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Hypoglycemic and Hypolipidemic Activities of *Aloe vera* Leaf Mucilage in Alloxan-Induced Diabetic Rats

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Abstract

The present study aimed to evaluate the hypoglycemic and hypolipidemic activities of *Aloe vera* mucilage in alloxan-induced diabetic rats. Adult male Wistar rats were assigned into 4 groups (6 rats/group), as follows: the first group (C) served as the controls. The second group of rats (AL) received a single subcutaneous dose of alloxan at 120 mg kg^{-1}bw. These groups received 1 mL of NaCl 9%. The third group (AL+Av) represented diabetic rats treated with 1 mL of mucilage extracted from *Aloe vera* leaves. The fourth group (C+Av) corresponded to control rats administered with 1 mL of *Aloe vera* mucilage. NaCl or *Aloe vera* mucilage were intraperitoneally injected to the rats.
Diabetic rats exhibited significant hyperglycemia accompanied by glycosuria. We also observed a significant reduction in the liver weight and glycogen content of the specimen. A reduced level of serum insulin was also observed among diabetic rats. However, the levels of serum triglycerides and total cholesterol increased in alloxan-induced diabetic rats. *Aloe vera* mucilage administration to diabetic rats partially and totally corrected glycaemia and liver glycogen content and serum insulin level, respectively. The rats' lipid status has also been improved. Medicinal plants, including *Aloe vera,* are expected to correct hyperglycemia and hyperlipidemia in diabetic patients to prevent the adverse effects of synthetic drugs.

Keywords: *Aloe vera*, Diabetes Mellitus, Rats, Liver, Insulin secretion

Introduction

Diabetes Mellitus (DM) is a prevalent metabolic disorder characterized by high blood glucose levels, predisposing to cardiovascular diseases (1). It is the underlying cause of approximately 5% of all deaths worldwide annually (2). This disease is due to insufficient insulin production or the lack of insulin action. There are two types of DM. Type 1 diabetes or Insulin-Dependent Diabetes Mellitus (IDDM) results from an absolute lack of insulin; it is diagnosed in late childhood. Patients with this diabetes type require regular insulin administration and a healthy diet. However, repeated insulin administration before every meal can lead to severe complications, including severe hypoglycemia. Type 2 diabetes, recognized as Non-Insulin-Dependent Diabetes Mellitus (NIDDM) is featured by peripheral insulin resistance. In fact, despite hyperinsulinemia, there is a lack of insulin effect. Obesity is a common symptom of type 2 diabetes. This disease may be controlled by a healthy diet and oral hypoglycemic medications, such as sulfonylureas, thiazolidinediones, biguanides, and alpha-glucosidase inhibitors. The continued administration of synthetic therapeutic agents could be associated with undesirable effects (3). Thus, there is a growing interest in applying traditional medicinal plants and other dietary supplements to manage diabetes (4).
Plants play a crucial role in preserving human health; they represent an essential part of the diet and significantly contribute to the treatment of many ailments (5-6). In developed countries, over 25% of the prescribed drugs come from plant species (7-9). According to the World Health Organization (WHO), about three-quarters of the African, Asian, and Latin America countries' populations rely on plant-based preparations in their traditional healthcare systems (10-13). Such data emphasized the need to explore novel and efficient plant-derived compounds for commercialization. *Aloe* is a succulent plant belonging to the *Liliacea* family.

It comprises more than 200 species around the world (14). *Aloe vera*, also known as *Aloe barbadensis*, is the most widely used species of the genus Aloe. It has antioxidant, anti-inflammatory, anti-tumor, and laxative properties. Moreover, it has been used for centuries in pharmaceutical and cosmetic products (15, 16). *Aloe vera* leaves contain numerous bioactive compounds, including anthraquinones, carbohydrates, enzymes, non-essential, and essential amino acids, minerals, and vitamins (17). The present work aimed to investigate the hypoglycemic and hypolipidemic activities of *Aloe vera* mucilage in alloxan-induced diabetic rats for the first time.

Materials and methods

Plant material and mucilage preparation

Aloe vera fresh leaves were collected in September from Kairouan City, Tunisia. The plant was botanically identified, according to the flora of Tunisia, by Mrs. Wided Chaibi, Professor of Vegetal Biology at the Faculty of Sciences of Tunis. The mucilage extracted from *Aloe vera* fresh leaves was scraped, grounded, then, filtered on Büchner.

Animals

The experimental protocol was performed by the general guidelines concerning the use and care of laboratory animals (18). Animals' handling was approved by the Committee for Ethics of Sfax Sciences Faculty (ethics approval number: 1204).

Adult male rats of Wistar strain (15 weeks old, weighing 200–250 g) were obtained from the Central Pharmacy (SIPHAT, Tunis, Tunisia). They were housed under standard laboratory conditions (ambient temperature: 21 ± 1 °C, relative humidity: 40%, photoperiod cycle: 12:12 h light-dark). Furthermore, they were kept acclimating for 1 week before the experiments' onset. Animals had unrestricted access to food (SNA, Sfax, Tunisia) and water.

Induction of experimental diabetes

DM was experimentally induced in overnight fasting rats (for 12 h) by injecting a single subcutaneous dose (120 mg kg^{-1}bw) of alloxan monohydrate dissolved in distilled water. The development of diabetes was firstly recognized by observing polyuria and polydipsia. After 48 h of alloxan injection, blood glucose levels were measured using a glucometer (Esprit 2, BAYER, France). Only rats having fasting blood glucose levels >200 mg/dL were considered as diabetic and selected for the experiment. However, rats with fasting blood glucose levels <200 mg/dL were excluded from the study.

Experimental design

The study rats were assigned into 4 groups of 6 animals each. The first group (C) served as the negative control, where rats Intraperitoneally (IP) received daily 1mL of saline solution. The second group (C + Av) received daily 1 mL (IP) of *Aloe vera* mucilage and served as the positive controls. The third group (AL) constituted alloxan-induced diabetic rats. The fourth group (AL + Av) included diabetic rats, which were daily administered with 1 mL (IP) of *Aloe vera* mucilage.

During the experimental period (three weeks), all rats survived. Then, they were sacrificed by decapitation to avoid animal stress. Blood samples were collected; then, centrifuged at 2200×g for 15 min. The obtained serum samples were maintained at -20 °C until use for the biochemical assays. Some portions of rats' hepatic tissues of all groups were collected to determine their glycogen contents.

Biochemical assays

Estimation of liver glycogen content: Liver glycogen content was spectrophotometrically measured at 620 nm using O-toluidine reagent (19).

Determination of glucose level: Serum glucose levels were determined by enzymatic methods, using commercially available reagent Kits (Biomaghreb, Tunisia, Ref. 20121).

Determination of serum insulin concentration: The measurement of serum insulin concentration was performed using rat insulin Enzyme-Linked Immunosorbent Assay (ELISA) kit (Ref. RIT-461 No. AKRIN-010T, Shibayagi, Co., Ltd, Japan.).

Serum total cholesterol and triglycerides levels: Serum total cholesterol and triglycerides levels were assayed applying commercially available reagent kits (Biomaghreb, Tunisia, Ref. 20111; 20131, respectively).

Glucose Tolerance Test (GTT): GTT was performed in the control and treated rats 24 h prior to the sacrifice day. Blood samples were collected from the tail vein of overnight fasted rats (the control and treated groups) to obtain baseline blood glucose levels. Thereafter, glucose was injected IP at a dose of 2 g kg^{-1}bw to the control and treated rats. Blood was obtained from the rats' tail vein at 30, 60, and 120 min after glucose loading. Furthermore, blood glucose levels were estimated using a glucometer (Esprit 2, BAYER, France).

Statistical analysis

The obtained data were expressed as mean±SD. They were subjected to a one-way Analysis of Variance (ANOVA), followed by Fisher's protected least significant difference test, as a posthoc test for between-group comparisons, using StatView. Differences were considered as statistically significant at $P<0.05$.

Results

Blood glucose levels and daily water consumption

Regarding table 1, alloxan administration to adult rats at 120 mg kg^{-1}bw increased the blood glucose level by 151% in two days, compared to the control rats. This parameter remained high throughout the first and second weeks of treatment, reaching a rate of 345 mg/dL; It corresponded to an increase of 46%, compared to the value obtained after 48h. The treatment of diabetic rats by *Aloe vera*

mucilage reduced blood glucose levels by 27% and 61% after 7 and 14 days of treatment, respectively. The administration of the *Aloe vera* mucilage for 21 days to the control rats slightly changed (+11%) the serum glucose level (P<0.05).

Our results revealed a significant increase (+82%) in the daily water consumption of alloxan- diabetic rats, after one week of treatment, compared to the controls. This effect was accompanied by a polyuria estimated to 64 mL/diabetic rats, as reported by our previous study (19). Over the last two weeks of the experimental period, the daily water consumption of diabetic rats was more pronounced. We also noted a significant decline in drinking water consumption, which was more pronounced after 14 and 21 days of treatment with the *Aloe vera* mucilage, compared to the diabetic rats (Table 2).

Hepatic glycogen content

The achieved results revealed that alloxan treatment provoked a significant decrease in the liver weight (-26%) and glycogen content (-89%), compared to the controls. Administrating *Aloe vera* mucilage increased the liver weight (+11%) and its glycogen content (+104%), compared to those of the diabetic animals, exceedingly even the control values. Compared to the negative control group, positive control group treated with *Aloe vera* mucilage demonstrated no change in the liver weight and its glycogen content (Table 3).

Serum insulin level

In alloxan-diabetic rats, serum insulin levels were significantly reduced by 41%,compared to the controls.

This parameter indicated a significant increase (+40%w) when *Aloe vera* mucilage was administered to the diabetic rats. The serum insulin level of positive control group treated with the *Aloe vera* mucilage was not statistically different from that of the negative control group (Figure 1).

Lipid profile

Regarding Table 3**,** after 21 days of treatment, alloxan administration increased the serum levels of triglycerides and total cholesterol by 76% and 22%, respectively,

Table 1. Blood glucose level (mg/dL) at 2, 7, 14, and 21 days after the daily administration of crude *Aloe vera* mucilage in the normal and alloxan-diabetic rats

Groups	**Blood glucose (mg/dL)**			
	2nd day (initial) (mean ± SD)	**7th day (mean ± SD)**	**14th day (mean ± SD)**	**21st day (final) (mean ± SD)**
Controls	93.6 ± 15.8	76.3 ± 2.5	91 ± 8	113.4 ± 7.31
C +Av	87.6 ± 4.5	80.3 ± 2.5	92.3 ± 12.5	125.5 ± 10*
AL	235.6 ± 16.1***	256 ± 46***	305 ± 22***	345.0 ± 26***
AL + Av	255.6 ± 22***	186 ± 5***	118.3 ± 7.5 ###*	117.4 ± 11 ###*

Each value represents score of the mean ± SD score of 6 serum samples per group.
Treated groups (AL); (AL + Av); (C + Av) vs control group (C): *P<0.05; ***P<0.001.
(AL + Av) group vs. (AL) group: ###P<0.001.

Table 2. Drinking water intake (mL/day/rat) at 7, 14, and 21 days after the daily administration of crude *Aloe vera* mucilage in the normal and alloxan-diabetic rats

Groups	**7thday**	**14thday**	**21stday**
Drinking water intake (ml/day/rat)			
Controls	22.33 ± 2.70	20.21 ± 2.29	19.66 ± 0.70
C +Av	27.63 ± 7.93	21.69 ± 8.60	23.08 ± 1.06
AL	40.76 ± 8.08***	61.12 ± 5.69***	67.33 ± 3.29***
AL + Av	32.54 ± 9.67 #**	45.07 ± 3.68 ## **	49.41 ± 2.94 ##**

Each value represents the mean±SD score of 6 serum samples per group.
Treated groups (AL); (AL + Av); (C + Av) vs. control group (C): **P<0.01; ***P<0.001.
(AL + Av) group vs. (AL) group: #P<0.05; ##P<0.01.

Table 3. Liver weight (g), hepatic glycogen levels (mg/g), blood glucose level (mg/dL), serum triglycerides and total cholesterol levels (mg/dL) after the daily administration of crude *Aloe vera* mucilage in the normal and alloxan-induced diabetic rats

Groups	Controls	C + Av	AL	AL + Av
Liver weight (g)	12.52 ± 1.05	12.08 ± 1.02	9.20 ± 2.16***	10.30 ± 2.10##*
Hepatic glycogen (mg/g)	29.63 ± 4.54	29.08 ± 2.60	3.17 ± 0.92***	36.24 ± 3.18###
Blood glucose (mg/dL)	113.50 ± 7.03	125.90 ± 10.07*	345.00 ± 26.6***	117.4 ± 12.00###*
Triglycerides (mg/dL)	100.42 ± 6.77	108.97 ± 6.09*	176.98 ± 14.34***	113.78 ± 20.38###
Cholesterol (mg/dL)	54.97 ± 3.11	52.34 ± 3.42	67.46 ± 3.80***	50.76 ± 4.11###

Each value represents the mean±SD score of 6 serum samples per group.
Treated groups (AL); (AL + Av); (C + Av) vs. control group (C): *P<0.05; ***P<0.001.
(AL + Av) group vs. (AL) group: ##P<0.01; ###P<0.001.

compared to the control rats. Administrating *Aloe vera* mucilage countered the rise of these parameters, compared to the diabetic rats. Compared to the negative control group, treating positive control group with the *Aloe vera* mucilage alone had no effect on the serum level of total cholesterol; while it caused a slight change (11%) in that of triglycerides (P<0.05).

Glucose tolerance test

Figure 2 showed the effects of *Aloe vera* mucilage on Glucose Tolerance Test (GTT). After 1 h of glucose (2 g kg^{-1}bw) administration, blood glucose levels reached a peak in the diabetic rats. Although glucose levels started to decline, they remained high after 2 h. In diabetic rats administered with *Aloe vera* mucilage, we observed a significant decrease (-40%) in glucose levels at 120 min, compared to the values recorded at 30 and 60 min.

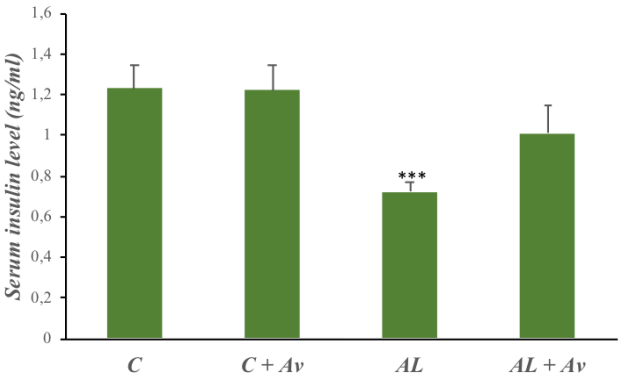

Figure 1 Serum insulin level (ng/ml) after the daily administration of crude *Aloe vera* mucilage in the normal and alloxan-induced diabetic rats.
Each value represents the mean ± SD of 6 serum samples per group.
Treated groups (AL); (AL + Av); (C + Av) vs control group (C): *P < 0.05; ***P < 0.001. (AL + Av) group vs (AL) group: ##P< 0.01.

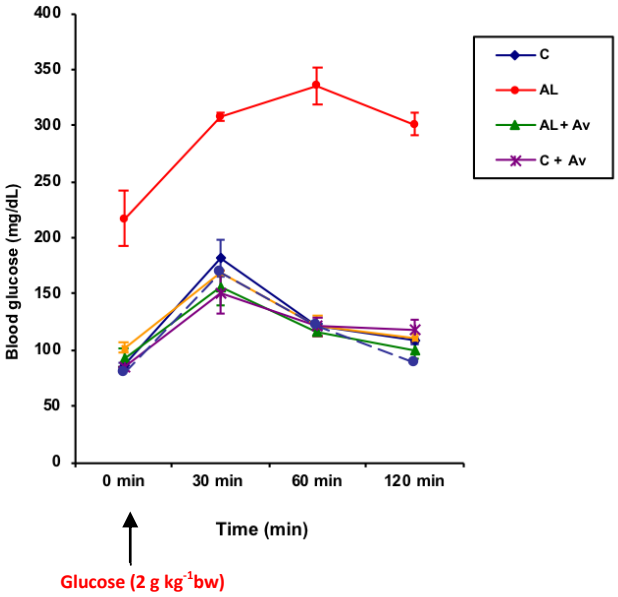

Figure2 Glucose tolerance test in control rats (C), diabetic rats (AL), diabetic rats co-treated with Aloe vera mucilage (AL+Av) and rats treated with Aloe vera mucilage (C+Av) before the intraperitoneal injection of glucose (2 g kg-1bw) and after 30, 60 and 120 min of the injection. The number of rats per group is 6.

Discussion

The obtained data suggested that alloxan induced a significant hyperglycemia along with glycosuria in the experimental rats. In fact, in alloxan diabetic rats, blood glucose level reached a value of 345 mg/dL. This result exceeds the renal threshold for glucose reabsorption corresponding to 180 mg/dL; the value at which glucose spills into the urine. These findings concurred with the previous results of Verma et al. (20). This could be explained by the destruction of pancreatic beta cells following the administration of alloxan; in turn, it provoked insulin deficiency as reported by Leite et al.

(21). Decreased serum insulin levels in alloxan-treated rats in our study supported these findings. Hyperglycemia in DM caused diverse derangements in metabolic and regulatory processes, which increased the osmotic pressure, accordingly. This hyperosmolarity could be detected by hypothalamic osmoreceptors localized in the supraopticnuclei, which discharged ADH, an antidiuretic hormone, causing water retention and thirst sensation. Our data highlighted that alloxan treatment significantly increased daily water consumption accompanied by an important polyuria. The *Aloe vera* mucilage property to decrease the blood glucose level might be due to its bioactive substances, such as polysaccharides and glycoproteins. With hypoglycemic effects, such sibstances consequently potentiate insulin secretion from the few surviving pancreatic beta cells, as described by Hikino et al. (22) and Beppu et al. (23). To our knowledge, the anti-diabetic effect of *Aloe vera* mucilage has not been documented. Limited studies have investigated the pulp of *Aloe vera* leaves without gel (24) and the alcoholic extract of *Aloe vera* gel (25). These investigations reported the anti-diabetic effects of this plant. In addition, no effects have been reported in control rats treated with *Aloe vera* mucilage. Our results clearly indicated that *Aloe vera* mucilage exerted its hypoglycemic effect only in a diabetic state. This was observed by stimulating the insulin secretory capacity of the remaining surviving pancreatic beta cells. In other words, insulin levels were increased by 40% in the diabetic rats treated with *Aloe vera* mucilage. We have also demonstrated in our previous study (26) that insulin levels increased by 78% after the administration of *Centaurium erythraea* to diabetic rats.

In the present study, the observed increase in serum glucose levels in alloxan-treated rats was accompanied by reduced liver glycogen content. This could be explained by the stimulation of glycogenolysis and inhibition of glycogenesis in the absence of insulin secretion. The treatment of diabetic rats, for 21 days with *Aloe vera* mucilage, totally corrected the liver glycogen content. This might be due to the activation of glycogen synthesis in the liver by inhibiting the activity of phosphorylase, the enzyme catalyzing glycogenolysis, and by stimulating the activity of glycogen synthase. Our findings were consistent with those of Rajasekaran et al. (27); they have reported an enhanced hepatic glycogen content following *Aloe vera* gel extract administration to streptozotocin-induced diabetic rats. Compared to the negative control group, treating control rats with the *Aloe vera* mucilage revealed no significant change in the liver glycogen content.

Similarly, the lipid status of diabetic rats has been disturbed. We observed an increase in the serum triglycerides and total cholesterol levels in the alloxan-treated rats. Such changes could be explained by an increase in lipolysis, following a decrease in insulin secretion. Metabolic derangements, leading to cholesterol and triglycerides accumulation, have been reported in insulin-deficient diabetic patients (28). According to Rodier et al. (29), the disturbed lipid status, following insulin deficiency, could be corrected by administering insulin to diabetic patients. Our study indicated that *Aloe vera* mucilage administered to alloxan diabetic rats significantly reduced serum total cholesterol and triglycerides levels. The lipid-lowering activity of *Aloe vera* might be due to its richness in polysaccharides. In fact, when applied as antilipidemic agents, coating of the abdominal wall has been suggested as a major mechanism of action of gelling polysaccharides. This is because the gelation process retards enzyme mobilization to starch hydrolysis and glucose resorption (30, 31).

We injected a saturated glucose solution to different animal groups to test their insulin resistance. In addition, the observed decrease in the blood glucose levels of control rats could be attributed to insulin secretion by beta cells, which activated glycogenesis and inhibited glycogenolysis. However, in alloxan-induced diabetic rats, the blood glucose levels remained high after two hours of saturated glucose solution injection. This might be due to insulin deficiency in diabetic rats. After their treatment with *Aloe vera* mucilage, the elevated blood glucose was progressively corrected after 2 h. These results indicated that the plant mucilage has a hypoglycemic effect, as demonstrated above. This agrees with the findings of Quanhong et al. (32). They performed an investigation on diabetic rats treated with the protein-bound polysaccharides isolated from pumpkins.

Conclusion

The collected results demonstrated that *Aloe vera* mucilage corrected hyperglycemia and hyperlipidemia in an experimental model of DM due to its richness in polysaccharides and glycoproteins. Therefore, *Aloe vera* could be employed as an effective antidiabetic agent.

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Authors' contributions

Mediha Sefi, Mariem Chaabane, and Najiba Zeghal contributed to the conception and the redaction of the paper. Mediha Sefi performed also the experimental animal study and the different assays. Moez Rafrafi prepared the crude mucilage of *Aloe vera* leaf.

Conflict of Interests

The authors declare no conflicts of interest.

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