ORIGINAL ARTICLE

AMELIORATIVE EFFECTS OF *ALOE VERA* GEL EXTRACT ON CIRCULATORY AND TISSUE LIPID PROFILE STATUS IN STREPTOZOTOCIN-INDUCED DIABETIC RATS

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ABSTRACT

Diabetes is characterized by hyperglycaemia with alterations of lipid parameters. The effects of *Aloe vera* (*A.V*) gel extract on lipid profiles of streptozotocin-induced diabetic rats were investigated. Seventy-two male albino rats were randomly divided into six groups of 12 rats each; control, diabetic control, 4 ml/kg and 8 ml/kg body weight (b.w.) *A.V,* 10 mg/kg b.w. glibenclimide and non-diabetic 8 ml/kg b.w. *A.V* groups. They were treated for 14 and 28 days. The plasma and HDL lipid profiles (triacylglycerols, cholesterol and phospholipids) of the diabetic rats were significantly ($p<0.05$) increased, while those of the VLDL+LDL, RBC, RBC membrane and organs were observed to be significantly ($p<0.05$) reduced, when compared to the control after 14 and 28 days of treatment. *A.V* gel extract significantly ($p<0.05$) ameliorated the disruptions observed in the lipid profiles of the diabetic and thus provide a scientific rationale for the use of *Aloe vera* as a therapeutic agent.

Key Words: Diabetes, *Aloe vera,* streptozotocin, lipid profile, dyslipidemia

Introduction

Diabetes mellitus is a serious chronic metabolic disorder characterized by a decrease or cessation of insulin secretion in response to normal physiological stimuli by the pancreas, or reduced responsiveness of peripheral tissues to insulin[1]. *Diabetes mellitus* is one of the most common endocrine disorder and one of the leading causes of death in the world[2]. Diabetes affects approximately 6.4% of the world's population with the highest prevalence in North America and Caribbean (10.2%), followed by Middle East and North Africa (9.3%)[3]. Lipid metabolism in patients with diabetes may differ significantly from that in the non-diabetic state4. Diabetes is characterized by hyperglycemia together with biochemical alterations of glucose and lipid metabolism[5]. These traits are hypothesized to be responsible for the damage to cell membranes, which, in turn, results in an elevated production of reactive oxygen species-ROS and other complications[6]. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction and failure of various organs, especially the eyes, kidneys, nerves, hearts and blood vessels[6]. Hyperglycemia and hyperlipidemia are two important characters of *Diabetes mellitus* in which diabetic patients experience various vascular complications such as atherosclerosis, coronary heart disease, diabetic nephropathy and neuropathy[7,8]. The prevalence of dyslipidemia in *Diabetes mellitus* is 95%[9]. Cardiovascular disease is the major cause of death in persons with type 1 diabetes. Early detection and

treatment of hyperlipidemia in diabetic patients reduces the risk for cardiovascular and cerebrovascular diseases[10]. Dyslipidemia has been shown to be a significant coronary heart disease risk factor in diabetes[11,12]. Thus, it seems important to pay attention to lipid abnormalities, in patients with diabetes, at least to reduce cardiovascular disease in this population. Sulfonylureas such as glibenclamide stimulate insulin secretion from the existing pancreatic cells and are widely used to treat type-1 diabetes. Glibenclamide principally acts by inhibiting ATP-sensitive K^+ (K-ATP) channels in the plasma membrane[13]. The inhibition of ATP sensitive channels leads to membrane depolarization, activation of voltage-gated Ca^{2+}-channels, increased Ca^{2+} influx, a rise in cytosolic [Ca^{2+}] and thereby insulin release. Though sulfonylureas are valuable in treatment of diabetes, their use is restricted by their limited action, pharmacokinetic properties, secondary failure rates and accompanying side effects[14]. These drugs have side effects and thus search for a new class of compounds is essential to overcome these problems[15]. Management of diabetes without any side effect is still a challenge to the medical system leading to increasing demand for natural products with antidiabetic activity and fewer side effects[14].

Plants have played a significant role in maintaining human health and improving the quality of life for thousands of years[15]. Many herbs and plant products have been shown to have hypoglycemic action. *Aloe vera* is one of such antidiabetic plants that have maintained its popularity for a long period of time[16]. *A. vera* is a medicinal plant that is claimed to have hypoglycemic effect with fewer side effects and less expensive without toxicity[17]. Numerous clinical studies have been published that demonstrate *Aloe vera's* antidiabetic properties. The hypoglycemic efficacy of aloe gel was confirmed in streptozotocin-induced diabetes[18]. The aim of this present study was to evaluate the effects of *A. vera* gel extract on circulatory and tissue lipid profiles (triacylglycerol, cholesterol and phospholipids) in STZ-induced diabetic rats.

Materials and Methods

Preparation of *Aloe vera* gel Extract

Aloe vera plant was obtained from a reputable botanical garden in Abeokuta, Ogun State, Nigeria and identified at the herbarium, in the Department of Botany, Federal University of Agriculture, Abeokuta, Nigeria where a voucher number (FUNAAB H0020) was deposited. The leaves were washed thoroughly under a running tap water, to remove debris, after which they were cut open. The gel was scooped into an electric blender and then homogenized to obtain the gel extract. The extract was prepared daily for each administration over the twenty-eight days of experimental period[19].

Experimental Animals

Male wistar albino rats, healthy with no sign of injury, weighing between 150-200 g, obtained from a reputed animal house in Alabata, Abeokuta, Nigeria were used for the study. The rats were allowed to acclimatize for two weeks before the commencement of the experiment, in the animal house of the Department of Biochemistry, Federal University of Agriculture, Abeokuta. The animals were kept in well-ventilated cages at ambient conditions. They were fed normal laboratory chow and water ad *libitum*.

Induction of *Diabetes Mellitus*

Rats were fasted for 12 h prior to induction of diabetes by intraperitoneal injection of 55 mg/kg b.w. streptozotocin (Sigma, St Louis, MO, USA) freshly dissolved in 0.1 M cold sodium citrate buffer, pH 4.5[20]. Control rats received

equivalent amounts of buffer intraperitoneally. Hyperglycaemia was confirmed 3 days after induction via blood glucose level measurements after a 12 h fast. Animals with a fasting blood glucose level greater than 200 mg/dl were considered diabetic and included in the study[20].

Experimental Design

After acclimatization, the animals were randomly divided into six groups of twelve rats each; Group A (Normal control) were non-diabetic; Group B (diabetic control) were diabetic but not treated with the *A. vera* gel extract; Group C and D (diabetic test groups) were diabetic and treated daily with 4 ml/kg and 8 ml/kg body weight *A. vera* gel extract respectively; Group E were diabetic and treated with 10 mg/kg body weight of glibenclimide (the standard drug); Group F were non-diabetic but treated with 8 ml/kg body weight *A. vera* gel extract. The rats were checked daily and their body weights were recorded accordingly till the end of the experiment. Also, blood glucose was monitored weekly using a digital ACCU-CHEK glucose meter. Blood samples were collected from the tip of the rat's tail and placed on the strip attached to the glucometer, and the blood glucose concentration was then displayed on the screen after 5-10 seconds.

After 14 days of treatment (day 14), 6 rats from each group were sacrificed, and after another 14 days (day 28), the remaining 6 rats of each group were also sacrificed. After an overnight fast, the rats were weighed and sacrificed under light ether anaesthesia. Blood samples were collected by cardiac puncture using heparinized needle and syringes into heparinized tubes. The blood samples were centrifuged at 4,000 rpm for 10 minutes to separate the plasma from the red blood cells (RBC). The liver, kidney and intestinal segments were excised, washed immediately in ice-cold distilled water, mopped dried and stored in a freezer until analyzed.

Isolation of HDL and VLDL + LDL

The procedure of Gidez *et al.* (1982)[21] was used to isolate HDL from plasma. Heparin-$MnCl_2$ (20 μl) was added to 200 μl of plasma in a test tube and the resultant mixture was thoroughly mixed and allowed to stand for 10 min. This was centrifuged at 4000 rpm for 20 min and the supernatant decanted into Eppendorf tubes. The pellet was redisolved to solution by adding 200 μl of distilled water. The supernatant (HDL) and residue (very low density lipoprotein+low density lipoprotein [VLDL+LDL]) were stored in freezer until analyzed.

Washing of Red Blood Cells for Membrane Isolation

The washing and separation of red cell membrane was done according to the method described by Braun and Fromherz 1997)[22]. Briefly, packed cells (0.5 ml) were washed three times by gentle inversion with 2.0 ml of ice-cold 50 mM Tris-HCl buffer (pH 7.4) and centrifuged at 3500 rpm for 10 minutes at 25^{o}C until supernatant was clear.

Isolation of RBC Membrane

The isolation of RBC membrane was done according to the method described by Gurel *et al.* (2004)[23]. The already washed red blood cells were suspended in an equal volume (0.5 ml) of 50 mM Tris-HCl buffer (pH 7.4) on ice for 4 hours. The suspension was lysed by using 4 ml of 10 mM Tris-HCl buffer (pH 7.4). The tubes were kept on ice for 15 minutes, and then centrifuged at 12000 rpm at 4^{o}C for 20 minutes. The membrane was collected and washed several times by suspending in 10 mM Tris-HCl buffer (4 ml) until it became creamy white and supernatant was removed. 1ml of 50 mM Tris-HCl buffer (pH 7.4) was added to the membrane, in Eppendorf tubes and stored in the freezer until analyzed.

Extraction of lipids from RBC

Lipids were extracted from the RBC using chloroform - isopropanol (7:11, v/v) as described by Rose and Oklander (1965)[24]. Chloroform - isopropanol (0.9 ml) was added to 0.1 ml of RBC. The mixture was shaken every 5 minutes for 30 minutes, centrifuged at 4000 rpm for 10 minutes and the organic layer collected. An aliquot (0.1 ml) of 0.05 M KCl was then added to the organic layer, to remove other non-polar part from the mixture. This was vortexed at room temperature, for 5 minutes, centrifuged again at 4000 rpm for 10 minutes. The lower (organic) layer was taken and used for the lipid analysis.

Extraction of Lipids from VLDL+LDL, RBC Membrane and Organs

Lipids were extracted as described by Folch *et al.* (1957)[25], using chloroform - methanol (2:1, v/v) and following the same procedure as for that of RBC.

Biochemical Analysis
Plasma and HDL lipid profiles

The plasma and HDL concentrations of total cholesterol, triacylglycerol and phospholipid were determined spectrophotometrically using Cypress diagnostic kits (Langdorp, Belgium).

VLDL+LDL, RBC Membrane and Organs Lipid Profiles

For cholesterol determination, 0.1 ml of the sample extract was evaporated to dryness at 60^{o}C and 20 μl of Triton X-100/chloroform mixture (1:1, v/v) was added to the dried extract for resolution. This was evaporated again and then 1 ml of the cholesterol kit reagent was added, mixed and incubated for 30 min. before reading the absorbance. Triacylglycerol concentration was determined by evaporating to dryness 0.1 ml of the extract and then adding 0.1 ml of 97% ethanol to re-suspend the dried lipid. To this suspension, 1 ml of the triacylglycerol kit reagent was added, mixed and incubated for 30 min. before the absorbance reading was taken. For phospholipids determination, 0.1 ml of the extract was evaporated and 1 ml of the phospholipid kit reagent was added, mixed and incubated for 30 min. before taking absorbance reading.

Statistical Analysis

Values are expressed as mean$\pm$standard error of means (S.E.M). The level of homogeneity among the results of groups was tested using one way Analysis of Variance (ANOVA), with $p<0.05$ considered significant. Where heterogeneity occurred, the groups were separated using Duncan Multiple Range Test (DMRT) and student t-test. All analyses were done using Statistical Package for Social Sciences (SPSS) version 16.0.

Result

Table 1 gives the concentrations of blood glucose in the control and experimental groups of rats. Diabetic rats showed a significant ($p<0.05$) increase in blood glucose compared with corresponding control rats. Following oral administration of *A. vera* extract and glibenclamide, blood glucose concentrations decreased in both treatments, and dose-dependently in those treated with *A. vera* extract, while non-diabetic rats treated with 8 ml/kg *A.V* gel extract had blood glucose concentrations similar to those seen in control rats. Also, the blood glucose concentrations were observed to be significantly ($p<0.05$) decreased after 14 and 28 days of respective treatment in all groups, with those of 8 ml/kg b.w. *A.V* gel extract and 10 mg/kg b.w. glibenclimide being restored to non-diabetic states (glucose concentrations $<$200 mg/dl).

Table 2 shows the plasma concentrations of triacylglycerol, cholesterol and phospholipids. The concentrations of plasma cholesterol,

triacylglycerols and phospholipids were significantly ($p < 0.05$) increased in diabetic rats compared with corresponding control rats. Oral administration of *A.vera* gel extract and glibenclamide significantly reversed all these changes to near normal concentrations. Plasma concentrations of triacylglycerol of the respective groups were observed to have reduced significantly ($p < 0.05$), after 28 days of treatment when compared to the concentrations after day 14, except in the diabetic control and 4 ml/kg *A.V* gel extract treated diabetic groups where no significant ($p > 0.05$) difference was observed. Also, no significant ($p > 0.05$) difference was observed in plasma concentrations of cholesterol in the groups after 14 and 28 days, except in the diabetic control and 8 ml/kg *A.V* gel extract-administered non-diabetic rats, where a significant ($p < 0.05$) increase was observed. Plasma phospholipids were, however, observed to be significantly ($p < 0.05$) increased in all groups, except in the 8 ml/kg *A.V* gel extract-administered groups (both diabetic and non-diabetic) where no significant ($p > 0.05$) difference was observed, after 28 days of treatment when compared to the concentrations after day 14.

HDL concentrations of triacylglycerol, cholesterol and phospholipids are given in Table 3. After 28 days, there was a significant ($p < 0.05$) increase in HDL triacylglycerol, a significant ($p < 0.05$) decrease in the phospholipids concentrations of the diabetic groups, compared to their corresponding controls, while induction of diabetes had no significant ($p > 0.05$) effect on HDL cholesterol. Oral administration of *A.vera* gel extract reversed (except in phospholipids concentrations) these diabetes-induced changes to near normal levels, while having no significant ($p > 0.05$) effect on non-diabetic rats. Also, the HDL triacylglycerol concentrations of the control and 8 ml/kg *A.V* gel extract diabetic groups were significantly ($p < 0.05$) increased, while those of the diabetic, 4 ml/kg *A.V* gel extract diabetic and 8 ml/kg *A.V* gel extract non-diabetic groups had no significant ($p > 0.05$) difference. However those of the glibenclimide treated group were significantly ($p < 0.05$) decreased, after 28 days of treatment when compared to the concentrations after 14 days.

The VLDL+LDL concentrations of triacylglycerol, cholesterol and phospholipids are depicted in Table 4. After 14 days, the VLDL+LDL triacylglycerol concentrations of the diabetic group were seen to be significantly ($p < 0.05$) lower than that of the control group. But the different treatments appeared to have no significant effect ($p > 0.05$). In contrast after 28 days, the VLDL+LDL triacylglycerol concentrations of the diabetic group were observed to be significantly ($p < 0.05$) higher than that of the control group while the different treatments brought back the elevated concentrations to levels similar to those of the control groups. A significant ($p < 0.05$) increase was observed in VLDL+LDL cholesterol of the diabetic rats compared to the control groups, and this increase was sustained throughout the study duration, whereas, the VLDL+LDL concentrations of phospholipids were observed to be significantly ($p < 0.05$) decreased in the diabetic rats, when compared to the control group. However, oral administration of *A. vera* extract and glibenclamide to diabetic rats significantly reversed all these changes to near normal levels and in a dose-dependent manner for the *A.vera* administered groups. Also, a significant ($p < 0.05$) increase in the concentrations of VLDL+LDL cholesterol and phospholipids were sustained in all the respective groups, after 28 days of treatment when compared to the concentrations after 14 days.

Tables 5 and 6 give the effects of *A.vera* gel extract on RBC and RBC membrane triacylglycerol, cholesterol and phospholipids

concentrations of control and experimental rats. After 14 and 28 days, the RBC and RBC membrane lipid (triacylglycerols, cholesterol and phospholipids) concentrations of the diabetic group were significantly ($p<0.05$) lower than those of the control group. Oral administration of both doses of *A.vera* gel extract and glibenclimide significantly ($p>0.05$) increased the RBC lipid concentrations, improving the disruptions in lipid status of the RBC and RBC membrane, induced by diabetes.

Tables 7 and 8 show the effects of *A. vera* gel extract on liver and kidney lipid (triacylglycerols, cholesterol and phospholipids) concentrations of control and experimental rats. After 14 and 28 days of treatment, significant ($p<0.05$) decreases were observed in the liver and kidney lipid concentrations of the diabetic control group when compared to the control group. Oral treatment with 4 ml/kg and 8 ml/kg b.w. *Aloe vera* gel extract and glibenclamide significantly ($p<0.05$) reversed all these changes to near normal levels, except in liver triacylglycerol, where the treatments had no significant ($p>0.05$) effect. Also, comparing the 28 days treatment with the 14 days treatment, no significant ($p>0.05$) difference was observed for liver triacylglycerol in all groups except the diabetic control group and the glibenclimide treated group, where the concentrations were increased and decreased respectively. For liver cholesterol, only the control and 8 ml/kg b.w. *A.V* gel extract diabetic groups had significantly ($p<0.05$) increased higher concentrations after 28 days of treatment when compared to the concentrations after 14 days. No significant ($p>0.05$) difference was observed for liver phospholipids in all groups except the diabetic control and the 8 ml/kg b.w. *A.V* gel extract non-diabetic groups, where the concentrations were decreased and increased respectively, after 28 days of treatment when compared to the concentrations after 14 days. Also, no significant ($p>0.05$) difference was observed for kidney triacylglycerol in all groups except the diabetic control and the glibenclimide treated groups (where the concentrations were increased) and the 8 ml/kg b.w. *A.V* gel extract non-diabetic group (decreased concentrations), after 28 days of treatment when compared to the concentrations after 14 days. Kidney cholesterol of the diabetic control and the 8 ml/kg b.w. *A.V* gel extract non-diabetic group were significantly ($p<0.05$) increased, those of 4 ml/kg b.w. *A.V* gel extract diabetic group were significantly ($p<0.05$) decreased, whereas other groups had no significant ($p>0.05$) difference in their kidney cholesterol, after 28 days of treatment when compared to the concentrations after 14 days. Kidney phospholipids of the control, diabetic control and the 8 ml/kg b.w. *A.V* gel extract diabetic group were significantly ($p<0.05$) decreased, those of diabetic 4 ml/kg b.w. *A.V* and 8 ml/kg b.w. *A.V* gel extract non-diabetic groups had no significant ($p>0.05$) difference, whereas those of glibenclimide-treated group had significantly increased kidney phospholipids, after 28 days of treatment when compared to the concentrations after 14 days.

Tables 9 and 10 show the effects of *A. vera* gel extract on intestinal (ileum and jejunum) concentrations of triacylglycerol, cholesterol and phospholipids of control and experimental rats. A significant ($p<0.05$) decrease was observed in the intestinal lipid concentrations of the diabetic control group when compared to the non-diabetic control group. Also, oral treatment with 4 ml/kg and 8 ml/kg b.w. *Aloe vera* gel extract and glibenclamide significantly ($p<0.05$) reversed all these changes to near normal levels. No significant ($p>0.05$) difference was observed for ileum triacylglycerol in all groups except the diabetic control and the 8 ml/kg b.w. *A.V* gel extract non-diabetic groups, where the concentrations were decreased and increased

respectively, after 28 days of treatment when compared to the concentrations after 14 days. No significant ($p > 0.05$) difference was observed for ileum cholesterol in all groups except the 8 ml/kg b.w. *A.V* gel extract diabetic and glibenclimide groups (where the concentrations were increased), after 28 days of treatment when compared to the concentrations after 14 days.

Table-1: Effects of *Aloe vera* gel extract administration on blood glucose concentrations (mg/dl) of control and experimental groups of rats.

	Days		
Groups	**Day 0**	**Day 14**	**Day 28**
Control	100.00 ± 11.11^{a1}	99.99 ± 12.67^{a1}	96.14 ± 12.46^{a1}
Diabetic control	707.41 ± 48.15^{b3}	477.78 ± 40.06^{c2}	369.00 ± 31.00^{c1}
Diabetic+4 ml/kg A.V gel extract	707.41 ± 48.15^{b3}	300.00 ± 19.77^{b2}	237.00 ± 31.42^{b1}
Diabetic+8 ml/kg A.V gel extract	707.41 ± 48.15^{b3}	271.31 ± 18.84^{b2}	192.75 ± 34.72^{b1}
Diabetic+10 mg/kg glibenclimide	707.41 ± 48.15^{b2}	147.50 ± 26.25^{a1}	146.00 ± 22.37^{a1}
Non-diabetic+8 ml/kg A.V gel extract	100.00 ± 11.11^{a1}	91.67 ± 13.13^{a1}	121.75 ± 7.95^{a2}

Values are mean±S.E.M (n=6). Values with different superscript letters in a column, are significantly different from one another ($p < 0.05$). Values with different integer superscript along a row, are significantly different from one another ($p < 0.05$)

Table-2: Effects of *Aloe vera* gel extract administration on plasma lipid concentrations of control and experimental groups of rats.

	Triacylglycerol(mg/dl)		**Cholesterol (mg/dl)**		**Phospholipids (mg/dl)**	
Groups	**Day 14**	**Day 28**	**Day 14**	**Day 28**	**Day 14**	**Day 28**
Control	123.73 ± 8.17^{b2}	72.68 ± 12.02^{a1}	207.05 ± 6.74^{a1}	213.03 ± 8.04^{a1}	57.31 ± 0.99^{a1}	60.00 ± 1.25^{a2}
Diabetic control	262.8 ± 20.27^{d1}	220.94 ± 36.80^{c1}	248.83 ± 8.24^{c1}	271.52 ± 8.71^{c2}	63.11 ± 0.63^{b1}	67.97 ± 2.64^{b2}
Diabetic+4 ml/kg A.V gel extract	173.26 ± 39.67^{c1}	112.21 ± 30.13^{b1}	227.7 ± 10.63^{b1}	240.62 ± 21.57^{b1}	65.09 ± 0.92^{b1}	69.66 ± 2.95^{b2}
Diabetic+8 ml/kg A.V gel extract	151.63 ± 29.59^{c2}	72.68 ± 23.01^{a1}	215.5 ± 3.27^{a1}	267.02 ± 9.26^{c2}	67.63 ± 3.05^{b1}	67.64 ± 3.47^{b1}
Diabetic+10 mg/kg glibenclimide	091.28 ± 10.67^{a2}	50.39 ± 10.77^{a1}	238.27 ± 25.54^{b1}	270.74 ± 39.43^{c1}	67.35 ± 0.39^{b1}	74.76 ± 5.69^{b2}
Nondiabetic+8 ml/kg A.V gel extract	147.68 ± 19.42^{c2}	56.98 ± 16.57^{a1}	207.16 ± 2.22^{a1}	223.01 ± 3.46^{a2}	59.25 ± 0.65^{a1}	58.9 ± 0.67^{a1}

Values are mean±S.E.M (n=6). Values with different superscripts letters in a column, are significantly different from one another ($p < 0.05$). Values with different integer superscripts along a row, are significantly different from one another ($p < 0.05$).

Table-3: Effects of *Aloe vera* gel extract administration on HDL lipid concentrations of control and experimental groups of rats.

	Triacylglycerol (mg/dl)		Cholesterol (mg/dl)		Phospholipids (mg/dl)	
Groups	**Day 14**	**Day 28**	**Day 14**	**Day 28**	**Day 14**	**Day 28**
Control	124.64 ± 12.57^{d2}	63.41 ± 11.67^{a1}	63.41 ± 11.67^{a1}	125.52 ± 16.10^{a1}	75.22 ± 1.92^{a1}	79.5 ± 4.31^{b1}
Diabetic control	121.74 ± 24.70^{d1}	176.82 ± 73.82^{e1}	176.82 ± 73.82^{e1}	115.81 ± 19.98^{a2}	73.29 ± 1.32^{a2}	69.74 ± 1.48^{a1}
Diabetic+4 ml/kg A.V gel extract	96.38 ± 7.07^{b1}	99.82 ± 11.29^{c1}	99.82 ± 11.29^{c1}	136.74 ± 12.44^{a1}	71.69 ± 0.80^{a1}	69.38 ± 1.52^{a1}
Diabetic+8 ml/kg] A.V gel extract	160.29 ± 29.47^{e2}	108.7 ± 14.97^{c1}	108.7 ± 14.97^{c1}	171.95 ± 31.02^{a1}	74.15 ± 1.70^{a1}	71.4 ± 2.32^{a1}
Diabetic+10 mg/kg glibenclimide	78.63 ± 19.3^{a1}	112.57 ± 16.91^{c2}	112.57 ± 16.91^{c2}	122.85 ± 19.04^{a1}	69.49 ± 2.06^{a1}	72.83 ± 2.71^{a1}
Non-diabetic+ 8ml/kg A.V gel extract	110.87 ± 28.16^{d1}	90.22 ± 11.42^{b1}	90.22 ± 11.42^{b1}	133.22 ± 16.02^{a2}	78.63 ± 4.09^{a1}	74.29 ± 1.72^{a1}

Values are mean±S.E.M (n=6). Values with different superscripts letters in a column, are significantly different from one another ($p<0.05$). Values with different integer superscripts along a row, are significantly different from one another ($p<0.05$).

Table-4: Effects of *Aloe vera* gel extract administration on VLDL+LDL lipid concentrationsof control and experimental groups of rats.

	Triacylglycerol (mg/dl)		Cholesterol (mg/dl)		Phospholipids (mg/dl)	
Groups	**Day 14**	**Day 28**	**Day 14**	**Day 28**	**Day 14**	**Day 28**
Control	311.02 ± 32.74^{c2}	202.9 ± 18.12^{a1}	45.12 ± 2.91^{a1}	81.51 ± 2.45^{b1}	81.51 ± 2.45^{b1}	216.91 ± 3.48^{c2}
Diabetic control	260.87 ± 19.18^{b1}	263.29 ± 6.52^{b1}	139.24 ± 2.32^{c1}	$71.13 \pm 2.03a1$	71.13 ± 2.03^{a1}	100.83 ± 10.35^{a2}
Diabetic+4 ml/kg A.V gel extract	225.00 ± 22.46^{a1}	219.93 ± 12.09^{a1}	53.42 ± 3.41^{b1}	72.67 ± 6.35^{a1}	72.67 ± 6.35^{a1}	218.24 ± 4.63^{c2}
Diabetic+8 ml/kg A.V gel extract	211.89 ± 18.71^{a1}	228.99 ± 11.54^{a1}	48.50 ± 3.11^{a1}	$70.45 \pm 0.77a1$	70.45 ± 0.77^{a1}	157.26 ± 15.26^{b2}
Diabetic+10 mg/kg glibenclimide	221.02 ± 23.59^{a1}	184.55 ± 16.62^{a1}	48.53 ± 3.13^{a1}	80.25 ± 2.70^{b1}	80.25 ± 2.70^{b1}	179.28 ± 12.36^{b2}
Non-diabetic+ 8 ml/kg A.V gel extract	210.15 ± 22.15^{a1}	232.61 ± 17.59^{a1}	44.12 ± 1.90^{a1}	83.44 ± 2.57^{b1}	83.44 ± 2.57^{b1}	226.23 ± 17.85^{c2}

Values are mean±S.E.M (n=6). Values with different superscripts letters in a column, are significantly different from one another ($p<0.05$). Values with different integer superscripts along a row, are significantly different from one another ($p<0.05$).

Table-5: Effects of *Aloe vera* gel extract administration on RBC lipid concentrations of control and experimental groups of rats.

	Triacylglycerol (mg/dl)		Cholesterol (mg/dl)		Phospholipids (mg/dl)	
Groups	**Day 14**	**Day 28**	**Day 14**	**Day 28**	**Day 14**	**Day 28**
Control	78.52 ± 9.24^{c1}	89.88 ± 8.67^{c1}	22.99 ± 2.97^{c1}	32.09 ± 11.10^{c1}	131.6 ± 2.76^{e1}	120.98 ± 9.77^{c1}
Diabetic control	25.51 ± 1.38^{a1}	23.42 ± 8.38^{a1}	11.5 ± 5.07^{a1}	14.69 ± 4.47^{a1}	84.25 ± 4.22^{b1}	86.94 ± 1.62^{a1}
Diabetic+4 ml/kg A.V gel extract	44.43 ± 15.77^{b1}	27.9 ± 4.59^{a1}	19.64 ± 1.21^{b1}	22.51 ± 2.52^{b1}	61.56 ± 5.42^{a1}	98.19 ± 2.77^{b2}
Diabetic+8 ml/kg A.V gel extract	47.11 ± 6.87^{b1}	50.62 ± 16.74^{b1}	18.4 ± 3.67^{b1}	18.2 ± 2.00^{b1}	108.92 ± 14.06^{c1}	99.46 ± 3.05^{b1}
Diabetic+10 mg/kg glibenclimide	54.76 ± 15.03^{b1}	81.27 ± 15.89^{c1}	12.94 ± 2.52^{a1}	21.72 ± 9.01^{b1}	147.77 ± 2.03^{f2}	84.17 ± 3.75^{a1}
Non-diabetic+ 8ml/kg A.V gel extract	92.98 ± 6.86^{c1}	101.24 ± 16.66^{c1}	13.89 ± 3.36^{a1}	51.73 ± 12.37^{d2}	121.22 ± 21.68^{e1}	97.15 ± 2.49^{b1}

Values are mean $\pm$ S.E.M ($n=6$). Values with different superscripts letters in a column, are significantly different from one another ($p<0.05$). Values with different integer superscripts along a row, are significantly different from one another ($p<0.05$).

Table-6: Effects of *Aloe vera* gel extract administration on RBC membrane lipid concentrations of control and experimental groups of rats.

	Triacylglycerol (mg/dl)		Cholesterol (mg/dl)		Phospholipids (mg/dl)	
Groups	**Day 14**	**Day 28**	**Day 14**	**Day 28**	**Day 14**	**Day 28**
Control	15.12 ± 2.82^{b1}	31.27 ± 1.33^{d2}	44.8 ± 10.09^{c1}	123.59 ± 33.04^{d2}	13.68 ± 2.05^{a1}	34.29 ± 2.53^{c2}
Diabetic control	6.5 ± 2.37^{a1}	4.63 ± 2.12^{a1}	12.83 ± 0.92^{a1}	11.49 ± 2.03^{a1}	20.65 ± 1.40^{b1}	15.83 ± 9.66^{c1}
Diabetic+4 ml/kg A.V gel extract	7.62 ± 2.83^{a1}	11.83 ± 3.35^{b1}	11.36 ± 3.47^{a1}	28.07 ± 8.03^{b2}	18.2 ± 3.07^{b1}	29.09 ± 6.6^{b2}
Diabetic+8 ml/kg A.V gel extract	12.63 ± 1.94^{b1}	22.83 ± 2.44^{c2}	20.88 ± 3.36^{b1}	38.82 ± 8.74^{b2}	18.46 ± 0.74^{b1}	35.23 ± 1.1^{c2}
Diabetic+10 mg/kg glibenclimide	12.24 ± 1.35^{b1}	20.56 ± 7.35^{c2}	15.18 ± 2.28^{a1}	37.79 ± 6.36^{b2}	15.27 ± 0.76^{a1}	36.45 ± 3.24^{c2}
Non-diabetic+ 8 ml/kg A.V gel extract	20.19 ± 4.13^{b1}	19.34 ± 4.08^{c1}	55.05 ± 7.27^{c1}	71.36 ± 11.2^{c2}	16.33 ± 1.44^{a1}	33.83 ± 7.46^{c2}

Values are mean $\pm$ S.E.M ($n=6$). Values with different superscripts letters in a column, are significantly different from one another ($p<0.05$). Values with different integer superscripts along a row, are significantly different from one another ($p<0.05$).

Table-7: Effects of *Aloe vera* gel extract administration on liver lipid concentrations of control and experimental groups of rats.

Groups	Triacylglycerol (mg/dl)		Cholesterol (mg/dl)		Phospholipids (mg/dl)	
	Day 14	Day 28	Day 14	Day 28	Day 14	Day 28
Control	6.16 ± 0.7^{c1}	5.64 ± 0.59^{b1}	1.69 ± 0.32^{c1}	3.55 ± 0.36^{d2}	1.99 ± 0.20^{a1}	1.91 ± 0.08^{b1}
Diabetic control	4.67 ± 0.27^{b2}	3.73 ± 0.35^{a1}	0.54 ± 0.52^{a1}	0.41 ± 0.25^{a1}	2.36 ± 0.04^{b2}	1.63 ± 0.21^{a1}
Diabetic+4 ml/kg A.V gel extract	3.61 ± 0.65^{a1}	3.77 ± 0.45^{a1}	1.22 ± 0.32^{b1}	1.45 ± 0.44^{b1}	1.86 ± 0.08^{a1}	1.96 ± 0.09^{b1}
Diabetic+8 ml/kg A.V gel extract	4.01 ± 0.43^{a1}	4.11 ± 0.34^{a1}	1.33 ± 0.35^{b1}	2.68 ± 0.72^{c2}	2.13 ± 0.12^{a1}	1.91 ± 0.14^{b1}
Diabetic+10 mg/kg glibenclimide	3.79 ± 0.69^{a1}	5.48 ± 0.95^{b2}	1.32 ± 0.29^{b1}	1.64 ± 0.16^{b1}	2.09 ± 0.20^{a1}	1.52 ± 0.67^{a1}
Non-diabetic+ 8 ml/kg A.V gel extract	5.12 ± 0.94^{b1}	5.98 ± 0.51^{b1}	2.19 ± 0.29^{d1}	2.59 ± 0.25^{c1}	1.73 ± 0.14^{a1}	2.11 ± 0.08^{b2}

Values are mean±S.E.M (n=6). Values with different superscripts letters in a column, are significantly different from one another ($p<0.05$). Values with different integer superscripts along a row, are significantly different from one another ($p<0.05$).

Table-8: Effects of *Aloe vera* gel extract administration on kidney lipid concentrations of control and experimental groups of rats.

Groups	Triacylglycerol (mg/dl)		Cholesterol (mg/dl)		Phospholipids (mg/dl)	
	Day 14	Day 28	Day 14	Day 28	Day 14	Day 28
Control	3.26 ± 0.30^{d1}	3.49 ± 0.58^{c1}	2.26 ± 0.24^{b1}	2.19 ± 0.30^{b1}	2.10 ± 0.20^{a2}	1.15 ± 0.14^{b1}
Diabetic control	0.96 ± 0.14^{a1}	2.27 ± 0.03^{a2}	1.96 ± 0.19^{b2}	1.64 ± 0.06^{a1}	1.35 ± 0.19^{c2}	1.00 ± 0.07^{b1}
Diabetic+4 ml/kg A.V gel extract	2.50 ± 0.38^{c1}	2.83 ± 0.37^{c1}	1.71 ± 0.27^{b1}	2.29 ± 0.09^{b2}	0.84 ± 0.10^{a1}	0.67 ± 0.16^{a1}
Diabetic+8 ml/kg A.V gel extract	1.58 ± 0.27^{b1}	2.14 ± 0.31^{a1}	1.35 ± 0.10^{a1}	1.71 ± 0.28^{a1}	1.42 ± 0.13^{c2}	0.69 ± 0.05^{a1}
Diabetic+10 mg/kg glibenclimide	1.83 ± 0.24^{b1}	3.28 ± 0.89^{c2}	2.15 ± 0.3^{b1}	2.03 ± 0.16^{b1}	1.10 ± 0.08^{b1}	1.46 ± 0.13^{c2}
Non-diabetic+ 8 ml/kg	3.83 ± 0.19^{e2}	3.09 ± 0.34^{c1}	2.56 ± 0.18^{c2}	1.99 ± 0.17^{b1}	0.69 ± 0.12^{a1}	0.77 ± 0.06^{a1}

Values are mean±S.E.M (n=6). Values with different superscripts letters in a column, are significantly different from one another ($p<0.05$). Values with different integer superscripts along a row, are significantly different from one another ($p<0.05$).

Table-9: Effects of *Aloe vera* gel extract administration on ileum lipid concentrations of control and experimental groups of rats.

	Triacylglycerol (mg/dl)		Cholesterol (mg/dl)		Phospholipids (mg/dl)	
Groups	**Day 14**	**Day 28**	**Day 14**	**Day 28**	**Day 14**	**Day 28**
Control	2.92 ± 0.57^{b1}	3.66 ± 0.89^{b1}	21.58 ± 0.26^{a1}	1.66 ± 0.05^{b1}	1.22 ± 0.06^{a1}	1.08 ± 0.06^{b1}
Diabetic control	1.31 ± 0.27^{a1}	1.97 ± 0.13^{a2}	1.16 ± 0.38^{a1}	1.39 ± 0.14^{a1}	1.09 ± 0.10^{a1}	1.11 ± 0.12^{b1}
Diabetic+4 ml/kg A.V gel extract	2.81 ± 0.49^{b1}	3.28 ± 0.52^{b1}	2.37 ± 0.31^{b1}	1.89 ± 0.53^{b1}	1.23 ± 0.10^{a1}	1.10 ± 0.11^{b1}
Diabetic+8 ml/kg A.V gel extract	3.04 ± 0.54^{b1}	2.87 ± 0.59^{b1}	2.78 ± 0.41^{b2}	1.35 ± 0.16^{a1}	1.39 ± 0.11^{a2}	1.10 ± 0.08^{b1}
Diabetic+10 mg/kg glibenclimide	2.95 ± 0.43^{b1}	2.29 ± 0.29^{b1}	2.48 ± 0.28^{b2}	1.23 ± 0.37^{a1}	1.39 ± 0.15^{a1}	1.60 ± 0.34^{c1}
Non-diabetic+ 8ml/kg	5.14 ± 0.55^{c2}	1.56 ± 0.16^{a1}	2.26 ± 0.29^{b1}	1.93 ± 0.30^{b1}	1.25 ± 0.12^{a2}	0.56 ± 0.26^{a1}

Values are mean±S.E.M (n=6). Values with different superscripts letters in a column, are significantly different from one another ($p<0.05$). Values with different integer superscripts along a row, are significantly different from one another ($p<0.05$).

Table-10: Effects of *Aloe vera* gel extract administration on jejunum lipid concentrations of control and experimental groups of rats.

	Triacylglycerol (mg/dl)		Cholesterol (mg/dl)		Phospholipids (mg/dl)	
Groups	**Day 14**	**Day 28**	**Day 14**	**Day 28**	**Day 14**	**Day 28**
Control	2.17 ± 0.30^{a1}	2.42 ± 0.60^{b1}	1.98 ± 0.13^{a1}	2.43 ± 0.54^{c1}	1.00 ± 0.01^{b1}	1.06 ± 0.03^{c2}
Diabetic control	3.11 ± 0.39^{b2}	0.87 ± 0.26^{a1}	1.81 ± 0.09^{a2}	1.63 ± 0.05^{a1}	0.96 ± 0.02^{a2}	0.85 ± 0.03^{b1}
Diabetic+4 ml/kg A.V gel extract	1.70 ± 0.31^{a1}	1.60 ± 0.49^{b1}	1.67 ± 0.05^{a1}	1.94 ± 0.04^{b2}	1.03 ± 0.06^{b2}	0.92 ± 0.04^{b1}
Diabetic+8 ml/kg A.V gel extract	1.80 ± 0.25^{a1}	1.75 ± 0.12^{b1}	2.13 ± 0.06^{b1}	2.06 ± 0.06^{b1}	1.09 ± 0.05^{b2}	0.85 ± 0.04^{b1}
Diabetic+10 mg/kg glibenclimide	1.31 ± 0.23^{a1}	1.74 ± 0.18^{b1}	1.94 ± 0.12^{a1}	1.75 ± 0.07^{a1}	0.92 ± 0.04^{a2}	0.84 ± 0.05^{b1}
Non-diabetic+ 8 ml/kg	1.74 ± 0.18^{a1}	2.13 ± 0.49^{b1}	1.66 ± 0.10^{a1}	2.05 ± 0.19^{c2}	1.04 ± 0.07^{b2}	0.68 ± 0.04^{a1}

Values are mean±S.E.M (n=6). Values with different superscripts letters in a column, are significantly different from one another ($p<0.05$). Values with different integer superscripts along a row, are significantly different from one another ($p<0.05$).

Also, no significant ($p > 0.05$) difference was observed for ileum phospholipids in all groups except the 8 ml/kg b.w. *A.V.* gel extract diabetic and non-diabetic groups (where the concentrations were increased), after 28 days of treatment when compared to the concentrations after 14 days. In jejunum triacylglycerol, only the diabetic control group had significant ($p < 0.05$) increase, after 28 days of treatment when compared to the concentrations after 14 days. However, the 4ml/kg b.w. *A.V* gel extract diabetic and 8 ml/kg b.w. *A.V* gel extract non-diabetic groups had significantly ($p > 0.05$) increased jejunum cholesterol, in contrast, those of the diabetic group were significantly

($p > 0.05$) lowered while other group showed no significant ($p > 0.05$) difference), after 28 days of treatment when compared to the concentrations after 14 days. For jejunum phospholipids, all groups had significantly ($p > 0.05$) lowered concentrations, except in the control group, where the reverse was the case), after 28 days of treatment when compared to the concentrations after 14 days.

Discussion

Diabetes mellitus is a complex metabolic disorder associated with chronic hyperglycaemia and hyperglucosuria arising from insulin deficiency. It is accompanied by dyslipidemia, a major risk factor contributing to cardiovascular diseases[26]. Hyperglycemia and hyperlipidemia are two important characters of Diabetes mellitus in which diabetic patients experience various vascular complications such as atherosclerosis, coronary heart disease, diabetic nephropathy and neuropathy[7]. A prominent biochemical mechanism of the pathogenesis of these complications is disorder of lipid metabolism[5,27]. Management of diabetes without any side effect is still a challenge to the medical system, leading to increasing demand for natural products with antidiabetic activity and fewer side effects[13]. The ability of a hypolipidemic agent to lower blood glucose levels is a significant advantage in the management of *Diabetes mellitus*[27]. The present study thus evaluates the effects of *A. vera* gel extract on lipid status of various blood components and organs in rats with STZ-induced diabetes.

Streptozotocin is a compound commonly used for the induction of diabetes in experimental rats[28]. Streptozotocin causes diabetes by rapid depletion of β-cells, which leads to a reduction of insulin release. In STZ-induced diabetes, the increase in blood glucose levels is usually accompanied by an increase in plasma cholesterol, triacylglycerol, and phospholipids concentrations[29]. This was seen to be the case in this present study, with the diabetic control groups having elevated plasmalipid (triacylglycerol, cholesterol and phospholipids) concentrations, compared to their corresponding control groups. This marked hyperlipidaemia that characterizes the diabetic state may be regarded as a consequence of the uninhibited release of fat depots from adipose tissue and the liver in response to energy demands of cells already deprived of glucose due to insulin deficiency or resistance that defines diabetes[30]. Insulin deficiency results in activation of hormone-sensitive lipase (HSL) and consequently enhanced release of free fatty acids from adipose tissue[30]. Thus, excess fatty acids in the plasma produced by the STZ-induced diabetes promote the conversion of excess fatty acids into phospholipids and cholesterol in the liver. These two substances, along with excess triacylglycerol formed in the liver, may be discharged into the blood in the form of lipoproteins[30]. resulting in hyperlipidaemia. However, oral administration of *A. vera* gel extract (at doses of 4 ml and 8 ml/kg b.w.) ameliorated the dyslipidemia observed in the STZ-induced diabetic rats and in a dose dependent manner, which may be presumably mediated by a control of lipid metabolism. The

results of Rajasekaran *et al.* (2006) supports the results of this study which confirmed that oral administration of *A. vera* gel extract for 21 days resulted in a significant reduction in plasma cholesterol and triacylglycerol[31]. Also, Kim *et al.* (2009) confirmed that administration of processed *A. vera* gel for 8 weeks caused a significant decrease in serum triacylglycerol[32].

The increase in HDL triacylglycerol observed in the diabetic group compared to the control, is in accordance with the suggestion that HDL particles from patients with diabetes are often enriched in triacylglycerol[33,34]. This modification has been attributed to increased cholesteryl ester transfer between lipoproteins[34]. The increase of plasma triacylglycerol drives the exchange of core lipids between triglyceride rich lipoproteins (TRLs) and HDL particles. There is increased cholesterol ester transfer protein (CETP)-mediated transfer of esterified cholesterol to TRLs and of triglyceride to the HDL particles, resulting in the triglyceride enrichment of the HDL particles[35]. A significant increase was observed in VLDL+LDL cholesterol, and this increase was sustained throughout the study duration. VLDL+LDL are the main carriers of cholesterol to the adrenals and adipose tissue, where there are receptors requiring Apo B-100 that are able to take in the VLDL+LDL by a similar process to that occurring in liver[36]. Higher concentrations of VLDL+LDL cholesterol as observed in the untreated diabetic group of this study have been associated with increasing severity of cardiovascular disease, although the experimental correlations are not as good as for HDL[11,12]. However, treatment with *A. vera* gel was observed to lower the elevations in the VLDL+LDL cholesterol, suggesting that it may reduce the risks of cardiovascular diseases, commonly associated with diabetes.

The lipid concentrations of RBC, RBC membrane and the various organs (liver, kidney, ileum and jejunum) were significantly ($p < 0.05$) reduced in the diabetic control groups compared to the control. The body obtains glucose from three main places: the intestinal absorption of food, the breakdown of glycogen, the storage form of glucose found in the liver, and gluconeogenesis, the generation of glucose from non- carbohydrate substrates in the body[37]. Insulin plays a critical role in balancing glucose levels in the body. Insulin can inhibit the breakdown of glycogen or the process of gluconeogenesis, it can stimulate the transport of glucose into fat and muscle cells, and it can stimulate the storage of glucose in the form of glycogen[37]. However, in the presence of insulin deficiency or resistance, the cells are unable to take up glucose for use and thus have to divert to other sources of energy[37]. In such a metabolic state, glucagon becomes secreted by the alpha cells of the pancreatic islets of Langerhans[37]. Glucagon, a catabolic hormone, stimulates glycogenolysis, release of fats from adipose tissue, lipolysis and even protein degradation; all in other to supply the cells' energy needs, resulting in weight loss, increased production of ketone bodies (ketosis) that are eventually released into the blood (ketonemia) and finally have to be excreted in the urine (ketonuria)[37]. This increased breakdown of lipids maybe responsible for the observed reduction in lipid concentrations of the RBCs and in the organs. However, treatment with *A. vera* gel extract improved the lipid profiles, also in a dose dependent manner. The observed decrease in lipid concentrations may also be as a result of the insulinogenicactivity of the gel extract. Rajasekaran and Sathishsekar (2007) reported that treatment of STZ-diabetic rats with *Aloe vera* plant extract resulted in the activation of β-cells and granulation returning to normal, showing an insulinogenic effect and an increase in plasma insulin[38]. This insulinogenic activity, may also explain the antihyperglycaemic activity of *A. vera* observed on the elevated plasma lipid concentrations as an increase in plasma insulin

will cause cells to absorb more of these energy molecules, leading to a decrease in their plasma concentrations.

Though the ameliorative effects of the administered *A. vera* gel extract were observed to be dose-dependent in the measured parameters, comparing the effects after 14 days and 28 days showed no definite significant difference ($p > 0.05$), suggesting that the effects may not necessarily be time-dependent.

The results demonstrated that diabetes induces abnormalities in lipid metabolism. It also showed that oral administration of *A. vera* gel extract was able to significantly improved the lipid profiles of the various compartments to varying extent, with the 8 ml/kg b.w. dose having a more pronounced effect, comparable to that of glibenclimide (the standard drug used in this study). It can thus be concluded that oral administration of the *A. vera* gel extract possess antihyperlipidaemic activity, and improves the dyslipideamia commonly associated with diabetes. Also, the extract showed no significant negative effect on the lipid profiles, as evidenced in the lipid profiles of non-diabetic rats treated with 8 ml/kg bw *A.V* gel extract. All in all, this study shows that *A. vera* could be used safely as a therapeutic agent in the management of diabetes-induced dyslipideamia and to prevent the development of disorders relating to *Diabetes mellitus*, cardiovascular diseases among others.

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