



Full Length Research Paper

Anti-diabetic effects of the methanolic extract of the rind of *Citrullus lanatus* (watermelon) in alloxan induced diabetes in male albino wistar rats

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Abstract

The aim of the present study is to determine the anti-diabetic effects of the methanolic extract of the rind of *Citrullus lanatus* (water melon) in alloxan induced diabetes in male albino wistar rats. Thirty five rats weighing between 180g and 250g were randomly assigned to seven groups: 1 to 7. Diabetes was induced in all the rats except Group 1 by intraperitoneal injection of 150mg/kg bw of alloxan. Group 1 rats served as positive control and received 2ml/kg bw of extract vehicle; Group 2 rats served as negative controls: the untreated diabetic group; Groups 3, 4 and 5 rats received 100mg/kg bw, 200mg/kg bw and 500mg/kg bw of the methanolic extract of the rind of *Citrullus lanatus* respectively; while Group 6 received 600µg/kg bw of oral glibenclamide, and Group 7 received (10iu/kg) of subcutaneous insulin. The drugs and extracts were administered orally via oral cannula for 30days. After a 24 hour fast, blood samples were collected from anaesthetized rats using chloroform and via cardiac puncture for biochemical and hematological assays. Results obtained showed that administration of the extract caused significant decrease in the levels of triglycerides, low density lipoprotein-cholesterol, very low density lipoprotein-cholesterol; with increases in high density lipoprotein-cholesterol in Groups 4 and 5 only compared to Group 2 rats ($p < 0.05$). Treatment with the extract caused significant lowering of the levels of urea and creatinine in Groups 3, 4 and 5 rats compared with Group 2 rats ($p < 0.05$). There was significant decrease in the levels of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and glycosylated hemoglobin in rats of Groups 3, 4 and 5 compared to Group 2 rats ($p < 0.05$). The results obtained from the extract groups were fairly similar to that obtained for rats in Groups 6 and 7 treated with standard anti-diabetic agents. The results suggest that the methanolic extract of the rind of *Citrullus lanatus* could possibly normalize some biochemical and hematological abnormalities associated with the pathophysiology of diabetes mellitus in a dose dependent manner.

Keywords: *Citrullus lanatus*, anti-diabetic, glycosylated hemoglobin, biochemical parameters, rats.

INTRODUCTION

Diabetes mellitus is a complex and multifarious group of disorders characterized by hyperglycemia, alterations in lipid and protein metabolism due to an absolute or relative lack of insulin (Noor *et al.*, 2008). It is now recognized as one of the leading causes of death in developing countries, where the high prevalence of the

disease can be attributed to improved nutritional status coupled with a gross lack of modern facilities for early diagnosis of the disease (Ogbonnia *et al.*, 2010).

In orthodox medicine, there is still no satisfactory effective therapy available for diabetes, therefore, it has become therefore necessary to search for an economic

and effective treatment, especially for use in developing and under developed countries. Many indigenous medicinal plants have been found to be useful in the management of diabetes (Elujoba *et al.*, 2005). Plant medicine (phytomedicine) has been used in health care delivery in many parts of Africa and the rest of the world (Elujoba *et al.*, 2005). Effective health cannot be achieved in Africa, unless orthodox medicine is complemented with traditional medicine (Elujoba *et al.*, 2005). At least 80% of Africans depend on plant medicine for their health care (Sofowora, 1993). Fruits and vegetables have been recognized as natural sources of various bioactive compounds (Pennington and Fisher, 2010) which could be attributed to their phytochemical constituents such as flavonoids, anthocyanin, ascorbic acid, tocopherol, phenolic compounds, dietary fiber, and carotenoids present in fruits and vegetables (Gonzalez-Aguilar *et al.*, 2008). One of such medicinal plant is *Citrullus lanatus*. The fruit is a berry with a thick smooth exterior rind [exocarp] and a sweet, edible, juicy and fleshy center [mesocarp and endocarp]. The rind is usually discarded though it may be applied to feeds or used as fertilizer; but it is also edible and may be used as a vegetable (Pons, 2014). The rinds can also be fermented, blended and consumed as juice. The rind can be stir fried, stewed or more often pickled. Pickled *Citrullus lanatus* rind is also commonly consumed in the southern United States (Mandel *et al.*, 2005). The inner portions of the rind which is usually light green or white contains many hidden nutrients and is also edible; however, most times it is avoided due to its unappealing flavor. It contains mainly citrulline which is a known stimulator of nitric oxide (Rimando and Perkins-Veazie, 2005). The rind has been shown to contain alkaloids, saponin, cardiac glycosides, flavonoids, phenol, moisture, lipid, protein, fiber and carbohydrates (Erukainure *et al.*, 2010). In a recent report from our center, we have described the ameliorative effects of the rind of *Citrullus lanatus* on lead acetate induced toxicity on semen parameters and reproductive hormones of male albino wistar rats (Kolawole *et al.*, 2014).

The aim of the present study is to determine the possible anti-diabetic effects of the methanolic extracts of the rind of *Citrullus lanatus* (watermelon) in alloxan induced diabetes in male albino wistar rats.

MATERIALS AND METHODS

Plant material and preparation of extracts

Fresh plant and fruits of watermelon were obtained from a local market in Rivers State, Nigeria. The plant and fruits were authenticated by Dr Chimiezie of the Department of Plant Science and Biotechnology, University of Port Harcourt, Nigeria. The rinds were peeled off from the whole fruit washed thoroughly, sun-

dried and milled into a fine powder. The method of extraction employed is percolation (Adesanya *et al.*, 2011). 24g of the powdered sample was soaked in a beaker containing 100ml of 98% methanol for a period of 48 hours and then filtered with a What man No. 1 filter paper size. The volume of filtrate obtained was 150ml before concentration; the filtrate was subsequently concentrated using a rotary evaporator. The weight of residue obtained was 8.5g.

Determination of median lethal dose (LD₅₀)

Acute toxicity study (LD₅₀) was determined using the method described by Lorke, 1989. The (LD₅₀) of the extract was found to be greater than 2000mg/kg body weight.

Experimental design

Thirty five male albino wistar rats were used for this study. The rats were aged 8 to 10 weeks and weighed between 170 and 200g. They were divided into seven Groups: 1 to 7 of 5 rats each. Rats in each group were numbered 1 to 5 and placed in separate cages in the Animal House of Madonna University, Nigeria under natural day and night cycles. The rats had free access to normal rat chow and tap water *ad libitum*. They were allowed two weeks of acclimatization to the environment before experimentation.

Induction of diabetes

After an overnight fast, diabetes was experimentally induced in all the rats except Group 1 rats by intra peritoneal injection of alloxan monohydrate (Sigma-Aldrich, United Kingdom), dissolved in normal saline at a dose of 150 mg/kg bw (Mbaka *et al.*, 2009). After 72 hrs of induction, the blood sugar level was monitored with a glucometer (Accu-Chek ,Roche Diagnostics Germany) and the rats with a blood sugar level >200 mg/dl were classified as diabetic and used for the study (Ogbonnia *et al.*, 2010). The rats were subsequently treated as follows:

Group 1: Positive Control. Rats in this group were given 2ml/kg bw of extract vehicle.

Group 2: Negative Control. These were untreated diabetic rats.

Group 3: Low Dose Extract Group. Rats in this group were treated with 100mg/kg bw of the extract of the rind of *Citrullus lanatus*.

Group 4: Medium Dose Extract Group. Rats in this group were treated with 200mg/kg bw of the extract of the rind of *Citrullus lanatus*.

Group 5: High Dose Extract Group. Rats in this group were treated with 500mg/kg bw of the extract of the rind of *Citrullus lanatus*.

Table 1: Effect of the extract of the rind of *Citrullus lanatus* on blood glucose concentration

Groups	Blood glucose concentration at end of first week of treatment (mg/dl)	Blood glucose concentration at end of second week of treatment (mg/dl)	Blood glucose concentration at end of third week of treatment (mg/dl)	Blood glucose concentration at end of fourth week of treatment (mg/dl)
Group 1 : Positive Control	63.00 ± 3.67	51.00 ± 3.28	50.60 ± 3.43	54.00 ± 2.45
Group 2: Negative Control	439.20 ± 29.09	500.60 ± 31.79	464.00 ± 26.38	470.00 ± 25.49
Group 3: Low dose extract	391.00 ± 60.00	282.80 ± 22.87*	360.00 ± 47.85	306.00 ± 25.21*
Group 4: Medium dose extract.	303.00 ± 47.91*	312.00 ± 38.91*	254.00 ± 32.64*	204.00 ± 23.79*
Group 5: High Dose Extract.	305.00 ± 47.20*	275.00 ± 38.34*	228.00 ± 15.90*	122.00 ± 18.86*
Group 6:Glibenclamide.	325.40 ± 36.03*	288.80 ± 25.19*	219.40 ± 46.92*	191.40 ± 37.77*
Group 7: Insulin.	353.20 ± 30.49*	248.00 ± 32.46*	202.00 ± 20.34*	134.00 ± 13.64*

All values=Mean±SEM; * significantly different from values of Group 2 at (p<0.05)

Group 6: Standard Drug Group I. Rats in this group were treated with 600µg/kg bw oral Glibenclamide (Ogbonnia *et al.*, 2010).

Group 7: Standard Drug Group II. Rats in this group were treated with 10 iu/kgbw subcutaneous insulin (Jafari *et al.*, 2004).

The extract of the rind of *Citrullus lanatus*, drugs and extract vehicles were administered daily using an oral cannula. All the rats were treated for 30 days.

Determination of liver enzymes, lipid profile, urea, creatinine and glycosylated hemoglobin levels

After a 24 hour fast, the rats were placed under chloroform anesthesia with chloroform and blood carefully obtained via direct cardiac puncture. The collected blood was transferred into both heparinized and plain tubes. Whole blood, plasma and serum was appropriately obtained for the determination of the various parameters: urea, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), very low density lipoprotein cholesterol (VLDL-C) and triglycerides (TG) concentration using commercial kits obtained from Randox Laboratories, UK. Urea, creatinine and glycosylated hemoglobin were determined by the use of commercial kits also.

Statistical analysis

Data are presented as mean±SEM. Statistical

significance was determined using the one way analysis of variance. Differences were considered statistically significant at a p value less than 0.05.

RESULTS

Effect of the extract of *Citrullus lanatus* on blood glucose concentration

Table 1 shows the effect of the extract of the rind of *Citrullus lanatus* on blood glucose levels from the first to the fourth week of treatment. At the different doses administered, the extract was found to significantly reduce the blood glucose level of rats in Groups 3, 4, and 5 (p< 0.05) progressively from the end of first week of treatment all through to the fourth week. These effects were similar to that of both glibenclamide and insulin respectively as seen in Groups 6 and 7 rats. No significant changes were seen in blood glucose concentration amongst rats in Group 1 and 2 all through the study.

Effects of the extract of *Citrullus lanatus* on assay of liver enzymes

The effects of the extract of the rind of *Citrullus lanatus* on the assayed liver enzymes: alkaline phosphatase (ALP), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) is as shown in Table 2. Administration of the extract caused a significant reduction in the levels of alkaline phosphatase (ALP) in Groups 3, 4 and 5 compared to Group 2 rats. Although the

Table 2: Effect of the extract of the rind of *Citrullus lanatus* on some liver enzymes

Groups	Alkaline phosphatase (ALP) (IU/L)	Alanine aminotransferase (ALT) (IU/L)	Aspartate transaminase (AST) (IU/L)
Group 1 : Positive Control	50.2±3.27	18.8±1.56	37.4±0.97
Group 2: Negative Control	65.4±2.03	20.0±3.7	43.4±3.36
Group 3: Low dose extract	53.4±3.37*	20.6±1.16	43.8±1.62
Group 4: Medium dose extract.	57.4±1.29*	18±0.63	38.8±2.13*
Group 5: High Dose Extract.	53±0.84*	19.6±1.03	36±1.84*
Group 6:Glibenclamide.	49.2±3.5*	18.2±2.0	31.4±2.56*
Group 7: Insulin.	51.8±2.4*	14.6±1.6*	42.4±2.37

All values=Mean±SEM; * significantly different from values of Group 2 at $p<0.05$

Table 3: Effect of the extract of the rind of *Citrullus lanatus* on the serum lipid profile

Groups	Total cholesterol (mmol/L)	Triglyceride (mmol/L)	High density Lipoprotein (mmol/L)	Low Density Lipoprotein (mmol/L)	Very Low Density Lipoprotein (mmol/L)
Group 1 : Positive Control	3.34 ± 0.10	1.50 ±0.06	1.24 ±0.04	1.46 ±0.04	0.68 ±0.01
Group 2: Negative Control	3.58 ± 0.02	1.76 ±0.02	1.14 ±0.04	1.64 ±0.06	0.80 ±0.04
Group 3: Low dose extract	3.36 ± 0.09	1.56 ±0.02	1.26 ±0.02	1.52 ±0.02	0.71 ±0.02
Group 4: Medium dose extract.	3.26 ±0.04*	1.38 ±0.02*	1.26 ±0.02*	1.26 ±0.02*	0.63 ±0.01*
Group 5: High Dose Extract.	3.22 ±0.05*	1.54 ±0.02*	1.30 ±0.00*	1.22 ±0.03*	0.70 ±0.15*
Group 6:Glibenclamide.	3.42 ±0.07*	1.58 ±0.04*	1.22 ±0.04*	1.48 ±0.04*	0.72 ±0.11*
Group 7: Insulin.	2.94 ±0.06*	1.16 ±0.02*	1.26 ±0.02*	1.44 ±0.02*	0.53 ±0.01*

All values=Mean±SEM; * significantly different from values of Group 2 at $p<0.05$

extract had no significant effects on the levels of alanine aminotransferase (ALT) in all the treated rat groups: Groups 3, 4 and 5 as compared to Group 2 rats; a significant reduction in alanine aminotransferase (ALT) levels was observed in Group 7 rats as compared to Group 2 rats. A significant ($p<0.05$) reduction in levels of aspartate aminotransferase (AST) was observed in Groups 4, 5 and 6 rats as compared to Group 2 rats. No significant changes were observed in the other rats groups for the values of aspartate aminotransferase (AST).

Effect of the extract of *Citrullus lanatus* on the serum lipid profile

The effect of the extract of the rind of *Citrullus lanatus* on

lipid profile is shown in Table 3. At different doses administration of the extract, caused a significant reduction in the values of total cholesterol, triglyceride and low density lipoprotein cholesterol in Groups: 4 and 5 compared to Group 2 rats ($p<0.05$); an effect similar to that of both glibenclamide and insulin and seen in both Groups 6 and 7 rats respectively. However, the extract caused a significant elevation in the values of high density lipoprotein cholesterol in Groups 3, 4 and 5 rats; an effect similar to that of both glibenclamide and insulin and seen in Groups 6 and 7 rats respectively. The effect of the extract on very low density lipoprotein cholesterol was a reduction in Groups 4 and 5 rats, an effect consistent with the effects of insulin in Group 7 rats. However, glibenclamide caused an elevation and insulin a reduction in very low density lipoprotein cholesterol concentration as seen in Group 6 and 7 rats respectively.

Table 4: Effect of the extract of the rind of *Citrullus lanatus* on urea, creatinine and glycosylated hemoglobin concentration

Groups	Urea (mmol/L)	Creatinine (mmol/L)	Glycosylated hemoglobin (mg/g Hb)
Group 1 : Positive Control	6.50±0.30	1.01 ± 0.04	5.18 ± 0.09
Group 2: Negative Control	14.40±1.70	1.44 ± 0.04	10.92 ± 0.08
Group 3: Low dose extract	11.00±0.20*	1.22 ± 0.04*	8.74 ± 0.07*
Group 4: Medium dose extract.	9.20±0.82*	1.09 ± 0.10*	9.86 ± 0.08
Group 5: High Dose Extract.	10.40±1.11*	1.13 ± 0.11*	8.86 ± 0.13*
Group 6:Glibenclamide.	10.10±0.76*	1.14 ± 0.05*	7.96 ± 0.07*
Group 7: Insulin.	10.00±0.66*	1.17 ± 0.06*	4.70 ± 0.06*

All values=Mean±SEM; * significantly different from values of Group 2 at p<0.05

Effect of the extract of the rind of *Citrullus lanatus* on urea, creatinine and glycosylated hemoglobin concentration

The effect of the extract on urea, creatinine and glycosylated hemoglobin concentration is as shown in Table 4. The extract was found to cause a significant reduction in the concentration of all biochemical and hematological parameters in all extract treated groups: Groups 3, 4 and 5 as compared to Group 2 rats (p<0.05). These findings are similar to the effect of both glibenclamide and insulin seen in Groups 6 and 7 rats respectively for these parameters.

DISCUSSION

The present study determined the effects of the methanolic extract of the rind of *Citrullus lanatus* (watermelon) on blood glucose concentration, liver enzymes, serum lipid profile and urea, creatinine and glycosylated hemoglobin concentration following alloxan induced diabetes in male albino wistar rats. This is with the view to determine the anti-diabetic potentials of *Citrullus lanatus* rind.

A significant reduction in blood glucose concentration following treatment with the extract was observed in diabetic rats compared with both non extract treated diabetic rats and rats treated with standard anti-diabetic agents. The presence of plant secondary metabolites like flavonoids and polyphenols, reported to be present in *Citrullus lanatus* extract, and known for their antioxidant and possible hypoglycemic activities (Mowla *et al.*, 2009) may explain these effects of the extract of *Citrullus lanatus* seen in the present study. Furthermore, watermelon is a rich source of a precursor (i.e., citrulline) for arginine synthesis in humans. Dietary arginine supplementation has been shown to decrease plasma

glucose concentration in diabetic rats (Kohli *et al.*, 2004) likely due to nitric oxide mediated increases in blood flow, enhanced glucose uptake by skeletal muscle, and improvements in insulin sensitivity in tissues via increasing availability of tetrahydrobiopterin (Shi *et al.*, 2004). The reduction in the blood glucose caused by *Citrullus lanatus* extract was fairly similar to the standard anti-diabetic agents used. However, predictably the effect of insulin was more pronounced compared with glibenclamide and *Citrullus lanatus* extract.

Glycosylated hemoglobin is known to be increased in uncontrolled diabetes and the increase is directly proportional to the fasting blood glucose levels. Measurement of glycosylated hemoglobin concentration remains the standard biochemical marker for the long term assessment of glycemic control in patients with diabetes (Fonseca, 2003). In diabetes, the excess glucose present in the blood reacts with hemoglobin to form glycosylated hemoglobin (Kumar *et al.*, 2005). Administration of *Citrullus lanatus* extract to alloxan induced diabetic rats possibly reduced the formation of glycosylated hemoglobin by virtue of its hypoglycemic activities. Since the level of glycosylated hemoglobin has been shown to be a good index of blood glucose concentration (Haller *et al.*, 2004); the decreased level of glycosylated hemoglobin in *Citrullus lanatus* treated diabetic rats seen in the present study confirms fairly its hypoglycemic activities.

The abnormally high concentration of serum lipids in diabetics is mainly due to increase in the mobilization of free fatty acids from the peripheral fat depots (Bopanna *et al.*, 1997). Increased levels of triglycerides, low density lipoprotein-cholesterol (LDL-C), very low density lipoprotein-cholesterol (VLDL-C), cholesterol and decreased high density lipoprotein cholesterol (HDL-C) have been associated with diabetic mellitus (Nikkila, 1984). In the present study, the rise in blood glucose concentration was associated with an increase in

cholesterol, triglycerides, LDL-C, VLDL-C and reduction in HDL-C in the diabetic rats. The extract of extract of the rind of *Citrullus lanatus* was found to significantly reduce cholesterol, triglyceride and LDL-C concentration and significantly increase the HDL-C concentration in the diabetic treated rats. This effect of extract of the rind of *Citrullus lanatus* fairly parallels the effects observed for insulin in the present study. The mechanism of the action of the extract of the rind of *Citrullus lanatus* on fat metabolism is uncertain. However, these effects could be attributed to its constituent phenolic compounds, reported to possess a number of biological properties such as anti-apoptosis, antiaging, anticarcinogen, anti-inflammation, antiatherosclerosis, cardiovascular protection and improvement of endothelial function, as well as inhibition of angiogenesis and cell proliferation activities (Han *et al.*, 2007). Several studies have described the antioxidant properties of medicinal plants which are rich in phenolic compounds (Krings and Berger, 2001). In addition, nitric oxide synthesized from arginine plays an important role in regulating the oxidation of fatty acids and glucose (Jobgen *et al.*, 2006); and watermelon is a bio available source of a precursor (i.e. citrulline) for arginine synthesis in humans.

The increased concentration observed in the levels of the liver enzymes in diabetic rats is consistent with the report of Gonzalez *et al.*, 1992 and Nwanjo, 2007. Diabetes mellitus is associated with high levels of circulatory cholesterol and other lipids (Huupponen *et al.*, 1984) and this accounts for the atherosclerosis, and severe coronary heart disease which leads to increase levels of transaminases, marker enzymes important in heart and liver damage (Vaishwanar and Kowale, 1976). The extract of the rind of *Citrullus lanatus* was found to reduce the levels of ALP, however, the effects of the extract on other liver enzymes investigated did not follow a clear pattern of effects compared to the effects of both insulin and glibenclamide in the present study.

The increase in creatinine and urea levels in the diabetic untreated groups compared to the normal value suggested that renal dysfunction associated with diabetic condition may have been initiated by the diabetic agent (Tietz, 1982). In this study the elevated serum levels of urea and creatinine in the diabetic rats were reduced by the extract

In conclusion, the present study reports that the administration of the methanolic extract of the rind of *Citrullus lanatus* in alloxan induced diabetic male albino wistar rats caused a reduction in blood glucose and glycosylated hemoglobin concentration, reduction in the concentration of cholesterol, triglyceride, low density lipoprotein cholesterol and increased high density lipoprotein cholesterol concentration with associated reduction in the concentration of both urea and creatinine concentrations in male albino wistar rats. The results suggest that the methanolic extract of the rind of *Citrullus lanatus* could possibly normalize some biochemical and

hematological abnormalities associated with the pathophysiology of diabetes mellitus in a dose dependent manner.

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