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Effectiveness of *Aloe vera versus* Glibenclamide on Serum Lipid Parameters, Heart and Skin Lipid Peroxidation in Type-II Diabetic Rats

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Many secondary plant metabolites have been reported to possess lipid-lowering properties. *Aloe vera* which has been extensively used for medical and cosmetic purposes contains multiple constituents with potential biological activities. This study was undertaken to investigate the beneficial effects of *Aloe vera* extracts in comparison to glibenclamide on serum lipid parameters, liver glycogen and on heart and skin lipid peroxidation. Type II diabetes was induced by 100 mg/kg, streptozotocin injection to neonatal rats (n0-STZ). The diabetic rats were separated into four groups and each group was given the following samples by gavage, daily for 15 d: **I**. Diabetic (Control): 6 mL/kg phosphate buffered saline (PBS); **II**. Diabetic + *Aloe* gel: 10 mL = 63 mg/kg *Aloe vera* leaf gel extract; **III**. Diabetic + *Aloe* pulp: 500 mg/kg *Aloe* pulp extract; **IV**. Diabetic + Glibenclamide: Glibenclamide (1 mg/kg). On day 15, blood and liver, skin and heart tissues were taken from each rat. In diabetic group given *A. vera* extracts, serum total cholesterol, LDL-cholesterol, atherogenic index (AI), total lipid, sialic acid, skin and heart tissues lipid peroxidation (LPO) levels decreased, whereas serum HDL-cholesterol, liver glycogen, serum total protein levels increased, in comparison to diabetic controls. In the diabetic group given glibenclamide, AI and heart LPO which were diminished in Aloe given groups were rised, whereas HDL-cholesterol, liver glycogen which were increased in Aloe groups were reduced. These results reveal that diabetes mellitus increased oxidative damage in skin and heart tissue and that *Aloe vera* has an ameliorating effect better than glibenclamide on the oxidative stress *via* its antioxidant property. The administration of *A. vera* extracts may be also able to reduce hyperlipidemia which is one of the complications related to the risk of diabetes.

Key Words: *Aloe vera*, Glycogen, Skin lipid peroxidation, Heart lipid peroxidation, Serum lipid parameters, Type-II diabetes.

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INTRODUCTION

Diabetes mellitus is a multifactorial disease that has a significant impact on the health, quality of life and life expectancy of patients, as well as on the health care systems[1]. Currently there are over 150 million diabetics worldwide and this number is likely to increase to 300 million or more by the year 2025 due to the increase in sedentary lifestyle, consumption of energy rich diet and obesity[2,3]. Diabetes is characterized by hyperglycaemia together with biochemical alterations of glucose and lipid metabolism. Diabetes is associated with the generation of reactive oxygen species (ROS) causing oxidative damage particularly to heart, kidneys, eyes, nerves, liver, small and large vessels and gastrointestinal system. Involvement of oxidative stress is implicated in the progression of complications in diabetes mellitus. Tissue antioxidant status is reported to be an important factor in the etiology of diabetes and its complications[4].

In the last 20 years, herbal remedies[5,6] has gained interest particularly in the oral treatment of non insulin dependent diabetes. Ethnobotanical information indicates that more than 800 plants are used as traditional remedies for the treatment of diabetes, but only a few have received scientific scrutiny[7]. Among these plants, the popularity of *Aloe* species has increased over the past 20 years.

Aloe vera (L.) Burm. fil. (synonym *A. barbadensis* Miller) belongs to the Liliaceae family, of which there are about 420 species[8]. This plant is native in Africa but is now indigeneous to dry sub-tropical climates including the south of Turkey. *Aloe* species have been used for centuries for their various healing properties[9]. *Aloe vera* is also widely used for various cosmetic and nutraceutical purposes. The plant was shown to possess wound and burn healing[10], antiinflammatory[9] antibacterial[11] and antitumor activities[12]. There have also been reports on the antidiabetic activity of *Aloe* extracts[13,14]. The extract obtained from the parenchymatous gel is mostly used for these purposes. In our previous studies[15-19], the blood glucose lowering effect of *Aloe vera* leaf pulp and gel extracts as well as the effect of the same extracts on the antioxidant systems of lens, liver, kidney and pancreas in n0STZ-induced type-II diabetic rats were reported.

The present study was undertaken to assess the effect of *Aloe vera* leaf gel and pulp extracts on liver glycogen and serum lipids and sialic acid of type II diabetes in n0STZ-induced diabetic rats and to compare these effects with the known antidiabetic drug glibenclamide. In addition, the purpose of this study was to investigate whether *Aloe vera* leaf gel and pulp extracts have a protective effect on the heart and skin of diabetic rats and whether this effect is related to the oxidative/antioxidative system.

EXPERIMENTAL

Specimens of *Aloe vera* (L.) Burm. fil. (Arabic: Sabr, Sabar, Saber; Turkish: Sarisabir; Hindi: Gwarparha, Ghritkumari) were collected from Kale (Demre) in Antalya, identified by N. Sütlüpinar and cultivated in the greenhouse of the Faculty of Pharmacy, Istanbul University. Voucher specimen was deposited in the Herbarium of the Faculty of Pharmacy, Istanbul University (ISTE). Herbarium code number: ISTE-65118. Fresh leaves of this cultivated plant were used in this study.

Preparation of the samples: *A. vera* leaves were weighed, washed and cut from the middle, the gel was separated by scratching with a spoon.

(a) *Aloe vera* leaf gel extract: The gel was homogenized in a Waring blender, then diluted with an equal volume of phosphate buffered saline (PBS) and homogenized for a second time. The extract was kept at 4 ºC overnight, then filtered through cloth. The clear filtrate was kept at -20 ºC in small portions.

(b) *Aloe vera* leaf pulp extract: The leaf pulps were cut in small pieces and homogenized with PBS by means of Moulinex Masterchief blender. The extract was kept at 4 ºC overnight, then filtered through cloth and the filtrate centrifuged at 20 000 rpm for 0.5 h at 2 ºC in a refrigerated centrifuge (Cryofuge 20-3 Heraeus-Christ). The green pellet was discarded and the clear yellow supernatant was taken and lyophilized (Labconco apparatus). 7.5 % *Aloe* leaf pulp extract was prepared by dissolving the powder in PBS and mixing thoroughly *via* magnetic stirrer.

(c) Glibenclamide suspension: 5 mg glibenclamide was suspended in 21 mL PBS, 4 mL propylene glycol was added and the mixture was kept in an ultrasonic water bath for 45 min until a homogenous suspension was obtained.

Type-II diabetic model: The experiments were reviewed and approved by Animal Care and Use Institute's Committee of the Istanbul University. To date, research on traditional antidiabetic plants has been especially focused on streptozotocin (STZ)-induced type-I diabetic rats. It is assumed that herbal medicine can only be effective as an alternative to oral hypoglycemic agents, in type-II diabetes, where pancreatic islets are not totally destroyed. That's why, n0STZ-induced type-II diabetic rats[20] were used in present investigation as well as glibenclamide, a known hypoglycemic agent, for comparison. Wistar pups were injected intraperitoneally on day 2 after birth with STZ, 100 mg/kg, freshly dissolved in cold citrate buffer (1 mM, pH 4.5). These animals were controlled for occurence of diabetes after 6 weeks and the diabetics (fasting blood glucose levels 104-170 mg/dl; mean 137 mg/dl) were taken in experiment when they were 2 months old (90-120 g weight). The animals were fed with laboratory pellet and water allowed *ad libitum*.

Animal groups: Type-II diabetic rats were separated into 4 groups of 7-10 animals. Each group was given the samples cited below:

I. Diabetic (Control): 6 mL/kg PBS; **II**. Diabetic + *Aloe* gel: 10 mL = 63 mg/kg *Aloe vera* leaf gel extract; **III**. Diabetic + *Aloe* pulp: 500 mg/kg *Aloe* pulp extract; **IV**. Diabetic+Glibenclamide: Glibenclamide (1 mg/kg).

Administration of samples: Each group of animal was administered daily during 15 d, the above mentioned extracts by oral gavage under mild ether anesthesia. The animals were sacrificed on the 15th day. Blood and liver, skin and heart tissues samples were taken from all groups. Each tissue sample was homogenized in saline solution (1/10 w/v) by means of a glass homogenizer. The homogenates were centrifuged in a Hereaus refrigerated centrifuge (4000 rpm/10 min) at 4 ºC. The clear supernatants were used for lipid peroxidation (LPO) and protein analysis.

Biochemical assays: Serum total lipid and cholesterol levels were evaluated by the methods of sulpho-phospho-vanillin[21] and acetic anhydride/ sulphuric acid[22], respectively. HDL-cholesterol was measured using phosphotungstic acid-magnesium chloride mixture[23] and LDL-cholesterol was calculated according to the Friedwald formula[24]. Serum triglyceride concentration was measured colorimetrically as reported by Soloni[25].

Atherogenic index (AI) was calculated according to the formula[26] given below:

$$AI = \frac{(\text{mg \% cholesterol} - \text{mg \% HDL-cholesterol})}{\text{mg \% HDL-cholesterol}}$$

Serum sialic acid was determined by Warren's method with slight modifications[27]. Skin and heart tissue LPO levels were determined by the method of Ledwozyw *et al.*[28]. The tissue homogenates were boiled with thiobarbituric acid, then extracted with *n*-butanol. The thiobarbituric acid reactive substances (TBARS), which are undertaken as index of lipid peroxidation, were measured at 532 nm and expressed as malondialdehyde (MDA), nmol MDA/mg protein. Protein contents in serum and tissues were determined by the Lowry method using bovine serum albumin as standard[29]. Glycogen was determined directly in liver tissue by the colorimetric anthrone method[30]: Liver tissue was digested in hot concentrated 30 % KOH, precipitated with ethanol, hydrolyzed and glycogen was determined as reducing sugar in the hydrolyzate.

Statistical evaluation: The results were evaluated using an unpaired t-test, Anova variance analysis and regression analysis using the NCSS statistical computer package. A p value less than 0.05 was considered as significant.

RESULTS AND DISCUSSION

Table-1 shows the levels of serum cholesterol, HDL-cholesterol, LDL-cholesterol and cholesterol/HDL ratio in experimental groups of rats. There was a significant difference in the serum total cholesterol, HDL- and LDL-cholesterol and cholesterol/HDL ratio between groups (Table-1). In the control diabetic groups, an increase in total cholesterol, LDL-cholesterol and cholesterol/HDL ratio were observed. But, HDL-cholesterol levels were significantly reduced in the diabetic control animals compared to the other groups (P_{Anova} = 0.015). The total cholesterol and LDL-cholesterol and cholesterol/HDL ratio in diabetic + *Aloe* extracts exhibited a decrease compared to the diabetic control group. The decrease produced by glybenclamide was insignificant, showing that *Aloe* extracts were more effective than glibenclamide for all parameters (Table-1). HDL-cholesterol levels in blood serum were significantly decreased in the diabetic animals as compared to the other groups (P_{Anova} = 0.015). Treatment with *Aloe* extracts for 15 d increased the serum HDL-cholesterol levels in diabetic rats contrarily, this beneficial effects was not seen by glibenclamide treatment. Atherogenic index (AI) was significantly decreased in diabetic + *Aloe* extracts compared to the control whereas the contrary is true for diabetic + glibenclamide group. The changes in serum total lipid, triglyceride (TG), LDL/HDL, HDL/TG levels are given in Table-2. There was a significant difference in the serum total lipid and LDL/HDL levels between groups (Table-2). Administration of *Aloe* extracts was found to reduce total lipid, LDL/HDL in diabetic rats. But in diabetic + glibenclamide rats, an insignificant increase in serum LDL/HDL levels was observed. *Aloe* extracts and glibenclamide administration did not significantly effect serum triglyceride (TG) levels showing that *Aloe* extracts as well as glibenclamide did not effect dietary fat intake. In diabetic rats treated with *Aloe* extracts, HDL/TG levels increased when compared to the untreated diabetic rats whereas the same ratio was decreased in diabetic + glibenclamide group. *Aloe* extracts were again more effective than glibenclamide (Table-2).

Serum sialic acid levels were higher in diabetic control groups when compared to other groups (Table-3). Oral administration of *Aloe* extracts decreased significantly serum sialic acid levels in diabetic rats (Pt-test = 0.073, Pt-test = 0.036) whereas the decrease produced by glibenclamide was insignificant. Serum total protein levels were lower in diabetic groups when compared to other groups. Oral administration of *Aloe* extracts and glibenclamide increased insignificantly the serum total protein levels in diabetic rats (Table-3).

As shown in Table-4, a significant difference was observed in liver glycogen levels between treated groups and untreated type-II diabetic rats (P_{Anova} = 0.033). Liver glycogen levels were increased significantly in the

TABLE-1
SERUM TOTAL CHOLESTEROL, HDL-CHOLESTEROL, LDL-CHOLESTEROL, CHOLESTEROL/HDL LEVELS AND ATHEROGENIC INDEX (AI) IN TYPE-II DIABETIC RATS FOR ALL GROUPS

Group	Total chol. (mg/dL)	$P_{t\text{-test}}$	HDL-chol. (mg/dL)	$P_{t\text{-test}}$	LDL- chol. (mg/dL)	$P_{t\text{-test}}$	Chol./ HDL	$P_{t\text{-test}}$	AI	$P_{t\text{-test}}$
Diabetic (Control)	156.68 ± 7.88		57.66 ± 8.02		122.95 ± 0.90		3.57 ± 0.33		1.86 ± 0.08	
Diabetic+*Aloe* gel	122.36 ± 8.84	0.0040	77.05 ± 0.07	0.003	89.81 ± 2.80	0.004	1.52 ± 0.04	0.0001	0.52 ± 0.04	0.0001
Diabetic (Control)	156.68 ± 7.88		57.66 ± 8.02		122.95 ± 0.90		3.57 ± 0.33		1.86 ± 0.08	
Diabetic+*Aloe* pulp	109.46 ± 7.98	0.0001	70.40 ± 7.79	0.120	83.44 ± 2.35	0.002	1.71 ± 0.29	0.0001	0.71 ± 0.29	0.0001
Diabetic (Control)	156.68 ± 7.88		57.66 ± 8.02		122.95 ± 0.90		3.57 ± 0.33		1.86 ± 0.08	
Diabetic+Glibenclamide	143.02 ± 6.57	0.1060	48.40 ± 2.26	0.285	120.76 ± 8.43	0.750	3.02 ± 0.72	0.4060	2.02 ± 0.72	0.6190
P_{Anova}	0.0001		0.015		0.002		0.008		0.015	

Mean ± SD

TABLE-2
SERUM TOTAL LIPID, TRIGLYCERIDE (TG), LDL/HDL AND HDL/TG LEVELS IN TYPE-II DIABETIC RATS FOR ALL GROUPS

Group	Total lipid (mg/dL)	$P_{t\text{-test}}$	TG (mg/dL)	$P_{t\text{-test}}$	LDL/HDL	$P_{t\text{-test}}$	HDL/TG	$P_{t\text{-test}}$
Diabetic (Control)	382.81 ± 12.61		62.94 ± 2.43		1.62 ± 0.04		0.90 ± 0.38	
Diabetic+*Aloe* gel	338.75 ± 5.39	0.0001	61.08 ± 2.32	0.504	1.16 ± 0.04	0.008	1.25 ± 0.04	0.411
Diabetic (Control)	382.81 ± 12.61		62.94 ± 2.43		1.62 ± 0.04		0.90 ± 0.38	
Diabetic+*Aloe* pulp	354.37 ± 9.39	0.0060	64.61 ± 0.95	0.330	1.18 ± 0.27	0.094	1.086 ± 0.21	0.522
Diabetic (Control)	382.81 ± 12.61		62.94 ± 2.43		1.62 ± 0.04		0.90 ± 0.38	
Diabetic+Glibenclamide	338.27 ± 4.34	0.0010	62.85 ± 0.02	0.988	2.55 ± 0.67	0.188	0.77 ± 0.15	0.575
P_{Anova}	0.0001		0.286		0.028		0.338	

Mean ± SD

TABLE-3
SERUM SIALIC ACID AND TOTAL PROTEIN LEVELS OF TYPE-II DIABETIC RATS FOR ALL GROUPS

Group	Sialic acid (mmol/L)	$P_{t\text{-test}}$	Total protein (g/dL)	$P_{t\text{-test}}$
Diabetic (Control)	2.56 ± 0.30		4.54 ± 0.48	
Diabetic + *Aloe* gel	2.02 ± 0.36	0.073	4.84 ± 0.20	0.382
Diabetic (Control)	2.56 ± 0.30		4.54 ± 0.48	
Diabetic + *Aloe* pulp	2.19 ± 0.15	0.036	4.76 ± 0.26	0.523
Diabetic (Control)	2.56 ± 0.30		4.54 ± 0.48	
Diabetic + Glibenclamide	2.36 ± 0.82	0.619	4.93 ± 0.11	0.209
P_{Anova}	0.401		0.376	

Mean ± SD

TABLE-4
GLYCOGEN LEVELS IN LIVER TISSUE OF TYPE-II DIABETIC RATS FOR ALL GROUPS

Group	Glycogen (mg/100 mg)	$P_{t\text{-test}}$
Diabetic (Control)	40.2 ± 4.38	
Diabetic + *Aloe* gel	58.6 ± 13.2	0.018
Diabetic (Control)	40.2 ± 4.38	
Diabetic + *Aloe* pulp	41.5 ± 14.51	0.836
Diabetic (Control)	40.2 ± 4.38	
Diabetic + Glibenclamide	38.5 ± 2.64	0.502
P_{Anova}	0.033	

Mean ± SD

group given *Aloe* gel extract compared to diabetic controls (Pt-test = 0.018), no significant difference was observed in the groups treated with *Aloe* pulp extract and glibenclamide.

The LPO levels in skin and heart tissues were insignificantly higher in diabetic rats than the other groups ($P_{Anova} = 0.095$, $P_{Anova} = 0.077$). Compared to the diabetic control group results, LPO levels in skin tissue were decreased in groups given *Aloe* gel and pulp extracts and glibenclamide (Table-5). In heart tissue, *Aloe* pulp and gel extracts insignificantly reduced LPO levels in comparison to diabetic controls, whereas the increase with glibenclamide was also found insignificant (Table-5).

Diabetes mellitus is probably the fastest growing metabolic disease in the world and as knowledge of the multifactorial/heterogeneous nature of the disease increases so does the need for more challenging and appropriate therapies[31]. Traditional plant remedies have been used throughout the world for a range of diabetic complications[32]. Plant drugs are frequently considered

TABLE-5
LIPID PEROXIDATION LEVELS IN SKIN AND HEART TISSUES OF TYPE-II DIABETIC RATS FOR ALL GROUPS

Group	Skin LPO (nmol MDA/ mg protein)	$P_{t\text{-test}}$	Heart LPO (nmol MDA/ mg protein)	$P_{t\text{-test}}$
Diabetic (Control)	5.97 ± 1.26		1.35 ± 0.18	
Diabetic + *Aloe* gel	4.46 ± 0.95	0.077	0.99 ± 0.39	0.102
Diabetic (Control)	5.97 ± 1.26		1.35 ± 0.18	
Diabetic + *Aloe* pulp	4.18 ± 1.22	0.045	1.01 ± 0.38	0.100
Diabetic (Control)	5.97 ± 1.26		1.35 ± 0.18	
Diabetic + Glibenclamide	4.43 ± 0.94	0.058	1.46 ± 0.18	0.521
P_{Anova}	0.095		0.077	

Mean ± SD

to be less toxic and free of side effects than synthetic ones. In previous studies[15], treatment with *Aloe vera* extracts showed a hypoglycemic effect on diabetic rats. Therefore, in order to assess the mechanism of this effect, in this study we have investigated the effect of *Aloe vera* extracts on serum lipid profile, liver glycogen and biomarkers of oxidative stress in skin and heart tissues of diabetic rats.

Lipid profile was shown to be altered in the serum of diabetic patients[33] and rats[34]. In the present study, diabetic rats exhibited hypertriglyceridemia, hypercholesterolemia and hyperlipidemia, while *Aloe* extracts treatment significantly decreased serum total cholesterol, total lipid levels and LDL-cholesterol levels as well as increased serum HDL-cholesterol levels, suggesting that *Aloe vera* extracts could improve the disorder of lipid metabolism in diabetes[35].

Significant lowering of total cholesterol, total lipid, LDL-cholesterol and rise in HDL-cholesterol is a very desirable biochemical state for prevention of atherosclerosis and ischemic condition. The same facts are true for people with type II diabetes[35]. Various studies on medicinal plants have reported a similar lipid lowering activity[36]. Few studies about the effect of *Aloe* on lipid profile are cited in literature[37]. HDL-cholesterol is recognized as a factor that protects against development of atherosclerotic disease and low HDL-cholesterol is associated with an increased risk of cardiovascular heart disease in individuals both with and without diabetes. Total cholesterol/ HDL, LDL/HDL-cholesterol and HDL/TG ratios are also predictor of coronary risk[38]. In the present study, it was observed that *Aloe* extracts had positive effect on these ratios. From these results, we can assume that *Aloe* extracts might have some protective effects against cardiovascular disease risk in diabetes. In present study diabetic rats exhibited abnormality in

lipid metabolism as evidenced from the significant elevation in atherogenic index. Treatment with *Aloe* extracts for 15 d significantly decreased atherogenic index in diabetic rats indicating its potent antihyperlipidemic and antiatherogenic activities. The present finding is desirable biochemical state for prevention of atherosclerosis.

Serum total sialic acid has received considerable attention as a possible marker for cardiovascular disease and mortality[39]. Various factors might cause an elevation in the concentration of serum sialic acid. Among these factors, the first is an increase in the synthesis of sialic acid in insulin-independent tissues, such as the liver and the brain and the second is an increase in the activity of sialiltransferase, which transfers the sialic acid residues to the glycolipids and glycoproteins[40]. The inhibitory action of *Aloe* extracts on serum sialic acid level which was increased in diabetic rats could be associated with reduced risk of cardiovascular disease in diabetes.

Lipid, carbohydrate and protein metabolisms are altered in diabetes. These alterations can result in liver damage. It is well known that serum total protein levels are decreased in this case. In this study, the fact that *Aloe* extracts increased serum total protein levels is in accordance with our previous study on the beneficial effect of *Aloe* on liver function[17].

Liver plays an important role in buffering the postprandial hyperglycemia and is involved in synthesis of glycogen[41]. Insulin is the main regulator of glycogenesis in liver. The decrease in hepatic glycogen content in diabetes has been reported[42]. The decrease in hepatic glycogen observed in diabetic control group is probably due to the lack of insulin in diabetic state which results in the inactivation of glycogen synthase systems. The significant increase in the glycogen levels of the *Aloe vera* extract treated diabetic animals may be due to the reactivation of glycogen synthase systems. This focus is the one possible way of antidiabetic action of this extract by improvement of glycogenesis process[43]. Along with hyperglycaemia and abnormalities in serum lipids, diabetes is associated with a significant increase in thiobarbituric acid reactive substances (TBARS) which are considered as an index of endogenous lipid peroxidation[44].

Lipid peroxidation is a marker of cellular oxidative damage initiated by reactive oxygen species[45]. Over the long term, hyperglycemia generates a large number of ROS which induce cell oxidative stress[46]. ROS are the main factors which generate LPO. Free radicals attack double bonds of polyunsaturated fatty acids and decompose lipids in small molecules such as malondialdehyde[47]. LPO is supposed to cause the destruction and damage of cell membranes leading to changes in membrane permeability and fluidity, enchancing the protein degradation rates. Previous studies have reported that there was an increased lipid peroxidation in liver[17,32], kidney[18], lenses[48], heart[49] and skin[50] of diabetic rats.

Skin is a major candidate and target of oxidative stress. In diabetes, increased lipid peroxidation damage skin integrity and decrease resistance against harmful substances[51]. In contrast to clinical reports of the useful activity with *Aloe* gel[10], there were also a few cautionary accounts on its harmful effect[52]. However all these studies were undertaken with topical application of the gel and to our knowledge this is the first study treating with the effect of *Aloe* leaf gel and pulp extracts on the skin LPO, after oral treatment. The results of the present study show that *Aloe* extracts have a beneficial effect on skin and heart by lowering LPO levels. This indicates that *Aloe* extracts may inhibit oxidative damage of skin and heart tissues. Antioxidant effects have been reported for some plants that contain several compounds like flavonoids, phenolic compounds, ascorbic acid and tocopherol[51]. The effectiveness of *Aloe* may be due to its polysaccharides[53], antioxidant enzymes[54], phenolic compounds[55], aloesin derivatives[56], reported as antioxidants in literature.

As a result, it may be concluded that, probably due to its antioxidant effects *Aloe* extracts are more effective in comparison to glibenclamide in the protection of serum lipid profile and of skin and heart tissues from the damage of diabetes.

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