OPEN ACCESS
Scholars International Journal of Traditional and Complementary Medicine
Abbreviated Key Title: Sch Int J Tradit Complement Med
ISSN 2616-8634 (Print) |ISSN 2617-3891 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Original Research Article

Antihyperglycemic and Histological Effect of *Aloe vera* on Alloxan-Induced Diabetes in Wistar Rats

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DOI: 10.36348/sijtcm.2023.v06i08.001 | **Received:** 14.06.2023 | **Accepted:** 19.07.2023 | **Published:** 02.09.2023

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Abstract

Introduction: Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia and is associated with various complications if not properly managed. *Aloe vera*, a medicinal plant with diverse pharmacological properties, has shown promise as a potential therapeutic intervention for diabetes. This study aimed to investigate the antihyperglycemic and histological effects of *Aloe vera* in an alloxan-induced diabetic Wistar rat model. ***Method:*** Forty-eight Wistar rats were divided into six groups and treated with different regimens of *Aloe vera* and metformin, a standard antidiabetic drug. The effects of the treatments on blood glucose levels and histology of the pancreas, liver, and kidney were evaluated. ***Result:*** The results of the study revealed that alloxan injection induced hyperglycemia and pathological changes in the pancreas, liver and kidney of Wistar rats. The treatment with 100mg/kg, 200mg/kg and 400mg/kg of *Aloe vera* significantly reduced blood glucose levels in a dose-dependent manner. Additionally, *Aloe vera* administration preserved the histological integrity of the pancreas, liver, and kidney in diabetic rats. This preservation of organ histology can be attributed to the antioxidant, anti-inflammatory, and tissue-protective properties of *Aloe vera*. ***Conclusion:*** *Aloe vera* demonstrated antihyperglycemic effects and preserved organ histology in an alloxan-induced diabetic Wistar rat model. The bioactive compounds present in *Aloe vera* are believed to contribute to these effects. *Aloe vera* holds potential as an alternative or adjunctive therapy for diabetes management, but its clinical efficacy and safety need to be further explored.

Keywords: *Aloe vera*, Diabetes mellitus, merformin, Hyperglycemia, Histology, Dose-dependent response.

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both (Unwin *et al.*, 2002; American Diabetes Association, 2021; Omeodu *et al.*, 2022). It poses a significant global health burden, affecting millions of individuals worldwide and leading to various complications if left uncontrolled (International Diabetes Federation, 2019). Consequently, extensive research is being conducted to explore potential therapeutic interventions that can effectively manage diabetes and its associated complications (Akash *et al.*, 2013).

One promising avenue of investigation is the use of natural products derived from medicinal plants. *Aloe vera*, a succulent plant belonging to the Liliaceae family, has a long history of traditional medicinal use and is known for its diverse pharmacological properties (Surjushe *et al.*, 2008). It has been extensively studied for its potential antidiabetic effects and has shown promising results in preclinical and clinical studies (Shahzad *et al.*, 2016; Oluwagbemi *et al.*, 2021). Alloxan-induced diabetes in Wistar rats is a widely accepted experimental model used to study the pathophysiology of diabetes and evaluate the efficacy of potential antidiabetic agents (Dharmalingam et al., 2004; Isirima and Uahomo, 2023). Alloxan, a beta-cytotoxic compound, selectively destroys pancreatic beta cells, leading to insulin deficiency and subsequent hyperglycemia (Khamchan *et al.*, 2012). Therefore, this model provides a valuable platform to investigate the effects of therapeutic agents on glucose homeostasis and associated histological changes in pancreatic tissue (Venkatesan *et al.*, 2005).

The present study aims to investigate the antihyperglycemic and histological effects of *Aloe vera* on alloxan-induced diabetes in Wistar rats. By examining the potential therapeutic properties of *Aloe vera* in this experimental model, we can gain valuable insights into its mechanisms of action and evaluate its potential as an alternative or adjunctive treatment for diabetes. Several studies have reported the antidiabetic effects of *Aloe vera*

in both animal models and human subjects (Rajanandh *et al.,* 2009; Shahzad *et al.,* 2016). The plant possesses various bioactive compounds, including polysaccharides, glycoproteins, anthraquinones, vitamins, and minerals, which are believed to contribute to its pharmacological activities (Choudhury *et al.,* 2019). *Aloe vera* has been shown to enhance insulin secretion, improve insulin sensitivity, protect pancreatic beta cells, regulate glucose metabolism, and exert antioxidant and anti-inflammatory effects (Eshun and Qiao, 2010; Yagi *et al.,* 2010).

Furthermore, histological evaluation of pancreatic tissue in response to *Aloe vera* treatment can provide crucial insights into its potential regenerative or protective effects on pancreatic beta cells (Meheshwari *et al.,* 2012). Histopathological analysis allows for the assessment of structural changes, such as the integrity of pancreatic islets, acinar cells, and ductal cells, and the presence of inflammatory infiltrates or fibrosis (Mandal *et al.,* 2010). To date, limited research has focused on the histological effects of *Aloe vera* in alloxan-induced diabetic animal models. Therefore, this study seeks to bridge this knowledge gap and provide a comprehensive understanding of the potential benefits of *Aloe vera*.

MATERIALS AND METHODS

Experimental Animals

Animals used were two to three months old Wistar rats. Forty-eight (48) healthy adult Wistar rats with normal glucose levels, weighing between 150g and 200g were used in the current experiment. All animals were left to acclimatize for two weeks before the commencement of the experiment. The animals were housed in well-ventilated clean cages maintained under a 12-12h light-dark cycle at a temperature of 23±3^{o}C throughout the experimental period. Drinking water and food were provided ad libitum to the animals, but the food was withdrawn 2hr before and 2hr after the administration of the drugs to rule out the effect of food on the absorption of the drugs. All animals received human care according to the criteria outlined in the guide for the care and use of laboratory animals prepared by the National Academy of Science and published by the National Institute of Health (1996). The experimental study was conducted between 9am and 5pm. The experimental protocol and the number of animals used for the experiments were approved by the institutional review Ethics committee of the University of Port Harcourt.

Collection of Plant Materials, Drugs, and Reagents

The *Aloe vera* used for this investigation was acquired from Sampy Agrotech Company Nigeria Limited, 13, Divine School Road, UPE Sand-filled Area, Borikiri-Port Harcourt, Rivers State of Nigeria. The plant was identified and authenticated in the Department of Plant Science and Biotechnology, University of Port Harcourt. Alloxan and Metformin-50mg were purchased from Gold Sparkle Pharmaco Nig. Ltd., 5, Aggrey Road, Port Harcourt, Rivers State of Nigeria. Normal distilled water was used as a vehicle for dissolving both drugs. An oral route of administration was employed for both drugs.

Procedure for Preparation of *Aloe vera*

Fresh succulent leaves of *Aloe vera* were collected, and the inner gel component was removed from the leafy exudates. This was stored in a refrigerator.

Induction of Diabetes

Diabetes was induced by intraperitoneal injection with alloxan (150mg/kg body weight). The Wistar rats were fasted overnight before induction with alloxan (Das *et al.,* 2012). After 96hrs of alloxan administration, rats with moderate diabetes having hyperglycemia (blood glucose range of above 11.1mmol/l) were considered diabetic and were used for the study.

Experimental design

The experimental protocol as described by Lenzen (2008) was adopted in this study. Forty-eight Wistar rats were randomly divided into six (6) groups, with eight (8) animals in each group, and administered treatment as shown in the table below.

Table 1: Treatment Protocol

Group	Identification	No. of Rats	Treatment
Group 1	Normal Control	8	The control group and received distill water.
Group 2	Negative control	8	This group was administered with alloxan to induce diabetes and did not receive treatment.
Group 3	Positive control	8	This group was administered alloxan and treated with standard anti-diabetic drug (Metformin 50mg/kg orally).
Group 4	Low Dose	8	This group was administered with alloxan and received 100mg/kg of the extract.
Group 5	Medium Dose	8	This group was administered with alloxan and received 200mg/kg of the extract.
Group 6	High Dose	8	This group was administered with alloxan and received 400mg/kg of the extract.

Blood sugar Determination

Blood samples were collected in all groups. Blood glucose level was measured using Accu Check. In order to measure the blood glucose level, a small incision was made on the animal's tail using a lancet, and a drop of fresh blood was extracted and used for glucometery. These samples were collected in fasting condition and expressed in mmol/l on day 4 (96 hours), day 14, and day 28 of the experiment.

Histopathological section preparation

24 hours after the 28-day study period had ended, diethyl ether was used to sedate the animals. Animals were immediately dissected aseptically to remove the pancreas, liver, and kidney. These organs were then placed in 10% formalin and afterward reduced to a size of 2mm to 4mm thickness, allowing the fixative to easily penetrate the tissue. The tissues were subjected to various processing steps using conventional techniques as outlined in Baker's description from 1945, including fixation, dehydration, clearing, impregnation, embedding, sectioning, and hematoxylin and eosin (H&E) staining, before being mounted.

Method Statistical Analysis

Data were expressed as mean ± SEM (standard error of mean). Data were analyzed statistically using one-way analysis of variance (ANOVA) using the Dunnett method to assess any significant differences between the groups. Differences between groups at $p<0.05$ were considered to be statistically significant.

RESULTS

The results below revealed that alloxan injection led to a significant increase in serum glucose level in untreated diabetic group compared with the corresponding control group ($p<0.05$). Regarding the effect of *Aloe vera* on the glucose level, there was a significant decrease in plasma glucose concentration in *Aloe vera* low-dose (100mg/kg) treated group, *Aloe vera* medium-dose (200mg/kg) treated group, *Aloe vera* high-dose (400mg/kg) treated group, and metformin-50mg/kg treated groups respectively compared with a diabetic group as shown on the table above.

Table 2: Effect of *Aloe vera* and Metformin on blood glucose level in alloxan-induced diabetes in Wistar Rats

Group	Pre-induction	96 Hours after	Day 14	Day 28
Control	3.25±0.01	3.25±0.01[b]	3.25±0.01[b]	3.25±0.01[b]
Negative control	3.26±0.01	20.50±0.06[a]	22.37±0.09[a]	22.67±0.03[a]
Standard Drug	3.24±0.01	20.57±0.07[a]	11.23±0.07[a,b]	6.87±0.02[a,b]
100mg/kg AV	3.25±0.01	19.20±0.17[a]	6.19±0.01[a,b]	5.16±0.03[b]
200mg/kg AV	3.26±0.01	19.70±0.06[a]	6.14±0.01[a,b]	5.03±0.01[b]
400mg/kg AV	3.25±0.01	19.37±0.09[a]	5.05±0.01[b]	4.60±0.04[b]

Values are means ± Standard Error Mean (SEM). [a] significant at $p<0.05$ when compared to control; [b] significant at $p<0.05$ when compared to negative control, n=4; AV = Aloe vera

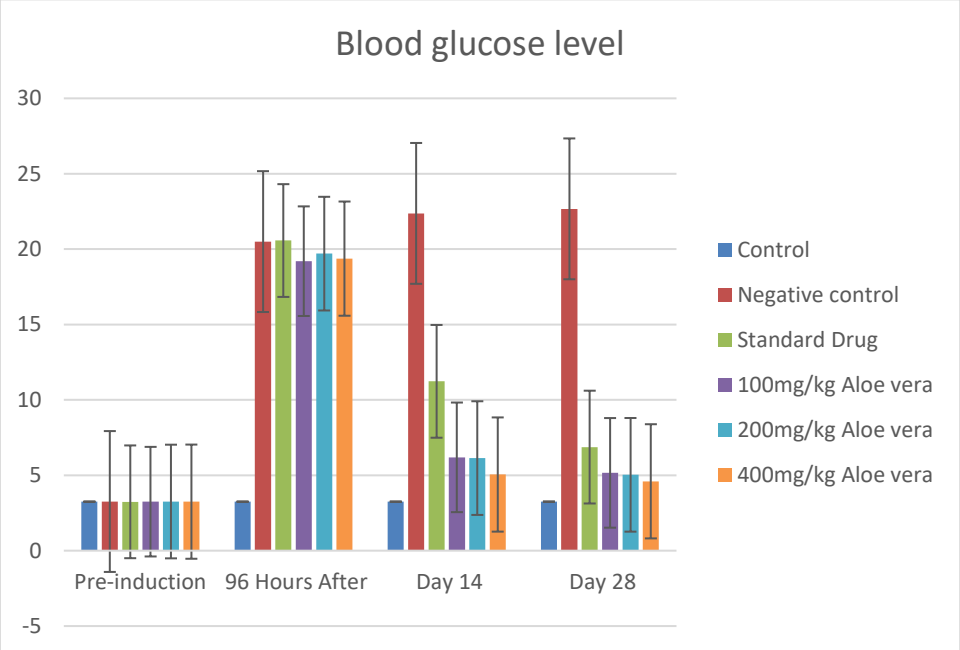

Figure 1: Effect of *Aloe vera* and metformin on blood glucose level in alloxan-induced diabetic Wistar Rats

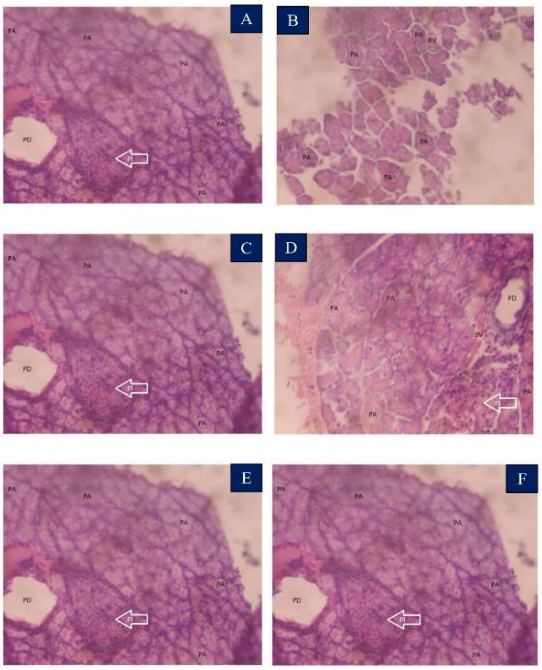

Figure 2 (A-F): The histology of the pancreas in each group after 14 days. (A) The normal group (group 1) showed intact pancreatic islets (PI), intact pancreatic acini (PA), and the presence of the pancreatic duct (PD). (B) Showed a distorted pancreas of the negative control group (group 2), which lacked pancreatic islets (PI). Instead, blood vessels (BV) and pancreatic acini (PA) were observed. (C) Shows a normal pancreas of the positive control group (group 3), which exhibited intact pancreatic islets (PI), intact pancreatic acini (PA), and the presence of the pancreatic duct (PD). (D) Shows normal histology of the pancreas from the low-dose group (group 4) treated with 100mg/kg *Aloe vera*. Similar to the normal group, it displayed intact pancreatic islets (PI), intact pancreatic acini (PA), and the presence of the pancreatic duct (PD). (E-F) Demonstrates a normal pancreas from the medium-dose (group 5, 200mg/kg *Aloe vera*) and high-dose (group 6, 400mg/kg *Aloe vera*) groups, respectively. Both groups displayed intact pancreatic islets (PI), intact pancreatic acini (PA), and the presence of the pancreatic duct (PD)

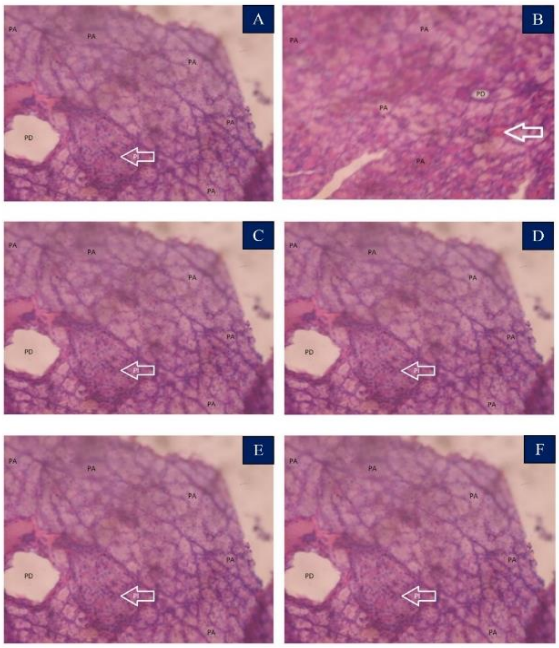

Figure 3 (A-F): The histology of the pancreas in each group after 28 days. (A) The normal group (group 1) displayed a normal pancreas with intact pancreatic islets (PI), intact pancreatic acini (PA), and the presence of the pancreatic duct (PD). (B) Shows a distorted pancreas of the negative control group (group 2). It reveals pancreatic acini (PA), shrunken pancreatic islets (PI), and the pancreatic duct. (C-F) Represented a normal pancreas from groups 3 (positive control), 4 (low-dose, 100mg/kg *Aloe vera*), 5 (medium-dose, 200mg/kg *Aloe vera*), and 6 (high-dose, 400mg/kg *Aloe vera*). All groups displayed intact pancreatic islets (PI), intact pancreatic acini (PA), and the presence of the pancreatic duct (PD)

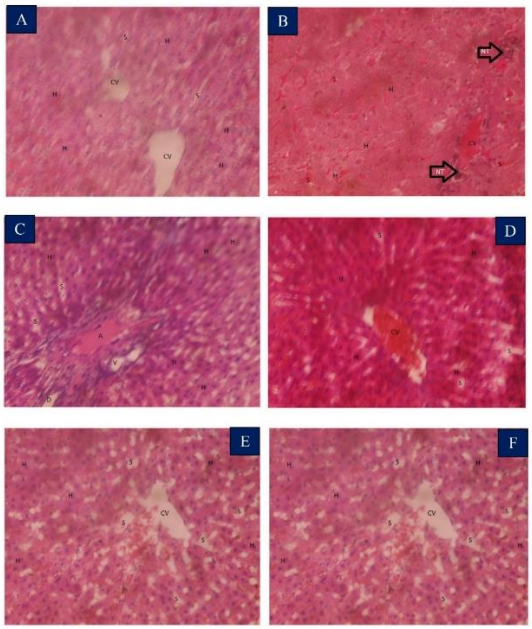

Figure 4 (A-F): The histology of the liver in each group after 14 days. (A) Presents the histology of the normal liver from group 1 (normal group), it shows, Patent Central Vain (CV), Intact Hapatocytes (H) and Sinusoids (S) Containing Kupffer Cells; (B) Presents the histology of the distorted liver from group 2 (negative control) Shows congested Central Vein (CV), Necrotic tissues (NT), Intact Hepatocytes (H) and Sinusoids (S); (C) Presents the histology of the normal liver from group 3 (positive control), it shows congested Hepatic artery (A), portal vein (V) and bile duct (D), Intact Hepatocytes (H), and Sinusoids (S); (D) Presents the histology of the normal liver from group 4 (low dose 100mg /kg *Aloe vera*), it shows a congested Central Vain (CV), Cords of normal Hepatocytes (H) and Sinusoids (S) Containing Kupffer Cells; (E-F) Presents the histology of the normal liver from group 5 and 6 (200mg/kg and 400mg/kg *Aloe vera*), it shows, Patent Central Vain (CV), Sinusoids (S) and Intact Hapatocytes (H)

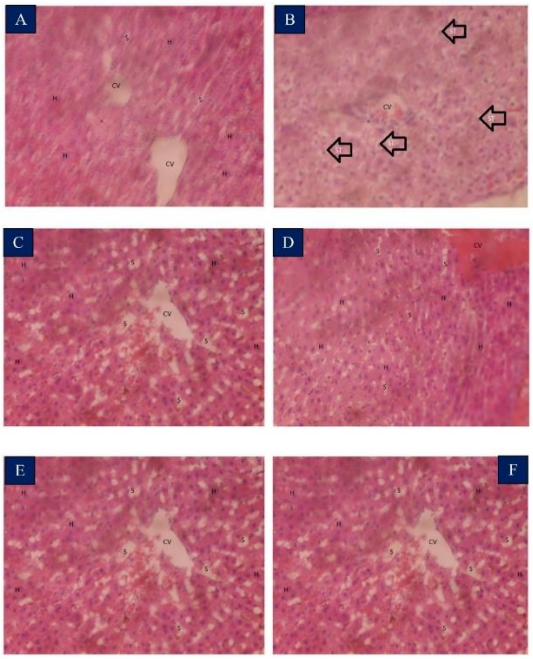

Figure 5 (A-F): The histology of the liver in each group after 28 days. (A) Presents the histology of the normal liver from group 1 (normal group), it shows, Patent Central Vain (CV), Intact Hapatocytes (H) and Sinusoids (S) Containing Kupffer Cells; (B) Presents the histology of the distorted liver from group 2 (negative control), it shows, Congested Central Vain (CV) and Hapatocytes with features of fatty changes, microvesicular steatosis (ST); (C) Presents the histology of the normal liver from group 3 (positive control), it shows, Patent Central Vain (CV), Sinusoids (S) and Intact Hapatocytes (H); (D) Presents the histology of the normal liver from group 4 (low dose 100mg/kg *Aloe vera*), it shows, Intact Hepatocytes (H), Sinusoids (S) and Congested Central Vein (CV); (E-F) Presents the histology of the normal liver from group 5 (200 and 400mg/kg *Aloe vera*) and 6 (400mg/kg *Aloe vera*), it shows, Patent Central Vain (CV), Sinusoids (S) and Intact Hapatocytes (H)

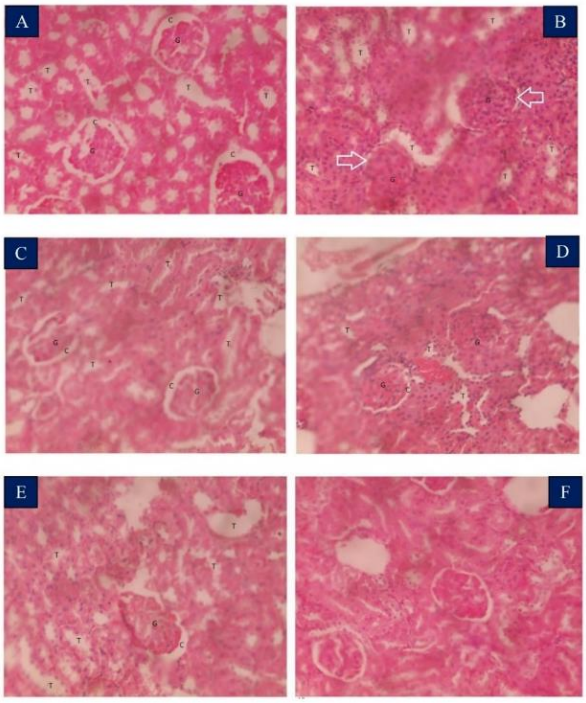

Figure 6 (A-F): The histology of the kidney in each group after 14 days. (A) Presents the histology of the normal kidney from group 1 (normal group), it shows, Glomerular tuft (G) Containing Mesangial cells, Mesemgial Matrix and Capillaries, Patent Bowman's Capsule (C) and Renal Tubules (T) lined with simple Epithelial Cells; (B) Presents the histology of the distorted kidney from group 2 (negative control), it shows, occluded Bowman's Capsular space (arrowed), Glomeruli (G) and Renal Tubules (T); (C) Presents the histology of the normal liver from group 3 (positive control), it shows, Glomerular tuft (G) Containing Mesangial cells, Mesemgial Matrix and Capillaries, Patent Bowman's Capsule (C) and Renal Tubules (T) lined with simple Epithelial Cells; (D) Presents the histology of the normal kidney from group 4 (low dose 100mg/kg *Aloe vera*), it shows, Glomerular tuft (G) Containing Mesangial cells, Mesemgial Matrix and Capillaries, Patent Bowman's Capsule (C) and Renal Tubules (T) lined with simple Epithelial Cells; (E) Presents the histology of the normal kidney from group 5 (medium dose of 200mg/kg *Aloe vera*), it shows, Glomerular tuft (G) Containing Mesangial cells, Mesemgial Matrix and Capillaries, Patent Bowman's Capsule (C) and Renal Tubules (T) lined with simple Epithelial Cells; (F) Presents the histology of the normal kidney from group 6 (high dose 400mg/kg *Aloe vera*), it shows, Glomerular tuft (G) Containing Mesangial cells, Mesemgial Matrix and Capillaries, Patent Bowman's Capsule (C) and Renal Tubules (T) lined with simple Epithelial Cells

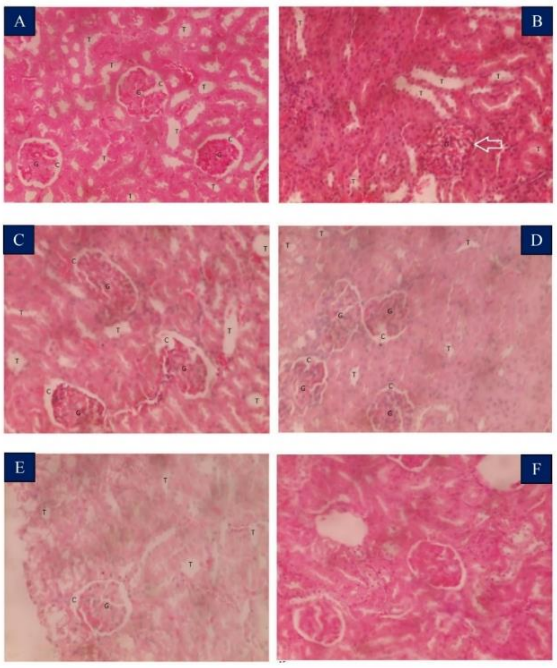

Figure 7 (A-F): The histology of the kidney in each group after 28 days. (A) Presents the histology of the normal kidney from group 1 (normal group), it shows; Glomerular (G) Containing Glomerunar Mesangial cells, Mesemgial Matrix and Capillaries, Patent Bowman's Capsule (C) and Intact Renal Tubules (T); (B) Presents the histology of the distorted kidney from group 2

(negative group), it shows, Occluded Bowman's Capsular space (arrowed), Glomeruli (G) and Renal Tubules (T); (C) Presents the histology of the normal kidney from group 3 (positive control), it shows, Glomerular tuft (G) Containing Mesangial cells, Mesemgial Matrix and Capillaries, Patent Bowman's Capsule (C) and Renal Tubules (T) lined with simple Epithelial Cells; (D) Presents the histology of the normal kidney from group 4 (low dose 100mg/kg *Aloe vera*), it shows, Glomerular tuft (G) Containing Mesangial cells, Mesemgial Matrix and Capillaries, Patent Bowman's Capsule (C) and Renal Tubules (T) lined with simple Epithelial Cells; (E) Presents the histology of normal kidney from group 5 (medium dose 200mg/kg *Aloe vera*), it shows, Glomerular tuft (G) Containing Mesangial cells, Mesemgial Matrix and Capillaries, Patent Bowman's Capsule (C) and Renal Tubules (T) lined with simple Epithelial Cells; (F) Presents the histology of the normal kidney from group 6 (high dose 400mg/kg *Aloe vera*), it shows, Glomerular tuft (G) Containing Mesangial cells, Mesemgial Matrix and Capillaries, Patent Bowman's Capsule (C) and Renal Tubules (T) lined with simple Epithelial Cells

DISCUSSION

Diabetes mellitus, a chronic metabolic disorder characterized by elevated blood glucose levels, poses a significant global health burden due to its associated complications (American Diabetes Association, 2020; World Health Organization, 2019). Uncontrolled diabetes can lead to various complications such as cardiovascular disease, neuropathy, nephropathy, and retinopathy (American Diabetes Association, 2020). Therefore, extensive research is required to explore therapeutic interventions that effectively manage diabetes and its complications. Natural products derived from medicinal plants have gained significant attention as potential sources of alternative treatments (Aleme *et al.,* 2022; Omeodu and Uahomo, 2023; Isirima and Uahomo, 2023). Among them, *Aloe vera*, a succulent plant with a long history of traditional medicinal use, has emerged as a promising candidate for managing diabetes and its complications. The plant possesses a wide array of bioactive compounds, including polysaccharides, glycoproteins, anthraquinones, vitamins, and minerals, which are believed to contribute to its pharmacological activities (Boudreau *et al.,* 2013; Zhang *et al.,* 2016). These bioactive compounds have been reported to enhance insulin secretion, improve insulin sensitivity, protect pancreatic beta cells, regulate glucose metabolism, and exert antioxidant and anti-inflammatory effects (Yagi *et al*., 2002; Eamlamnam *et al*., 2006; Boudreau *et al*., 2013; Zhang *et al*., 2016).

By harnessing these properties, *Aloe vera* holds great potential for managing the complications associated with diabetes and improving the overall well-being of individuals with the disease. Therefore, investigating the antihyperglycemic and histological effects of *Aloe vera* on alloxan-induced diabetes in Wistar rats can provide valuable insights into its therapeutic mechanisms and its potential as a natural remedy for diabetes and its related complications (Rajasekaran et al., 2006; Lenzen, 2008). The antihyperglycemic effects of *Aloe vera* observed in this study can be attributed to its bioactive contents, particularly anthraquinones, and polysaccharides. Yagi *et al*. (2002) and Eamlamnam *et al*. (2006) have demonstrated a significant reduction in blood glucose levels in diabetic animals treated with *Aloe vera*, indicating the hypoglycemic properties of the plant. These bioactive compounds are believed to contribute to improved insulin sensitivity and modulation of glucose metabolism, leading to decreased blood glucose levels (Yagi *et al.,* 2002; Eamlamnam *et al.,* 2006).

Furthermore, the dose-dependent response observed in this study is in line with the findings of Rajasekaran *et al*. (2006). Rajasekaran *et al*. (2006) investigated the effect of *Aloe vera* gel on diabetic rats and found that higher doses of *Aloe vera* resulted in a more significant reduction in blood glucose levels. This suggests that the therapeutic efficacy of *Aloe vera* may be influenced by the dose administered. The dose-dependent effect can be attributed to the concentration-dependent bioactivity of the bioactive compounds present in *Aloe vera* (Rajasekaran *et al.,* 2006). In terms of organ histology, the preservation of normal histological features observed in the pancreas, liver, and kidney with *Aloe vera* treatment is consistent with the protective effects reported in previous studies. Zhang *et al.,* (2016) demonstrated the protective effects of *Aloe vera* on pancreatic histology in diabetic rats, attributing it to the antioxidant and anti-inflammatory properties of *Aloe vera*. Boudreau *et al*. (2013) investigated the hepatoprotective effects of *Aloe vera* on liver histology and reported the preservation of normal histological features in *Aloe vera*-treated animals. Rajasekaran *et al.,* (2006) observed similar effects on kidney histology, suggesting that *Aloe vera* can protect against the damage caused by diabetes. These protective effects are likely due to the antioxidant, anti-inflammatory, and tissue-protective properties of *Aloe vera* (Zhang *et al.,* 2016; Boudreau *et al.,* 2013; Rajasekaran *et al.,* 2006).

Overall, the findings of this study, supported by previous research, suggest that *Aloe vera* has antihyperglycemic effects and can preserve the histological integrity of vital organs in diabetic animals. The bioactive compounds present in *Aloe vera*, such as anthraquinones and polysaccharides, play a significant role in reducing blood glucose levels and maintaining organ histology. However, further studies are necessary to explore the underlying mechanisms of action and validate these findings in clinical settings.

CONCLUSION

Aloe vera shows promise as an alternative or adjunctive therapy for the management of diabetes. Its antihyperglycemic effects, dose-dependent response, and preservation of organ histology suggest its potential usefulness in controlling blood glucose levels and mitigating organ damage associated with diabetes.

However, further investigations are needed to elucidate the underlying mechanisms of action and validate these findings in clinical settings.

RECOMMENDATION

It is recommended that additional research be conducted to explore the specific mechanisms through which *Aloe vera* exerts its antihyperglycemic effects and protects organ histology. Clinical trials involving human subjects would provide valuable insights into the efficacy and safety of *Aloe vera* as a therapeutic intervention for diabetes. Furthermore, studying the long-term effects and potential interactions of *Aloe vera* with other medications commonly used in diabetic management would contribute to a comprehensive understanding of its therapeutic potential.

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