Antidiabetic Effects of Some Tropical Fruit Extracts in Fructose Induced Insulin Resistant Wistar Rats

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Authors’ contributions

This work was carried out in collaboration with all authors. Authors DAW and MIK designed the study and supervised the whole research. Authors OAL and ARO participated in writing of the manuscript and submission for publication. All authors read and approved the final manuscript.

ABSTRACT

Aim: Fruit extracts of Apple (Malus domestica), coconut (Cocos nucifera) and cucumber (Cucumis sativus) were tested for their antidiabetic potential in rats with fructose-induced insulin resistance for 28 days.

Study Design: In-vivo antidiabetic study using fructose-induced insulin resistant rats.

Place and Duration of Study: Department of Biochemistry, Lagos State University, Ojo, Lagos, Nigeria, between March and May 2014.

Methodology: Wistar rats were randomized into 5 groups comprising 5 animals each. Group A (control) was fed on standard rat chow and distilled water ad libitum while Groups B-E were fed standard rat chow and 10% w/v fructose. Groups C-E were also administered 500 mg/kg body weight of apple, coconut and cucumber extracts for 28 days. At the end of the experiment, all animals were sacrificed and the serum glucose, lipid profile and electrolytes were determined.
**Results:** The fructose-fed rats had significantly decreased weight and increased blood glucose concentration ($P < 0.05$), when compared to the control rats. The fructose-fed rats also witnessed significant increase ($P < 0.05$) in total cholesterol and low density lipoprotein cholesterol (LDLC) concentration as well as significant decrease ($P < 0.05$) in the high density lipoprotein (HDLC) and serum electrolytes concentration compared to control. Administration of the aqueous extracts of apple, coconut and cucumber to the fructose-fed rats significantly increase ($P < 0.05$) their body weights, HDLC and serum electrolytes’ concentration in the rats while significantly reducing ($P < 0.05$) blood glucose, total cholesterol and LDLC.

**Conclusions:** Aqueous extracts of apple, coconut and cucumber displayed antidiabetic effect, but apple exhibited the most potent effect as it ameliorates most of the derangements observed in insulin-resistant rats.

**Keywords:** Diabetes; apple; coconut; cucumber; lipid profile; electrolytes.

### 1. INTRODUCTION

Insulin resistance is the inability of insulin to elicit its usual biological actions at circulating concentrations that are effective in normal subjects. Insulin resistance in the context of glucose metabolism indicates impaired regulation of endogenous glucose production. Inability of insulin to suppress very low density lipoprotein (VLDL) cholesterol production increases circulating serum triglycerides. On the other hand, resistance in adipose tissue increases the flux of non-esterified fatty acid (NEFA) both to the liver and skeletal muscle and impairs the action of insulin on glucose metabolism in these tissues [1].

The public health burden of type 2 diabetes mellitus (T2DM) [2] has dramatically increased worldwide. It has shown that the risk of developing clinical diabetes substantially increased in the state of impaired fasting blood glucose or impaired glucose tolerance. Fasting hyperglycemia is caused by unrestrained basal hepatic glucose output, primarily a consequence of hepatic resistance to insulin action [2,3]. Insulin resistance not only plays an important role in T2DM, but it is also an extremely common feature of a number of important human diseases including atherosclerosis, hypertension, and dyslipidemia [2,4,5]. Type 2 diabetes mellitus or non-insulin-dependent diabetes mellitus (NIDDM) is characterized by progressive impairment of glucose homeostasis and sensitivity to insulin, particularly in skeletal muscle and liver [6].

Available reports suggest that high dietary intake of fructose is an important causative factor in the development of insulin resistance and the associated metabolic syndrome [7-9]. Several studies have pointed to the pharmacological properties of tropical fruits in the management of diseases like cancer, hypertension, diabetes and coronary artery diseases. The aim of this study was to assess and compare the antidiabetic potential of aqueous extracts of apple, coconut and cucumber in fructose-induced insulin resistant wistar rats.

### 2. MATERIALS AND METHODS

#### 2.1 Preparation of Fruit Extracts

Fresh fruits of apple, coconut and cucumber, were obtained from Iyana-Iba market, Ojo Local Government in Lagos, Nigeria. All the fruits were washed thoroughly while the coconut shell was broken and separated from the endocarp (with water). The fruit samples were cut into pieces, and their content extracted using the household fruit extractor. The mixtures were filtered with muslin cloth and the extracts obtained were then frozen and freeze-dried in a lyophilizer (Virtis BenchTop, SP Scientific Series, USA). Dried extracts were dissolved in water to obtained 500 mg/kg of the extracts per body weight of the rats.

#### 2.2 Animals and Treatments

Experimental protocols were conducted in accordance with guidelines of the Institutional Animal Care and Use Committee and were approved by the Animal Ethical Committee of the Department of Biochemistry, Lagos State University, Ojo, Lagos, Nigeria. Twenty-five wistar rats, weighing 180–200 g were purchased from the animal house of the University of Agriculture, Abeokuta, Nigeria. The animals were conditioned at room temperature and natural photoperiods. After two weeks of acclimatization, the animals were divided into five groups of five animals each. Each group of rats was separately housed in standard cages and had free access to water and standard pellet diet. The first group (group A) was used as control and fed with...
standard rat chow and tap water. Insulin resistance was induced in the four other groups of animals (group B, C, D and E) by 10% w/v fructose dissolved in drinking water [10,11]. Group C, D and E were administered daily with 1 mL extract of apple, coconut and cucumber respectively while group B serves as insulin resistant control. The experiment lasted four weeks. Weight and blood glucose levels of the animals were measured both at the beginning and end of the experiment using a weighing balance and glucometer respectively.

2.3 Preparation of Serum

The animals were anaesthetized in a jar containing cotton wool soaked in halothane. When rats became unconscious, their neck region was quickly cleared of fur and skin to expose their internal jugular veins. The veins were slightly displaced (to prevent contamination of the blood with interstitial fluid) after which they were cut sharply with a sterile blade. The rats were then held head downwards, allowed to bleed into clean, dry centrifuge tubes. The blood samples were allowed to clot for 10 min at room temperature and subsequently centrifuged at 224 × g for 10 min with Uniscope Laboratory Centrifuge (model SM800B, Surgifriend Medicals, Essex, England). The sera were aspirated with Pasteur pipette and used for the determination of lipid profile and electrolyte concentration.

2.4 Determination of Biochemical Parameters

Total cholesterol, triglyceride, HDL-cholesterol, and LDL-cholesterol levels were measured spectrophotometrically using the methods described by Fredrickson et al. [12], Trinder [13], Albers et al. [14] and Bergmenyer [15] respectively. Serum magnesium and calcium were determined by the method of Farell [16] and Chauhan and Pande [17] respectively while sodium and potassium were measured using a flame photometer method [18].

2.5 Statistical Analysis

Data were presented as mean of 5 replicates ± standard error of mean (SEM). Data were subjected to One-Way Analysis of Variance (ANOVA) followed by test of significance using Bonferroni post hoc test. The level of statistical significance was taken at 5% confidence level.

3. RESULTS

Oral administration of fructose to albino rats produced a gradual state of hyperglycemia (116.70 mg/dL) which is significantly different (P<0.05) from the control (76.33 mg/dL) (Table 1). The administration of various fruit extracts to the fructose-fed rats significantly reduced (P<0.05) the blood glucose concentration of the rats when compared to fructose-fed rats only.

Fructose feeding significantly reduced body weights (137.7 g) of rats (P<0.05) when compared to the control rats (183.0 g) (Table 2). However, daily administration of fruit extracts to fructose-fed rats prevents this loss of weight by significantly increasing (P<0.05) their body weights when compared to the fructose-fed only.

Table 3 showed the effect of the fruit extracts administration on serum lipid profile in fructose-induced insulin resistance in rats. There was a significant increase (P<0.05) in the concentration of total cholesterol (99.15 mg/dL) and LDL-cholesterol (55.35 mg/dL) of fructose-fed rats when compared to the control rats (62.73 and 10.74 mg/dL respectively). Administration of the fruit extracts significantly reversed (P<0.05) the fluctuations caused by the fructose when compared to the fructose-fed rats only.

Table 1. Effect of fruit extracts administration on blood glucose level in fructose-induced insulin resistant rats

<table>
<thead>
<tr>
<th>Group</th>
<th>Glucose (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 1</td>
</tr>
<tr>
<td>Control</td>
<td>79.33±6.55</td>
</tr>
<tr>
<td>Fructose</td>
<td>67.35±4.63</td>
</tr>
<tr>
<td>Fructose + Apple</td>
<td>78.53±2.91</td>
</tr>
<tr>
<td>Fructose + Coconut</td>
<td>69.00±8.39</td>
</tr>
<tr>
<td>Fructose + Cucumber</td>
<td>72.12±4.04</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SEM, n=5 in each group. *P<0.05 compared to control; †P<0.05 compared to fructose-fed rats only (One way ANOVA followed by Bonferroni test)
and diabetes. Previous studies have shown that poorly controlled blood glucose increase the potassium concentration of fructose administration of various fruit extracts might affect blood glucose level of fructose resistant rats.

4. DISCUSSION

It is believed that poorly controlled blood glucose is the most important factor in the development of diabetes. Insulin resistance is considered as part of the metabolic risk profile including central obesity, cardiovascular diseases, hypertension, and diabetes. Previous studies have shown that long-term fructose feeding induces mild insulin resistance in experimental animals [19,20] with the characteristic loss in weight and increase in blood glucose level of fructose-fed rats. The administration of various fruit extracts to the fructose-fed rats led to reduced blood glucose level. This suggests that the fruit extracts might exert insulin-like effect on peripheral tissues by either promoting glucose uptake metabolism through inhibiting hepatic gluconeogenesis [21] or absorption of glucose into the muscle and adipose tissues [22].

The abnormally high concentrations of serum lipids in the fructose-fed rats are due mainly to increase in the mobilization of free fatty acids from the peripheral fat depots, because insulin inhibits the hormone sensitive lipase. Insulin deficiency or resistance may be responsible for dyslipidemia, because insulin has an inhibitory action on hydroxyl-β-methylglutaryl CoA.

### Table 2. Effect of fruit extracts administration on weight in fructose-induced insulin resistant rats

<table>
<thead>
<tr>
<th>Group</th>
<th>Weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 1</td>
</tr>
<tr>
<td>Control</td>
<td>157.3±1.45</td>
</tr>
<tr>
<td>Fructose</td>
<td>163.3±1.67</td>
</tr>
<tr>
<td>Fructose + Apple</td>
<td>167.7±8.69</td>
</tr>
<tr>
<td>Fructose + Coconut</td>
<td>163.7±5.81</td>
</tr>
<tr>
<td>Fructose + Cucumber</td>
<td>168.0±8.39</td>
</tr>
</tbody>
</table>

Values are expressed as means±SEM. n=5 in each group. *P<0.05 compared to control; **P<0.05 compared to fructose-fed rats only (one way ANOVA followed by Bonferroni test)

### Table 3. Effect of fruit extracts administration on serum lipid profile in fructose-induced insulin resistant rats

<table>
<thead>
<tr>
<th>Group</th>
<th>Lipids (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cholesterol</td>
</tr>
<tr>
<td>Control</td>
<td>62.7±1.75</td>
</tr>
<tr>
<td>Fructose</td>
<td>99.1±9.26ab</td>
</tr>
<tr>
<td>Fructose + Apple</td>
<td>47.51±5.76ab</td>
</tr>
<tr>
<td>Fructose + Coconut</td>
<td>54.56±9.59ab</td>
</tr>
<tr>
<td>Fructose + Cucumber</td>
<td>68.58±5.36</td>
</tr>
</tbody>
</table>

Values are expressed as means±SEM. n=5 in each group. *P<0.05 compared to control; **P<0.05 compared to fructose-fed rats only (one way ANOVA followed by Bonferroni test)

### Table 4. Effect of fruit extracts administration on serum electrolytes in fructose-induced insulin resistant rats

<table>
<thead>
<tr>
<th>Group</th>
<th>Minerals (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Calcium</td>
</tr>
<tr>
<td>Control</td>
<td>10.84±0.64</td>
</tr>
<tr>
<td>Fructose</td>
<td>5.72±0.58a</td>
</tr>
<tr>
<td>Fructose + Apple</td>
<td>11.07±1.73ab</td>
</tr>
<tr>
<td>Fructose + Coconut</td>
<td>7.13±1.56b</td>
</tr>
<tr>
<td>Fructose + Cucumber</td>
<td>8.11±0.87</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SEM. n=5 in each group. *P<0.05 compared to control; **P<0.05 compared to fructose-fed rats only (One way ANOVA followed by Bonferroni test)

All the electrolytes assayed for witnessed decrease in their concentrations in fructose-fed rat though it was significant (P<0.05) for both calcium and potassium only (above Table 4). This decrease was counteracted by various treatment schedules using the fruit extracts. However, the coconut extract was not able to increase the potassium concentration of fructose-fed rats. Though, there were fluctuations, none of the extracts was able to significantly increase (P>0.05) the sodium concentration depleted by the administration of fructose.
reductase (HMG-CoA reductase), a key rate-limiting enzyme responsible for the metabolism of cholesterol rich LDL particles. Insulin resistance initially causes an increase in free fatty acid mobilization from adipose tissue and this result in increased production of cholesterol rich LDL particles [23]. Fructose-feeding also stimulates the hepatic production of triglycerides, both by promoting the re-esterification of circulating non-esterified fatty acids and also by stimulating de novo fatty acid synthesis [24]. Increased delivery of triglycerides and non-esterified fatty acids to the muscle interferes with the utilization of glucose, through the principles of Randle cycle [25], and also impairs the insulin action. The administration of fruit extracts increased the level of serum HDL-cholesterol and decreased the levels of total cholesterol, triglycerides and LDL-cholesterol in the rats.

In biological systems, electrolytes are the substances that dissociate into ions in solution. Regular fasting is closely linked to calcium and magnesium homeostasis [26]. Thus, a link is observed in the progressive decrease, in serum magnesium and calcium in fructose-fed animals. Decreased level of magnesium results in the inhibition of Na⁺-K⁺-ATPase because magnesium is a cofactor for this enzyme [27]. Magnesium and calcium deficiency has been demonstrated in insulin resistance and may contribute to suppressing glucose metabolism and insulin action [28]. Previous study also showed that insulin resistance impedes cellular uptake of potassium and sodium [29]. High serum potassium concentration stimulates insulin secretion by the pancreas while low serum potassium has an inhibitory effect [30]. However, the fruit extracts were able to reverse the imbalances in the electrolyte concentration.

5. CONCLUSIONS

Feeding of 10% fructose solution to rats produced hyperglycemia and insulin resistance. It also leads to alterations in lipid profile and causes electrolyte imbalance. Administration of aqueous extract of apple, coconut and cucumber tend to ameliorate these alterations. However, out of the three fruits, apple seems to be the most effective. This study therefore suggests that apple, coconut and cucumber could be consumed by man as part of the dietary regimen in the management of diabetes mellitus.

CONSENT

It is not applicable.

ETHICAL APPROVAL

All authors hereby declare that "Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985) were followed.

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COMPETING INTERESTS

The authors hereby declare that there is no competing interest.

REFERENCES


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