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Haematological Values, Biochemical Parameters And Antioxidant Enzymes Concentration In Alloxan-Induced Diabetic Rats Treated With *Chrysophyllum albidum Leaf Extracts*

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Abstract
In this study, the anti-diabetic effects of three solvents (petroleum ether, ethanol and chloroform) extracts of *Chrysophyllum albidum* leaves were evaluated on alloxan induced diabetic rats. Thirty wistar rats of both sexes were assigned to 6 groups (A-F) of 5 rats each. Group A (normal rats) and groups B-F made diabetic via single dose administration of alloxan monohydrate (160 mg/kg). Group B (diabetic control) Groups C, D and E were treated with 500 mg/kg body weight of petroleum ether, ethanol and chloroform extract of *Chrysopyllum albidum* respectively. Group F was administered glibenclamide (3 mg/kg). All treatments were oral and lasted 14 days. Elevated blood glucose concentrations in the diabetic rats were significantly lowered following treatment with no significant difference observed in the activities of the different extracts ($P>0.05$). Treatment with the extracts caused further fall in the values of the already decreased red blood cell parameters (RBC, PCV and Hb) with the chloroform extract causing the highest fall and petroleum ether extract the least. WBC count was only significantly ($P<0.05$) higher in groups treated with petroleum ether and chloroform extracts. Elevations in AST, ALP, bilirubin, urea, creatinine, sodium, chloride, potassium, cholesterol and triglycerides concentrations observed in the diabetic rats were also significantly($P<0.05$) lowered following treatment with the extracts ($P<0.05$). All extracts also significantly improved the antioxidant strength of the diabetic treated rats. *Chrysophyllum albidum* may therefore be of value in the management of diabetes mellitus and its associated haematological and biochemical anormalies but should be used along with a haematinic agent.

Keywords: *Chrysophyllum albidum*, diabetes mellitus, rats, serum

Introduction

Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycemia due to anomalies in insulin secretion or action and causing impairments in the metabolism of glucose, lipid and protein with glycosuria, polydipsia and polyuria as most common clinical manifestations (Mayfiled, 1998 and Kim *et al*., 2006). Currently, it is estimated that about 2.8 % of global population is suffering from diabetes mellitus and projected that this prevalence rate may hit 4.4 % by the year 2030 with women and developing countries being more susceptible (Sarah *et al*., 2004 and Gill *et al*., 2009). The classification of diabetes mellitus into typed 1 and type 2 and their aetiologies are well documented (Akomas *et al*., 2014; Ijioma, 2015; Hussian and Theise, 2004). The failure of various organs including eyes, kidneys, nerves, heart and blood vessels in diabetics are thought to be associated with the oxidative stress and activities of free radicals generated from glucose auto-oxidation and protein glycosylation (Robertson, 2004 and Zozulinska *et al*., 1998). Currently available management strategies for diabetes mellitus have either been ineffective or too expensive for a larger number of affected individuals. The use of oral anti diabetic drugs is also limited by numerous adverse side effects which may include hematological, cutaneous and gastro intestinal reactions, hypoglycemic coma and impairment of liver and kidney functions. This may be the reason for the current continued search for alternative anti-diabetic agents and renewed interest in medicinal plants (Ijioma, 2015). The modulatory effects of medicinal plants against oxidative diseases like diabetes mellitus have been attributed to their antioxidant and free radical scavenging effects (Pourmorad *et al*., 2006). A number of these plants contain high amounts of naturally occurring antioxidants such as ascorbic acid, carotenoids, flavonoids and phenolic compounds (Duh *et al.,* 1999). These substances inhibit lipid peroxidation and scavenge free radicals and reactive oxygen species

(Sundararajan *et al*., 2006); hence the evaluation of their host plants for possible anti-oxidative disease effects. At the moment, only few medicinal plants used in traditional medicine for the treatment of diabetes have received scientific validation (Fattanel, 2012). *Chrysophyllum albidum* (African star apple) is a rain forest fruit tree belonging to family sapotaceae. The plant is called Udara by the Ibos, Efik and Ibibio, agbalumo by the Yorubas and agwalumo by the Hausas, all of Nigeria (Amusa *et al.,* 2013, Florence and Adiaha, 2005). Extracts from the leaves have been used in the treatment of malaria, high blood pressure, anaemia, stomach ache and diarrhea (Adisa, 2000 and Idowu *et al.,* 2006). The anti-platelet and hypoglycemic effects of the leaf extract have been reported (Adebayo *et al.,* 2010). Extracts from the plant's leaves has also been used in ethno-medicine to manage sprains, bruises, wounds, sterility, asthma and intestinal worms (Okunomo and Egho, 2010). The aim of this current study was to evaluate on comparative basis, the effect of petroleum ether, ethanol and chloroform leaf extracts of *Chrysophyllum albidum* on the haematology, biochemical and organ histology of all alloxan induced diabetic rats.

Materials and Methods

Sample collection

Fresh samples of *Chrysophyllum albidum* leaves were collected from Umuarigha Oboro village, Ikwuano LGA, Abia State. The plants were identified and authenticated by Dr. M.A. Jimoh, a botanist in the Department of Plant Science and Biotechnology, Michael Okpara University of Agriculture, Umudike, Abia State. A sample of the dried plant was assigned a voucher number MOUAU/ZEB/18/004 and was preserved in a herbarium of the Department of Zoology and Environmental Biology, in the same University.

Extract preparation and partitioning

The leaves were properly cleaned and air dried at room temperature on a laboratory bench in accordance with the technique described by Adebayo *et al*. (2010) and pulverized to powdered form. About 500g of the pulverized sample was macerated in 2.5 liter of absolute ethanol within 48 hours and was thoroughly shaken intermittently and filtered first with muslin cloth and with a whatman filter paper into a beaker. The filtrate was evaporated to dryness on a water bath at 55^0C to yield a crude semisolid mass, which weighed 41.3 g and represented a yield of 8.26%. About 20 g of the crude extract was weighed and partitioned using 3 different solvents (chloroform, petroleum ether and methanol) in accordance with the method used by Egua *et al*. (2013) to obtain extracts of the three solvents and the dry concentrated extract was stored in a refrigerator at 4^0C until required.

Experimental Animals

Thirty Wistar albino rat of both sexes, age 12 weeks, weighing 20-50g were procured from Ogive Integrated Farms, Abayi Osisioma L.G.A. Abia State. They had unrestricted access to standard feed and water. The animals were maintained under standard environmental conditions of temperature, relative humidity and dark and light cycle, in accordance with the guidelines of National Institute of Health Guide for the Care and Use of Laboratory Animals and animal ethics committee of the Department of Zoology and Environmental Biology. Body weight, food consumption and water intake were monitored throughout the period of administration.

Induction of diabetes

The mice were fasted overnight and then injected, intra-peritoneally, with a single dose of 0.5ml of 160 mg/kg body weight (b/w) of Alloxan monohydrate (a product of Mekphar Chemical Pharmceutical Joint-Stock Company, Chiminh City, Vietnam), dissolved in freshly prepared normal saline, to induce T2D, The control animals (nondiabetic) were injected with 0.5ml of the vehicle (normal saline). Stable hyperglycemia was confirmed on the ninth day using glucometer (ACCU-Check, Roche Diagnostics). Rats with fasting blood glucose greater than 180 mg/dl were considered diabetic and used for this study.

Animal grouping and treatment

After 2 weeks of acclimatization, animals were randomly assigned to six groups (n=6/group) of 5 rats each. Group A (normal control) and B (diabetic control):received distilled water (vehicle) daily; Group C: (diabetic + 500mg/kg *C. albidum* extract): received 500mg/kg body weight of the petroleum ether *C. albidum* extract ;Group D: (diabetic + 500mg/kg *C. albidum* extract): received 500mg/kg body weight of methanol *C. albidum* extract; Group E: (diabetic + 500mg/kg *C. albidum* extract): received 500mg/kg body weight of chloroform *C. albidum* extract; while Group F: (diabetic + glibenclamide): received 3.0 mg/kg body weight of standard drug (glibenclamide). All treatments were through oral administration and lasted for 14 days.

Blood collection

At the end of experiment, four (4) mice, from each group, were sacrificed and blood samples for hematological and biochemical assays were collected from each mouse through the orbital sinus with heparinized capillary tubes into EDTA treated bottles and plain bottles respectively, thereafter, mice were sacrificed. Hematological parameters were determined using standard procedures (Mukherjee *et al*., 2007). Haematological parameters include red blood cell (RBC) count, haemoglobin (Hb) concentration, Packed cell volume (PCV), white blood count (WBC), platelet (PLT) count, reticulocytes count and WBC differential count were determined for each blood sample collected in accordance with the standard techniques described by Baker *et al*. (1998) and Cheesbrough (2000).

Biochemical analysis

Alanine aminotransferase (ALT), aspartate aminotransfarase (AST), alkaline phosphatase (ALP), total biliribin, total protein, urea, creatinine, albumin, serum potassium, and serum sodium.

Statistical analysis

Data generated from the study were analyzed using statistical package SPSS version 22.0 (2020) Group comparisons were done using the analysis of variance (ANOVA). Significant differences between control and experimental were assessed by least significant difference (LSD). All data were expressed as mean ± SEM. P-values less than 0.05 were considered to be significant.

Results and Discussion

Results

Effect of administration of 3 solvent extract of Chrysophyllum albican on body weight changes in alloxan-induced diabetic mice

Body weight gain was significantly lower in the diabetic control group when compared with the normal control group ($P<0.05$). However, treatment with extracts also significantly increased body weight gains in the test group, ameliorating the effect of induction of diabetes on body weight. Comparative evaluation of the effect of the extracts on body weight showed that petroleum ether extract improved body weight more and was followed by chloroform extract while ethanol extract performed least. The three extracts however performed better than glibenclamide, the standard drug used in terms of body weight improvement (Table 1).

Effect of administration of 3 solvent extract of Chrysophyllum albican on blood glucose concentrations in alloxan-induced diabetic mice

Treatment of the diabetic rats with the extracts significantly lowered their elevated blood glucose concentrations and successfully returned the values to normal by end of the treatment period. No significant difference was observed between the activities of the different extracts ($P>0.05$).

Effect of the Chrysophyllum albican leaf extract on hematological parameters in alloxan-induced diabetic rats

The induction of diabetes mellitus caused significant decrease in red blood cell parameters (RBC, PCV and Hb) when compared with the normal rats ($P<0.05$). Treatment with the extracts caused further decrease in the values of these parameters with the chloroform extract causing the highest fall and petroleum ether extract the least. The group treated with glibenclamide however significantly improved red blood cell parameters when compared with the diabetic untreated group ($P<0.05$) and did not significantly differ from the values in the normal control group ($P>0.05$). WBC count was only significantly higher in groups treated with petroleum ether and chloroform extracts. Elevated platelets counts following the induction of diabetes was also significantly lowered following treatment with the extracts and the standard drug (Table 3).

Effect of the Chrysophyllum albidum leaf extract on liver function parameters in alloxan-induced of diabetic rats

The slight elevations in AST and ALP values observed in the diabetic rats following induction of diabetes mellitus was only significantly lowered in group treated with the standard drug (glibenclamide), but elevations in ALT values were significantly lowered following treatment with ethanol extract, chloroform extract and glibenclamide ($P<0.05$). All extracts also significantly lowered elevated bilirubin and improved the low total protein values in the diabetic rats (Table 4).

Effect of the Chrysophyllum albidum leaf extract on renal function parameters in alloxan-induced of diabetic rats

The elevated urea and creatinine concentrations in the diabetic rats were significantly lowered following chloroform extract treatment ($P<0.05$). Elevated sodium concentrations in the diabetic rats were also significantly lowered in all test groups following treatment with the extracts ($P<0.05$). Raised serum potassium concentration was also lowered after treatment with petroleum ether and chloroform extracts. Chloride concentration was only lowered in diabetic rats treated with ethanol extract and glibenclamide. The concentrations of bicarbonate did not significantly change in all test groups when compared with the diabetic untreated rats ($P<0.05$). These results are presented in Table 5.

Discussion

Higher extract yield (12.2%) obtained with ethanol after extractions with the three different solvents suggest that ethanol may have collected more of the bioactive compounds *Chrysophyllum albidum* than the other solvents (petroleum ether and chloroform) used which gave a yield of 9.70% each. The fact that ethanol is a polar solvent further suggests that the phytocomponents in *Chrysophyllum albidum* are more soluble in polar solvent than non-polar ones. This result agrees with Do *et al.,* (2014), who reported that extraction solvents usually affect the quality, quantity and pharmacology of plant extracts generated during extraction and that a polar solvent like ethanol is likely to give higher extract yield than non-polar ones. Improvements observed in the test groups following treatment also suggest that the various extracts used may contain active components with anti-diabetic properties. The higher weight gains in groups treated with petroleum ether and chloroform extracts may be due to the presence of more lipids in these extracts which may have augmented that which is present in the animal's body leading to increase in body weight. This probably indicates that the extract might not exert its hyperglycaemic effect through weight reduction. The presence of tannins in the extracts may have also contributed to the weight gains observed in the extract treated groups (Adewoye *et al*., 2012). The fall in blood glucose levels in the diabetic rats gives credence to the hypoglycaemic effect of *Chrysophyllum albidum* leaf extract and may have been achieved via one or a combination of mechanisms including reactivation of destroyed beta cells with subsequent increase in insulin production and secretion, decreased glucose absorption in the gastrointestinal tract and increased mobilization of glucose molecules into cells to be metabolized

(Ijioma *et al.,* 2014). These results obtained for *Chrysophyllum albidum* leaf extracts agree with an earlier report of Olorunnisola *et al*. (2008) and Adebayo *et al.,* 2010, on the anti-hyperglycemic and hypoglycaemic effects of ethanol extract of *C. albidum*. The Assessment of haematotogical parameters can be used to explain blood related functions of a plant extract (Yakubu *et al.,* 2007). Hence, analysis of blood parameters is relevant in risk evaluation as changes in the haematological system have higher predictive value for toxicity and state of health (Olson *et al*., 2000). The fall in red blood cells number, haemoglobin concentration and packed cell volume following induction of diabetes gives credence to the report that anaemia is one of the clinical manifestations of diabetes mellitus and is attributable to the destruction of RBC and reduced rate of its production in the bone marrow due to the oxidative effect of alloxan and increased in lipid peroxidation of the erythrocyte cell membrane (Akomas *et al*., 2014) all as a result of alloxan treatment. The further fall in the level of these blood parameters observed in the diabetic rats treated with the extracts suggest that the extracts may have some toxicity effects on blood, not minding its blood glucose lowering activity. Adewoye *et al*. (2012) had reported that methanol extract of *C. albidum* bark caused haemorrhagic anaemia in experimental rats. This RBC lowering effect of the extract may also be due to the antibiotic effects of the extract. Leaf extract of *Chrysophyllum albidum* is known to be a potent agent against malaria parasites (Adisa, 2000; Idowu *et al.,* 2006; Florence and Adiaha, 2015; Adewoye *et al.,* 2011). Agents with such effects have greatly been implicated in post treatment anaemia due to their destructive effects on red blood cells (Girdwood, 1976). The mild rise in WBC values, particularly in the groups treated with petroleum ether and chloroform extracts may be a normal reaction of the animals to foreign substances. It is established that leuococytosis may be a physiological response to a stimulated immune system aimed at protecting the body against infections caused by chemical and secondary infections (Celik and Suzek, 2008). There was a significant increase in the platelet count of diabetic control compared to the normal control. The increased platelet count in the diabetic rats suggests that thrombocytopaenia may be another clinical manifestation in diabetes mellitus, which may be why diabetics are usually prone to blood clotting disorders such as thrombosis (Ijioma, 2015). In diabetics, declined insulin release may cause loss of anti-platelets aggregation activity and defective endothelial production leading to bleeding disorders. Accumulation of products of advanced glycosylation in diabetics coupled with reduced membrane fluidity of platelets may also contribute to platelet hyper function as observed in this study. The lowering effects of the extracts on these platelets values suggest that the extracts may have some level of anti-platelet activity and may therefore be of further value in the management of blood clotting disorders and their associated cardioavascular challenges in diabetes mellitus rise in serum Aspartate aminotransferase (AST) and Alanine aminotrasferase (ALT) values beyond the upper limits of the normal ranges are usually indicative of liver toxicity and/or damage, while increase in alkaline phosphatase (ALP) may suggest biliary tract obstruction. Results of this study have shown no obvious changes in the values of these parameters following induction of diabetes and treatment with the extracts and may be explained by the shortness of the period of study. Liver damage has indeed been associated with chronic diabetes mellitus (Mohammed *et al*., 2016). The rise in bilirubin concentrations in the diabetic rats may be due to increased RBC haemolysis in the diabetic animals even as reductions in the values of this parameter in the extract treated groups suggest possible modulation and membrane stabilizing activities on the part of the extracts. Abiodun *et al*. (2011) had reported the hepato-protective effects of leaf extracts of *C. albidum* against carbon tetrachloride (CCl_4) induced liver damage in wistar rats. The increase in urea, creatinine and sodium concentrations in the diabetic rats may indicate threat on the renal system due to the oxidative effect of alloxan and also the oxidative stress which usually accompany diabetes mellitus (Pari and Uma, 2000). On these, the chloroform extract of *C. albidum* offered significant ameliorative effect, indicating possible area of usefulness of the agent.

Conclusion

If the results obtained in the present study can be extrapolated to humans, then the three solvent extracts of *Chrysophyllum albidum* could be of value in the management of diabetes mellitus having shown significant levels of anti-hyperglycaemia, improvements of haematological activities and good modulatory effects on liver and renal functions in diabetic rats. However the use of a haematinic agent alongside treatment may be encouraged due to the adverse effects of the extract on red blood cells.

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Table 1: Effect of administration of 3 solvent extract of *chrysophyllum albican* leaves on body weight in alloxan-induced diabetic mice

Groups	Body weight (g) initial	Body weight (g) during treatment	Body weight (g)
A (Normal control)	27.95	32.65	35.55
B (Untreated Diabetic control**)**	29.15	31.05	33.80
Petroleum Ether extract			
C(500mg/kg**)**	28.40	28.70	33.80
Ethanolic extract			
D (500mg/kg**)**	28.25	28.55	28.45
Chloroform extract			
E (500mg/kg**)**	30.55	30.40	31.45
F (Glibenclamide**)**	27.45	26.80	26.60

Group A(Normal control) Group B (Untreated Diabetic control), Groups C, D and E were treated with 500 mg/kg body weight of petroleum ether, ethanol and chloroform extract of Chrysopyllum albidum respectively while Group F (Glibenclamide)

Table 2: Effect of administration of 3 solvent extract of *Chrysophyllum albican* leaves on blood glucose concentrations in alloxan-induced diabetic mice.

Groups	Blood glucose level Baseline (mg/dl)	Blood glucose level Initial (mg/dl)	Blood glucose level Final (mg/dl)
A (Normal control)	117.50	93.50	96.50
B (Untreated Diabetic control **)**	92.00	368	380.00
Petroleum Ether extract			
C(500mg/kg**)**	69.50	314	68.00
Ethanolic extract			
D (500mg/kg**)**	98.00	388	76.00
Chloroform extract			
E (500mg/kg**)**	61.00	334.00	69.00
F (Glibenclamide**)**	74.00 mg/dl	244.00 mg/dl	81.00 mg/dl

Group A(Normal control) Group B (Untreated Diabetic control), Groups C, D and E were treated with 500 mg/kg body weight of petroleum ether, ethanol and chloroform extract of Chrysopyllum albidum respectively while Group F (Glibenclamide)

Table 3: Effect of the *Chrysophyllum albidum* leaf extract on haematological values in alloxan-induced of diabetic rats

Groups	RBC ($X10^{12}$/L)	PCV (%)	Hb(g/dL)	WBC ($X10^{9}$/L)	Platelet ($X10^{9}$/L)
A (Normal control)	7.85 ± 0.03^{a}	43.50 ± 0.87^{cd}	15.60 ± 0.64^{bc}	11.05 ± 0.20^{c}	235.00 ± 8.66^{d}
B (Untreated Diabetic control **)**	6.80 ± 0.06^{b}	42.50 ± 0.29^{d}	14.25 ± 0.09^{c}	11.30 ± 0.35^{c}	570.00 ± 11.55^{c}
Pet Ether extract					
C(500mg/kg**)**	6.75 ± 0.03^{b}	41.50 ± 0.87^{b}	14.20 ± 0.35^{ab}	12.80 ± 0.35^{b}	470.00 ± 40.41^{c}
Ethanolic extract					
D (500mg/kg**)**	5.35 ± 0.03^{c}	40.50 ± 0.29^{b}	13.65 ± 0.49^{ab}	11.20 ± 0.35^{c}	465.00 ± 20.21^{b}
Chloroform extract					
E (500mg/kg**)**	4.20 ± 0.13^{d}	38.50 ± 0.13^{bc}	13.30 ± 0.13^{bc}	14.60 ± 0.13^{a}	430.00 ± 10.13^{c}
F (Glibenclamide**)**	7.60 ± 0.17^{a}	44.00 ± 0.58^{a}	14.90 ± 0.98^{a}	11.60 ± 0.23^{c}	545.00 ± 14.43^{a}

Values are expressed as abc Means in the same row with different superscript are significantly different $p \leq 0.05$

Table 4: Effect of the *Chrysophyllum albidum* leaf extract on liver function parameters in alloxan-induced of diabetic rats

Groups	AST (IU/L)	ALT (IU/L)	ALP (IU/L)	Bilirubin (mg/dl)	Protein (g/dl)
A (Normal control)	42.15 ± 3.95^{b}	30.25 ± 2.28^{c}	21.30 ± 1.73^{bc}	1.55 ± 0.03^{ab}	5.05 ± 0.09^{a}
B (Untreated Diabetic control **)**	48.30 ± 0.58^{a}	40.60 ± 0.64^{a}	25.00 ± 2.60^{ab}	1.70 ± 0.06^{a}	4.25 ± 0.03^{b}
Pet Ether extract					
C(500mg/kg**)**	44.00 ± 6.52^{a}	39.15 ± 2.40^{ab}	23.10 ± 1.79^{bc}	1.10 ± 0.06^{c}	4.00 ± 0.12^{b}
Ethanolic extract					
D (500mg/kg**)**	47.35 ± 5.40^{a}	30.10 ± 0.06^{c}	25.75 ± 0.49^{a}	1.30 ± 0.06^{bc}	5.10 ± 0.29^{a}
Chloroform extract					
E (500mg/kg**)**	47.35 ± 8.46^{a}	33.25 ± 4.36^{bc}	21.45 ± 0.66^{bc}	1.55 ± 0.14^{ab}	4.85 ± 0.20^{a}
F (Glibenclamide**)**	41.70 ± 0.13^{b}	28.00 ± 0.13^{c}	18.90 ± 0.13^{c}	1.50 ± 0.13^{a}	4.60 ± 0.13^{c}

Values are expressed as Means SEM. Means marked * in the same column are significantly different from diabetic control at $p \leq 0.05$

Table 5: Effect of the *Chrysophyllum albican* leaf extract on kidney function parameters in alloxan-induced of diabetic rats

Groups	Urea(mg/dl)	Creatinine (mg/dl)	Na^{+}(mEq/L)	K^{+}(mEq/L)	Cl^{+}(mEq/L)	HCO_3^{-}(mmol/L)	Ca^{2+}
A (Normal control)	25.50±1.44^{b}	0.76±0.01^{b}	198.00±1.15^{d}	2.50±0.06^{d}	120.12±0.12^{a}	17.00±2.06^{a}	6.10±0.17^{a}
B (Untreated Diabetic control **)**	54.00±1.15^{a}	1.76±0.01^{a}	242.00±2.89^{b}	5.45±0.03^{a}	125.56±4.03^{a}	17.30±3.06^{a}	7.10±0.29^{a}
Pet Ether extract							
C(500mg/kg**)**	49.00±4.04^{a}	1.65±0.02^{a}	156.50±2.60^{f}	3.70±0.23^{b}	120.81±6.06^{a}	17.50±4.06^{a}	7.00±0.46^{a}
Ethanolic extract							
D (500mg/kg**)**	51.50±4.33^{a}	1.64±0.02^{a}	208.50±2.02^{a}	5.25±0.32^{a}	115.20±5.03^{a}	17.91±3.03^{a}	6.90±0.35^{a}
Chloroform extract							
E (500mg/kg**)**	23.00±1.02^{b}	0.82±0.02^{b}	256.00±2.22^{a}	3.00±0.22^{cd}	121.71±5.02^{a}	17.72±2.02^{a}	6.40±0.22^{a}
F (Glibenclamide**)**	48.00±3.46^{a}	1.63±0.02^{a}	183.50±2.60^{c}	3.10±0.00^{c}	115±4.03$^{\grave{}}$	16.5±2.03^{a}	6.90±0.35$^{a'}$

Values are expressed as Means SEM. Means marked * in the same column are significantly different from diabetic control at $p \leq 0.05$