocin-induced diabetic rats treated with 900 µg/kg body weight compared to the diabetic control group [20] and this has been corroborated by Kim et al., [21].

Table 1. Effect of raw and cooked ginger extracts on serum insulin in normal and STZ-induced diabetic rats

Groups	SI B (µg/L)	SI AS (µg/L)	SI 2W (µg/L)	SI 4W (µg/L)
N1S	0.071 ± 0.003	0.073 ± 0.003	0.072 ± 0.004	0.072 ± 0.003
N1R	0.073 ± 0.005	0.071 ± 0.001	0.065 ± 0.004 □	0.095 ± 0.003 □
N1Co	0.070 ± 0.003	0.073 ± 0.003	0.066 ± 0.004 □	0.103 ± 0.006 □
D1S	0.071 ± 0.005	0.055 ± 0.003 □	0.053 ± 0.002	0.050 ± 0.004
D1R	0.072 ± 0.002	0.055 ± 0.004 □	0.091 ± 0.003 □	0.104 ± 0.002 □
D1Co	0.073 ± 0.023	0,056 ± 0.003 □	0.083 ± 0.001 □	0.122 ± 0.004 □
D1D	0.071 ± 0.021	0.056 ± 0.021 □	0.093 ± 0.005 □	0.303 ± 0.021 □

□---Significantly different from the control group ($p < 0.05$)
N1S ---Normal control group
N1R ---Normal rats given raw ginger extract
N1Co --Normal rats given cooked ginger extract
D1S –Diabetic control group
D1R—Diabetic rats given raw ginger extract
D1Co – Diabetic rats given cooked ginger extract
D1D – Diabetic rats given glibeclamide
SI B—Serum insulin before diabetes induction
SI AS—Serum insulin after diabetes induction with streptozotocin
SI 2W—Serum insulin at 2 weeks of extracts administration.
SI 4W—Serum insulin at 4 weeks of extracts administration.

The increase in serum insulin by ginger extracts and the drug (glibenclamide) administration may be a consequence of the restorative or regenerative effect of these on the β islet cells of the pancreas which had earlier been destroyed by streptozotocin. Other possible cell molecular processes may be responsible.

3.2. Serum Insulin of Normal and HFD-Induced Diabetic Rats

The 12 weeks HFD consumption exerted a significant increase ($p<0.05$) in serum insulin compared to the normal group (Table 2). This may be a state of hyperinsulinemia commonly occurring in cases of insulin resistance which may be precipitated by chronic HFD or high fructose diet consumption [22,23].

Table 2. Effect of raw and cooked ginger extracts on serum insulin in normal and HFD-induced diabetic rats

Groups	SI B (µg/L)	SI 12HFD (µg/L)	SI 2W (µg/L)	SI 4W (µg/L)
N2S	0.075 ± 0.003	0.074 ± 0.003	0.072 ± 0.003	0.072 ± 0.003
N2R	0.073 ± 0.004	0.071 ± 0.003	0.065 ± 0.002 □	0.097 ± 0.002 □
N2Co	0.073 ± 0.003	0.072 ± 0.003	0.068 ± 0.002 □	0.092 ± 0.002 □
D2S	0.075 ± 0.003	0.094 ± 0.003 □	0.104 ± 0.004	0.105 ± 0.004
D2R	0.070 ± 0.002	0.093 ± 0.004 □	0.083 ± 0.003 □	0.070 ± 0.002 □
D2Co	0.070 ± 0.002	0.091 ± 0.003 □	0.086 ± 0.004 □	0.061 ± 0.002 □
D2D	0.073 ± 0.001	0.094 ± 0.004 □	0.092 ± 0.001 □	0.072 ± 0.002 □

□---Significantly different from the control group ($p < 0.05$)
N2S ---Normal control group
N2R ---Normal rats given raw ginger extract
N2Co --Normal rats given cooked ginger extract
D2S –Diabetic control group
D2R —Diabetic rats given raw ginger extract
D2Co – Diabetic rats given cooked ginger extract
D2D – Diabetic rats given Metformin
SI B—Serum insulin before HFD consumption
SI 12HFD—Serum insulin at 12 weeks HFD consumption
SI 2W—Serum insulin at 2 weeks ginger extracts administration.
SI 4W—Serum insulin at 4 weeks ginger extracts administration.

At two weeks of extracts' administration there was significant reduction ($p<0.05$) in serum insulin in both normal-treated and diabetic –treated groups but the reducing effect by the extracts was more than that of Metformin in the diabetic group (Table 2). Raw and cooked ginger extracts increased serum insulin significantly ($p<0.05$) at 4 weeks of extracts' administration in normal rats but continued to reduce this parameter in the diabetic-treated groups.. This consequently reduced the fasting blood glucose (FBG) from 213.56 mg/dl in diabetic control group to 114.67, 138.86 and 112.33 mg/dl by the raw extract, cooked extract and Metformin respectively while the normal FBG was 109.55 mg/dl [9].

This corroborates the results of Nammi et al. [22] who reported a lowering effect of ethanolic ginger extract (at 400 mg/kg body weight) on serum insulin from 14.7 µU/ml in HFD-induced diabetic rats (control) to 6.9 µU/ml and 6.1 µU/ml in ginger- and Rosiglitazone-treated groups respectively while the normal value was 5.8 µU/ml. This resulted into the lowering of FBG from 208.8 mg/dl in the diabetic control to 93.1 and 118.8 mg/dl by the ginger extract and the drug respectively while the normal value was 89.6 mg/dl.

Similarly, Kadnur and Goyal, [23] reported a significant lowering effect of methanolic ginger extract on serum insulin from 41.3 µU/ml in high-fructose diet-induced diabetic rats (control) to 34.0 µU/ml in ginger treated diabetic group thus reducing FBG from 116.1 mg/dl to 95.1 mg/dl respectively. Even though the ginger extracts did not increase serum insulin in HFD-diet induced diabetic rats there is clear evidence that the state of hyperinsulinemia commonly associated with insulin resistance was ameliorated thus lowering the FBG. This could be as a result of improved sensitivity of insulin receptors to insulin thus enhancing glucose uptake by the body tissues.

4. Conclusion and Recommendation

Raw and cooked ginger extracts enhanced insulin secretion in Streptozotocin-induced diabetic rats and reduced hyperinsulinemia precipitated by chronic high fat diet consumption.. These are the possible mechanisms of action of the hypoglycemic effect of ginger. However, the drug-nutrient interaction between the cooked extract and high fat diet consumption needs further exploration and the probable enhancement of glucose uptake by the body tissues (such as muscle and adipose tissues) by the ginger extracts needs to be ascertained.

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