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Original Research

Blood glucose-lowering effect of *Telfairia Occidentalis*: A preliminary study on the underlying mechanism and responses

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ABSTRACT: **The effects of aqueous extract of *Telfairia Occidentalis* leaf (*TO*) on plasma glucose, lactate dehydrogenase activity (LDH), insulin and cortisol levels in rats were investigated. Thirty male Wistar rats (200–250g) were randomly divided into 5 groups (n=6/group). Rats in the control group received 0.2 ml of normal saline while rats in other groups were orally treated with 100 or 200 mg/Kg of the extract for either 1 or 2 weeks. The results showed that there were significant increases in insulin and cortisol levels, decrease in glucose, and an insignificant increase in LDH activity in rats treated with 100 and 200 mg/Kg of the extract for 1 week. However, after 2 weeks of treatment with the same doses, there was no significant change in plasma insulin in the treated rats when compared with the control. In contrast, there was a significant decrease in plasma insulin levels when compared with what was obtained after one week of treatment. The reduction in plasma insulin was accompanied by increases in plasma glucose towards normal and significant increases in plasma cortisol and LDH activity. The results suggest that the blood glucose-lowering effect of *Telfairia Occidentalis* might be mediated at least in part by insulin. This effect elicited counterregulatory responses that included an increase in plasma cortisol and lactate dehydrogenase activity to probably stimulate cortisol-induced gluconeogenesis and favor lactate oxidation.**

KEYWORDS: **Cortisol; Insulin; Lactate dehydrogenase; Plasma glucose; *Telfairia Occidentalis.***

INTRODUCTION

Telfairia occidentalis (Fluted Pumpkin) is a leaf and seed vegetable. Nutritionally, the leaves of this herb are rich in minerals such as iron, potassium, sodium, phosphorus, calcium and magnesium; antioxidants such as thiamine, riboflavin, nicotinamide, and ascorbic acid; and amino acids such as alanine, aspartate, glycine, leucine and many others (Fasuyi and Nonyerem, 2007; Tindall, 1968). Studies have identified phytochemicals such as tannins, saponins, flavanoids and phenolics in the plant (Ekpenyong *et al.*, 2012; Adeniyi *et al.*, 2010).

The medicinal activities of *Telfairia occidentalis* have been reported by many investigators. The leaves contain essential oils, vitamins, while the root contains cucubitacine, sesquiterpene, lactones (Iwu, 1983). Its anti-anaemic (Dina *et al.*, 2006; Oboh, 2004; Alada, 2000), anti-convulsant (Gbile, 1986), anti-inflammatory (Oluwole *et al.*, 2003), purgative (Dina *et al.*, 2001), antimicrobial (Okokon *et al.*, 2007; Oboh *et al.*, 2006; Odoemena and Essien, 1995), anti-oxidant and hepatoprotective effects (Kayode *et al.*, 2010; Iweala and Obidoa, 2009; Kayode *et al.*, 2009; Adaramoye *et al.*, 2007; Nwanna and Oboh, 2007; Oboh *et al.*, 2006; Eseyin *et al.*, 2005a; Oboh, 2005; Oboh and Akindahunsi, 2004) have been reported.

Previous reports on its effects on blood glucose level are slightly contradictory. Its blood glucose-lowering effect was reported in rats (Eseyin *et al.*, 2010; Salman *et al.*, 2008; Nwozo, 2004; Emudianughe and Aderibigbe, 2002; Eseyin *et al.*, 2000) and mice (Aderibigbe *et al.*, 1999). More recently, it was also reported to cause an increase in blood glucose in normal (Adisa *et al.*, 2012) and diabetic rats (Eseyin *et al.*, 2005c). In addition to these conflicting reports, the mechanism(s) for either its hypo- or hyperglycemic effect remains unclear. There are physiological feedback mechanisms that serve to maintain glucose homeostasis. For instance, insulin release from the pancreas is enhanced during hyperglycemia in order to reduce blood glucose to normal, while cortisol, glucagon and epinephrine release during hypoglycemia play counterregulatory roles to raise blood glucose back to normal through the processes of glycogenolysis and gluconeogenesis. Whether or not such feedback mechanism and counterregulatory responses will be activated in *Telfairia occidentalis*-treated rats in order to stabilize blood glucose is not known. The reason for the conflicting reports on the effects of TO on blood glucose is unknown, but might be due to technical errors from different glucometers used to determine blood glucose in those previous studies.

In view of the above, this study was designed to investigate the actual effects of TO on blood glucose using the standard laboratory glucose oxidase method. In addition, the possible mechanism for the effects of TO on blood glucose was also investigated.

MATERIALS AND METHODS

Animals

Thirty male albino rats (200–250g) were used for the study. They were obtained from the animal house of the Department of Physiology, College of Health Sciences, University of Ilorin, Ilorin, Kwara state, Nigeria. They were housed at six animals per cage and provided with standard laboratory feed and water *ad libitum*. They were maintained in a well-ventilated room at 25 ± 2 °C on a 12-hour light/dark cycle. All authors hereby declare that "principles of laboratory animal care" (NIH publication No. 85-23, revised in 1985) were followed. All experiments were examined and approved by the University of Ilorin ethics committee. All necessary protocols were followed to ensure the humane treatment of the animals.

Selection of Telfaria Occidentalis (TO) leaf and preparation of aqueous extract

Fresh leaves of TO were sourced locally in Ilorin, Kwara state, Nigeria and authenticated by Mr Bolu Ajayi of the Department of Plant Biology, University of Ilorin, and a voucher number UIH1063 was deposited in the departmental herbarium. The leaves were washed with water to remove sand and other debris, air-dried and pulverized into powder using electric blender. A sample weighing 1000 g was soaked in 4 litres of distilled water for about 72 hours and stirred at intervals. The mixture was sieved with a clean white cloth. The filtrate was dried at 40 °C to obtain a solid extract. The dried weight of the extract was 200 g.

Experimental Treatments

Thirty male albino rats were divided in a blinded fashion to 5 groups (A-E, n=6 each). Group A was the control and received only standard feed and 0.2 ml of saline for 2 weeks. In addition to standard feed, groups B and C received 100 mg/Kg and 200 mg/Kg of *Telfairia occidentalis* (TO) respectively for 1 week, while groups D and E received 100 mg/Kg and 200 mg/Kg of TO respectively for 2 weeks. A day after the treatment in each group, blood sample from each rat was collected (by cardiac puncture) into lithium heparinized capillary tubes. Plasma was collected from each sample and preserved at -20 °C.

Measurement of plasma biochemical parameters

Plasma glucose was measured by standard laboratory procedure using the glucose oxidase method (Trinder, 1967). Serum insulin assay involved an enzyme linked immunosorbent method using a clinical kit supplied by Monobind Inc., Lake Forest, CA, USA. The protocol was carried out using the manufacturer's instructions. Spectrophotometric readings were taken on a microplate reader. Serum cortisol assay was done by the principle of competitive enzyme immunoassay using cortisol AccuBind ELISA kit (Monobind Inc., Lake Forest, CA, USA). Briefly, biotinylated antibody and enzyme-antigen conjugate were mixed with the native antigen contained in the serum. A competitive reaction results between the antigen in the serum and the enzyme-antigen conjugate for a limited number of antibody binding sites. A simultaneous reaction between the biotin attached to the antibody and the streptavidin immobilized on the microwell occurs. This caused the complex formed to bind to the solid surface of the microwell after decantation. The concentration of the cortisol in the serum sample was determined spectrophotometrically. Serum lactate dehydrogenase (LDH) assay was done spectrophotometrically with LDH kit supplied by Monobind Inc., Lake Forest, CA, USA.

Data processing

Data were analyzed using SPSS version 16.0 for windows. All values given were the Mean ± S.E.M. of the variables measured. Significance was assessed by the analysis of variance (ANOVA), followed by a post-hoc Least Significance Difference (LSD) test for multiple comparisons. P-Values of 0.05 or less were taken as statistically significant.

RESULTS

Effects of *Telfairia occidentalis* (TO) on glucose levels in rats

The plasma glucose levels in rats treated with TO for one week and two weeks are shown in Tables 1 and 2 respectively. There were significant reductions in plasma glucose levels after one-week treatment with 100 mg/Kg (p<0.001) and 200 mg/Kg (p<0.001) in animals treated with TO when compared to those in the control group. The decreases were 36.64% and 45.12% for 100 and 200 mg/Kg treatments respectively. In addition, 200 mg/Kg TO treatment caused a significant decrease in blood glucose when compared to the effect due to 100 mg/Kg administration.

Moreover, the two doses of TO also caused significant reductions in plasma glucose levels compared to the control after two weeks of treatment. However, plasma glucose levels were significantly higher in rats treated with 100 mg/Kg (p<0.05) and 200 mg/Kg (p<0.001) for two weeks when compared with the values obtained after one week treatment with the same doses. The increases were 14.00% and 56.44% for 100 and 200 mg/Kg treatments respectively.

Table 1: Effects of one week of treatment with Telfaria Occidentalis (TO) on plasma glucose, insulin, cortisol and lactate dehydrogenase (LDH) activity in rats.

	Control	100 mg/kg	200 mg/kg
Glucose (mmol/L)	8.20±0.10	5.22±0.08[***,]	4.50±0.22[***,#]
Insulin (μiu/ml)	16.76±0.76	18.83±0.30[*]	19.52±0.46[**,]
Cortisol (μiu/ml)	3.25±0.16	6.38±0.57[***]	6.50±0.55[***]
LDH (U/L)	96.16±17.46	100.55±1.92	240.45±55.60

Values are expressed as Mean ± SEM (n=6). [*]P<0.05, [**]P<0.01, [***]P<0.001 vs control; [#]P<0.05 vs 100 mg/Kg (n=6).

Effects of *Telfairia occidentalis* (TO) on plasma insulin levels in rats

The plasma insulin levels in rats treated with TO for one week and two weeks are shown in Tables 1 and 2 respectively. One week treatment with 100 mg/Kg (p<0.05) and 200 mg/Kg (p<0.01) of TO caused significant increases in plasma insulin levels compared to control. The increases were 12.35% and 16.47% respectively at 100 and 200 mg/Kg respectively. However, after two weeks of treatment, plasma insulin levels were similar to that of the control. Moreover, when plasma insulin levels obtained after two weeks of

treatment were compared to values obtained after one week of treatment with same doses, only 200 mg/Kg of TO caused significant reduction (p<0.001) in plasma insulin level after two weeks of treatment. The decrease in plasma insulin was 20.08%.

Effects of *Telfairia occidentalis* (TO) on plasma cortisol levels in rats

The plasma cortisol levels in rats treated with TO for one week and two weeks are shown in Tables 1 and 2 respectively. The two doses of TO caused significant increases (p<0.001) in plasma cortisol level compared to the effect of the control treatment after one week and two weeks of treatment. The increases in plasma cortisol levels were more than 100% in all the treated groups. There were no significant differences (p>0.05) in the plasma cortisol levels with different doses of TO either after one week or two weeks of treatment, neither were there significant differences (p>0.05) between treatment periods when exposed to same dose of TO.

Table 2: Effects of two weeks of treatment with Telfaria Occidentalis (TO) on plasma glucose, insulin, cortisol and lactate dehydrogenase (LDH) activity in rats.

	Control	100 mg/kg	200 mg/kg
Glucose (mmol/L)	8.20±0.10	6.08±0.42[***,$]	7.04±0.34[***,##,$$$]
Insulin (μiu/ml)	16.76±0.76	16.96±0.82	15.60±0.71[$$$]
Cortisol (μiu/ml)	3.25±0.16	7.00±0.90[***]	7.20±0.73[***]
LDH (U/L)	96.16±17.46	374.03±33.79[***,$$$]	1442.7±154.86[***,###,$$$]

Values are expressed as Mean ± SEM (n=6). [***]P<0.001 vs control; [##]P<0.01, [###]P<0.001 vs 100 mg/Kg; [$]P<0.05, [$$$]P<0.001 vs one week of same dose (see Table 1).

Effects of *Telfaria occidentalis* (TO) on lactate dehydrogenase (LDH) activity in rats

The LDH activities in rats treated with TO for one week and two weeks are shown in Tables 1 and 2 respectively. There was no change in the LDH activity of the rats treated with 100 mg/Kg of TO while there was an apparent but insignificant increase in those treated with 200 mg/Kg after one week of treatment. However, after two weeks of treatment, there were –fold and 14-fold increases in LDH activity in rats treated with 100 and 200 mg/Kg respectively when compared with the control. Moreover, the increase in LDH activity (P<0.0001) at 200 mg/Kg of TO was higher than that caused by 100 mg/Kg. In addition, after two weeks of treatment, LDH activity was significantly higher in rats treated with 100 mg/Kg (p<0.001) and 200 when compared with the LDH activity after one week of treatment with the same doses.

DISCUSSION

The blood glucose-lowering effect of Telfaria occidentalis (TO) observed in this study is consistent with previous reports in rats (Eseyin *et al.*, 2010; Salman *et al.*, 2008; Eseyin *et al.*, 2005b; Nwozo, 2004; Emudianughe and Aderibigbe, 2002; Eseyin *et al.*, 2000) and mice (Aderibigbe *et al.*, 1999) but at variance with that of Adisa *et al.* (2012) and Eseyin *et al.* (2005c) who reported its hyperglycemic effect in normal and diabetic rats respectively.

Perhaps, the most interesting observation in this study is the effects of 200 mg/Kg of TO on blood glucose and insulin. Treatment with 200 mg/Kg resulted in a significant increase in plasma insulin and consequently, a decrease in plasma glucose after one week of treatment. However, after two weeks of treatment, the significant decrease in plasma insulin resulted in a significantly higher blood glucose level when compared with the blood glucose after a week of treatment. This suggests the likely involvement of insulin in the blood glucose-lowering effect of TO. Thus, stimulation of the release of insulin could be involved in the mechanism of *Telfairia Occidentalis*-induced lowering of blood glucose. This is consistent with the well-documented hypoglycemic effect of insulin (Newmann *et al.*, 1983; Ashraf *et al.*, 1999; Alada *et al.*, 1996; Alada *et al.*, 2005).

In resting mammals, oxidation accounts for approximately half lactate disposal and gluconeogenesis approximately 20% (Brooks *et al.*, 1991; Stanley *et al.*, 1986). Lactate could therefore be an appropriate substrate in a low energy state such as that caused by TO because in addition to being an alternative energy source and sparing blood glucose to prevent further lowering of blood glucose, it could also serve as a gluconeogenic precursor to raise blood glucose to normal. The increase in LDH activity and cortisol therefore suggests that the increase in blood glucose could be through gluconeogenesis. However, it should be noted that despite the increased cortisol levels after one week of treatment with 100 and 200 mg/Kg, there was a significant reduction in blood glucose level. This could be due to the increased insulin levels. Insulin inhibits gluconeogenesis and acts predominantly by suppressing the expression of the genes for the key gluconeogenic enzymes phosphoenolpyruvate carboxykinase and glucose-6-phosphatase (Barthel and Schmoll, 2003). Thus, the increased insulin level probably inhibited or suppressed the actions of cortisol during the first week of treatment.

LDH catalyzes the interconversion of pyruvate and lactate (Gerhardt-Hansen, 1968; Markert and Appella, 1961) and one of the major fates of blood lactate is its conversion to glucose in the liver and kidney (Rehbinder, 1971). New lines of investigation now place lactate as an active metabolite, capable of moving between cells, tissues and organs, where it may be oxidised as a fuel or reconverted to form pyruvate

or glucose (Andrew *et al.*, 2005). For instance, Lactate, which is a substrate for lactate dehydrogenase, has been shown to maintain synaptic formation and sustain synaptic adaptation during hypoglycemia in the mammal hippocampus (Sakurai *et al.*, 2002; Schurr *et al.*, 1988). The increase in LDH activity in this study could also be to favour increase in lactate oxidation.

We observed that plasma cortisol levels increased significantly in all the treated groups when compared with the control. The increases in cortisol levels following lowering of blood glucose induced by TO is consistent with the high levels of cortisol seen in infants having hypoglycemia due to hyperinsulinism (Crofton and Midgley, 2004). Based on the data from this preliminary study, we speculate that the significant increases in the blood glucose of rats treated with 100 and 200 mg/Kg of TO for two weeks compared to those treated for one week with the same doses could at least be partly due to the gluconeogenic actions of the increased cortisol. At rest, some of the metabolic functions of cortisol related to fuel homeostasis include modest increases in hepatic glucose production and an increase in the rate of synthesis of gluconeogenic enzymes in the liver (Samra *et al.*, 1996; Friedman, 1994; Boyle and Cryer, 1991; De Feo *et al.*, 1989). Furthermore, it is well known that cortisol plays an important role in the defense against prolonged insulin-induced hypoglycemia at rest (Boyle and Cryer, 1991; De Feo *et al.*, 1989). Moreover, Hypercortisolemia has been reported to increase lactate gluconeogenesis (Lecavalier *et al.*, 1990).

Therefore, gluconeogenesis from lactate could probably be partly responsible for the increase in blood glucose after two weeks of treatment when compared with the first week. The question is what could then be responsible for the accumulation of the lactate used for gluconeogenesis? The possible answer to this could be that the increase in plasma insulin during the first week of treatment led to accumulation of lactate used for gluconeogenesis during the second week of treatment, although most of the lactate could have been oxidized. The stimulation of lactate accumulation by insulin in granulosa-luteal cells from normal ovaries has been previously reported. Insulin stimulates glucose uptake in granulose cells which in turn leads to glucose degradation to lactate (Yang *et al.*, 1997).

The fate of the glucose removed from the blood is either to go into the glycolytic pathway to produce pyruvate and lactate or be converted to glycogen. Since we did not measure glycogen, we could not actually determine the fate of the glucose removed from the blood by *Telfairia occidentalis.* Measurement of glycogen to investigate if glycogenolysis contributes to the increase in blood glucose after second week of treatment is also recommended in future studies. Estimation of blood lactate, another limitation of this preliminary study, will also shed light into the actual

role played by lactate (either oxidative or gluconeogenic) in the observed responses. Further studies on the effects of TO on glucose uptake, glycogenesis and other enzymes and hormones of glucose metabolism not measured in this preliminary study will also provide a better understanding of the effects of TO on glucose metabolism.

The increases in cortisol levels and LDH activity could therefore be construed as counterregulatory responses to the lowering of blood glucose induced by TO. While the actions of insulin and LDH could lead to accumulation of lactate, the increased cortisol level could stimulate lactate gluconeogenesis by increasing the synthesis and activity of gluconeogenic enzymes. Therefore, the hyperglycemia reported by Adisa *et al*. (2012) after thirty days of treatment with TO could be as a result of gluconeogenesis and/or glycogenolysis response to the reduction in blood glucose caused earlier during the treatment. In other words, the hyperglycemia was probably secondary to hypoglycemia. Another limitation of this study which could be accommodated in future studies is the short period of the experiment, which could not allow us to establish if hyperglycemia might later occur beyond 2 weeks. This might justify the hyperglycemia earlier reported following treatment of rats with TO for 30 days (Adisa *et al*., 2012).

In conclusion, the present study has shown that the blood glucose-lowering effect of TO could be insulin-dependent and the counterregulatory responses included an increase in cortisol and LDH activity to probably stimulate cortisol-induced gluconeogenesis and favor lactate oxidation.

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