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Assessment of the effect of *Aloe vera* extracts on oxidative stress, serum electrolytes and renal function in alloxan-induced diabetic Wistar rats

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Abstract

Background: Diabetes mellitus (DM) is a metabolic disorder of multiple etiology characterized by chronic hyperglycemia with disturbances in carbohydrates, fats, and protein metabolism, resulting from defects in insulin secretion action. The statistics of Nigerians living with DM is disturbing as the current prevalence among adults aged 20-69 years is reported to be 1.7 million. Morbidity and mortality of DM has attained public health significance. Multiple approach has been utilized in combating it, however, focused effort is geared towards using medicinal herbs for curing or management of this disease because they are less toxic and eco-friendly; and to this end *Aloe vera* ranks amongst the foremost.

Methodology: Twenty-five male wistar rats weighing 220-260g were randomly divided into five groups (n=5). Group A: Normal control rats, Group B: untreated diabetic rats. Group C: Diabetic rats +Aleovera rind extract (300mg/kg). Group D: Diabetic group treated with 300mg/kg *Aloe vera* Gel. Group E: Diabetic rats + Aloe vera rind + gel extract (150mg/kg +150mg/kg). Experimental diabetes was induced in the rats using Alloxan (150mg/kg) and animals showing fasting blood glucose level >200mg/dl were considered diabetic. The oral administration of Aloe vera extracts lasted for 14days.

Results: The results showed that*Aloe vera* gel extract appeared more potent in antioxidant effect by significantly increasing SOD levels (17. 94 ± 0.22) and significantly decreasing MDA levels (3.23 ± 0.12) when compared other *Aloe vera* treated groups and untreated group (9.87 ± 0.20 , 14.6 ± 0.53) (5.39 ± 0.19, 4.14 ± 0.26)respectively.Also, there was a significant decrease in K+ levels in *Aloe vera* rind treated group (4.19 ± 0.19) when compared with other groups (4.98 ± 1.4 , 4.77 ± 0.16 , 4.84±0.07, 4.68 ± 0.13).Urea and Creatinine levels in untreated diabetic rats significantly increased in the untreated group (7.74 ± 0.23, 84.2 ± 2.88)when compared to the normal group (4.7 ± 0.36, 65.4 ± 3.98)but showed no significant change upon treatment with Aloe vera extract.

Keywords: Aloe Vera; Diabetes Mellitus; Oxidative Stress; Serum Electrolytes; Renal Function.

1. Introduction

Diabetes mellitus (DM) is a metabolic disorder of multiple etiology characterized by chronic hyperglycemia with disturbances in carbohydrates, fats, and protein metabolism, resulting from defects in insulin secretion, insulin action or both (Zubin *et al*.,2018).American Diabetes Association(ADA)in 2017 stated that, chronic hyperglycemia is the hallmark of diabetes mellitus, a chronic condition characterized not only by hyperglycemia but also by alterations in

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protein and lipid metabolism. The main symptoms of diabetes include increased urination, increased thirst, fatigue, weight loss, blurred vision, increased hunger, and diabetes dermatomes(Hasonadan,2016).

In persistent hyperglycemia, there is formation of free radicals through glycations of non enzymatic proteins, gucose oxiations and increased lipid peroxidation.Also, unhealthy lfestyles may increase the leves of free radicals which the available antioxidant is not adequate to neutralize (Rivan et al., 2021). Oxidative stress caused by excessive free radicals is a fundamental factor that can establish a link between hyperglycemia and the vascular complications frequently encountered in diabetes, particularly Diabetic Kidney Disease (DKD)(Wang and Zhang 2024). Diabetic patients are at increased risk of dehydration due to osmotic diuresis. Undiagnosed or undertreated hyperglycemia overtime may lead to electrolyte imbalance and elevated renal burden of glucose excretion, which may alter fluid reabsorption in the kidney, (Mohan *et al*.,2024).

Throughout history, man has solely relied so much on medicinal plants for health and food. *Aloe vera* contains different substances such as minerals, vitamins, amino acids, enzymes, sterols, anthraquinone, flavonoids, terpenoids, coumarins, polysaccharides, sugars, and polyphenols. It is widely used for a variety of medicinal purposes which include; anthelmintic, hepatoprotective, antidiabetic, diuretic, antibacterial, antiviral, antioxidant, antiseptic, anti-inflammatory, anticancer, and cosmetic effects (Ahmed *et al.,* 2024).

DM has no cure at the moment so investigation into this disease continues.Hence, this study is aimed at assessing the effect of different parts of *Aloe vera* extracts on oxidative stress, serum electrolytes and renal function in alloxan-induced diabetic wistar rats.

2. Materials and Method

2.1. Experimental Animals

A total of twenty-five (25) male wistar rats weighing between 220-260g were used for this study. The rats were left to acclimatize for two (2) weeks. All laboratory animals used were kept on a 12 hour light and 12 hour dark cycle in well ventilated room. The rats were fed with vital feed grower mesh manufactured by Grand Cereals Ltd (a subsidiary of UAC Nigeria PLC, Plateau state). The rats had access to feed and distilled water *ad libitum*.

2.2. Plant Collection and Extract Preparation

Mature *Aloe vera* leaves were purchased in a local market, Eke Amobi in Nnewi, Anambra state. Plant identification was carried out and the specimen deposited in the Herbarium of Botany department in Nnamdi Azikiwe University, with a voucher number (N.A.U.H-60A). They were thoroughly washed with distilled water to remove dirt and debris, the apex and the base of the leaf was cut off using the surgical blade to prevent the sap/ latex from entering.

2.3. Gel extract

The leaves were cut open along its margin thus revealing the transparent mucilage/gel this was scooped into a beaker using a spatula and then homogenized to obtain a finer liquefied form of the gel, then filtered with a standard sieve to obtain, the aloe juice extract (Ritesh *et al.,* 2024). This was stored in a refrigerator till used.

2.4. Rind Extract

After removing the gel the rind was obtained. The rind was air dried for two weeks and grounded to powdered form.100 grams of the powdered rind was soaked in 300ml of distilled water for 48hrs and sieved with a standard sieve. The filtrate was oven dried at a temperature of 45^0c for 24hrs to obtain the extract in paste form. The extract was stored in the refrigerator. This was reconstituted in distilled water to an appropriate concentration before administration.(Jothi *et al.,* 2014)

2.5. Induction of diabetes mellitus

1200 mg of alloxan was measured in a dark environment and dissolved in 16mls of normal saline (0.9%) giving a yield of 75mg/ml (Erhirhie *et al.,* 2014). The colour of the solution obtained was pink to light purple. The experimental group fasted for 24 hours but allowed access to water.

After 24 hours of fasting, alloxan was administered using a single dose of 150mg/kg intraperitonially (Carlvalho 2003). Formula for determining volume of alloxan solution given: Weight of animal (g) /1000 x 2ml= Xmls ((Erhirhie *et al.,*

2014).No water or feed was given to the rats until after 30 minutes of administration. In order to prevent alloxan induced fatal hypoglycaemia 10% of glucose was given to the rats in solution bottles by oral gavage for the next 24 hours. After 72 hours of alloxan administration the fasting blood glucose level of the rats was determined from blood samples taken from the tail vein using an Evolve glucometer. Random blood glucose ≥ 200mg/dl indicates diabetes mellitus. Three days after induction, surviving and diabetic rats were divided into 5 groups with five rats each.

2.6. Experimental design and Extract Administration

After successful diabetes induction, the rats were randomly divided into 5 groups of 5 rats each.

- **Group I:** Positive control non-diabetic group received water and feed *ad libitum.*
- **Group II**: Negative control untreated diabetic group received water and feed *ad libitum*
- **Group III**: Diabetic group treated with 300mg/kg *Aloe vera* Green rind.
- **Group IV**: Diabetic group treated with 300mg/kg *Aloe vera* Gel.
- **Group V:**Diabetic group treated with 150mg/kg *Aloe vera* Rind and 150mg/kg of Aloe vera Gel

Extract administration commenced on confirmation of diabetes. These extracts were administered orally for 14 days by oral gavage.

2.7. Determination of oxidative stress biomarkers

12 hours after last administration and feeding, 5 ml of blood sample was drawn via ocular puncture and collected in plain bottles and mixed properly. The coagulated blood was centrifuged for 15 minutes to facilitate separation. Superoxide Dismutase (SOD) and Malondialdehyde (MDA) - a product of lipid peroxidation, were assayed using UV-VIS spectrophotometer (Model 752G, China) according to the standard method of Alam *et al* .,(2016) .

2.8. Determination of serum electrolytes

Serum sodium and potassium levels was analyzed using the ion selective electrode machine (ISE) by Biobase bioindustry company limited , model: BKE-C.

2.9. Determination of urea levels.

Urea level was determined using the standard assay kit following the diacetylmonoxime, and alkaline picrate method for creatinine level.

2.10. Statistical Analysis

Results were analyzed and expressed as mean ± SEM using statistical package for social sciences (SPSS version 25). The statistical significance between the means was analyzed using one way analysis of variance (ANOVA) followed by Turkey's multiple range test post-hoc analysis. A p - value of ≤ 0.05 was considered statistically significant.

3. Result

3.1. The Lethal Dose

3.1.1. Acute Toxicity Study

The acute toxicity (LD_{50}) of the extract was estimated in 12 albino rats by oral compulsion. This method was done in two phases which involved the administration of 3 different doses the first phase and 4 different doses for the second phase. The number of deaths in each group was recorded and LD_{50} was calculated as 2154.07mg/kg/bwt using the formular

$$LD_{50} = \sqrt{A \times B}$$

A= maximum dose with 0% mortality B= maximum dose with 100% mortality

Table 1a The comparison for sod and mda level between untreated diabetic group and aloe vera treated groups.

GROUPS	SOD(umol/ml) Mean±SEM	P-VALUE	MDA(nmol/ml) Mean±SEM	P-VALUE
A B	15.88±0.39 9.87±0.20	0.00*	4.15±0.21 5.39±0.20	0.00*
C	17.50±0.34	0.00*	3.62±0.20	0.00*
D	17.94±0.22	0.00*	3.23±0.12	0.00*
E	14.61±0.54	0.00*	4.14±0.26	0.00*

*=P≤0.05 is considered statistically significant .

Result shows significant decrease (P ≤0.05) in SOD level in group B (9.87±0.20) when compared with the control (15.88±0.39). Conversely, groups C (17.50±0.35) and D (17.94±0.22) showed significant increase when compared with the control. However, group E showed no significant change when compared with the control (15.88±0.39).

On the other hand, there was significant increase in SOD in control group A (15.88±0.39) and all the test groups when compared with group B (9.87±0.20).

Table 1b The comparison for sod and mda level between untreated diabetic group and aloe vera treated groups.

GROUPS	SOD(umol/ml) Mean±SEM	P-VALUE	MDA(nmol/ml) Mean±SEM	P-VALUE
A B	15.88±0.39 9.87±0.20	0.00*	4.15±0.21 5.39±0.20	0.00*
C	17.50±0.34	0.00*	3.62±0.20	0.00*
D	17.94±0.22	0.00*	3.23±0.12	0.00*
E	14.61±0.54	0.00*	4.14±0.26	0.00*

*=P≤0.05 is considered statistically significant .

Result showed a significant increase in MDA in group B (5.39±0.20) when compared with the control (4.15±0.21). Groups C (3.62±0.20) and D (3.23±0.12) showed significant decrease when compared with control (4.15±0.21). Furthermore, group E (4.14±0.26) showed no significant difference when compared with the control (4.15± 0.21). On the other hand, groups A and all the test groups showed significant decrease in MDA when compared with group B (5.39±0.20).

Table 2 The comparison between mean sodium, chloride and potassium concentrations for all groups.

GROUPS	SODIUM Mean±SEM	P-VALUE	CHLORIDE Mean±SEM	P-VALUE	POTASSIUM Mean±SEM	P-VALUE
A	141.00±1.84		102.96±2.24		4.98±0.14	
B	142.80±1.32	0.50	103.36±2.85	0.91	4.77±0.16	0.33
C	138.00±2.03	0.26	99.46±2.74	0.33	4.19±0.19	0.00*
D	141.40±2.38	0.88	96.18±2.01	0.69	4.84±0.07	0.51
E	145.20±1.36	0.12	97.660±2.51	0.15	4.68±0.13	0.16

*=P≤0.05 is considered statistically significant

There was no significant change in sodium level across the groups (A-E). Also there was no significant change in chloride level across the groups (A-E).

For K+ there was no significant change in the concentration in group B when compared to group A. Also, there was significant decrease in K^+ concentration in group C when compared to the control groups A and B(4.9 ± 0.14, 4.77 ± 0.15) and other *Aloe vera* treated groups D and E (4.82 ± 0.07). On the other hand, there was no significant change in K^+ concentration in group D and E when compared with group B.

However, there was a significant decrease in K+ levels in *Aloe vera* rind treated group (4.19 ± 0.19) when compared with other groups (4.98 ± 1.4 , 4.77 ± 0.16 , 4.84±0.07, 4.68 ± 0.13).

Table 3 The comparison for urea and creatinine level across the groups.

	UREA Mean±SEM		CREATININE Mean±SEM	
GROUPS		**P-VALUE**		**P-VALUE**
A	4.70±0.37		65.40±3.98	
B	7.74±0.23	0.00*	84.20±2.89	0.00*
C	7.13±0.09	0.00*	85.40±2.56	0.00*
D	6.80±0.19	0.00*	90.40±1.21	0.00*
E	6.88±0.20	0.00*	89.00±1.92	0.00*

*=P≤0.05 is considered statistically significant

There was a significant increase in urea level in group B (7.74 ± 0.23) when compared with group A (4.7 ± 0.37). There was no significant decrease in urea level amongst the *Aloe vera* treated groups when compared withgroup B. But amongst the *Aloe vera* treated groups C-E (Rind, Gel, Rind + Gel) there was no significant decrease in urea level.

For creatinine, there was a significant increase in group B (84.2 ± 2.88)when compared to group A (65.4 ± 3.98). Also there was no significant change in creatinine level in group B when compared to the *Aloe vera* treated groups C-E (Rind, Gel, Rind + Gel). Amongst the *Aloe vera* treated groups there was no significant difference in creatinine level.

4. Discussion

The occurrence of diabetes mellitus has become a serious threat to the health of mankind globally hence ,the urge to develop solutions with little or no side effects and at a cheaper rate. *Aloe vera* (*Aloebarbadenismill*) is one of the plants reported to possess antidiabetic effect (Ahmed *et al*., 2024).This study has evaluated the effects of different *Aloe vera* extracts on oxidative stress, serum electrolytes and renal function in alloxan-induced diabetic wistar rats. So as to ascertain the best part of *Aloe vera* to be consumed amongst individuals with diabetes mellitus for best result.

4.1. Effect on oxidative stress.

The untreated diabetic group(B) with highest blood glucose level had the lowest superoxide dismutase level (SOD) when compared to control and other diabetic group treated with *Aloe vera* extracts. This result agrees with the work done by Wulan *et al.,* 2019 and Lina *et al.,* 2017. This decrease in SOD levels in untreated diabetic group indicates oxidative stress caused by an increase in the production of free radicals through glucose autoxidation ,protein glycation and lipid peroxidation which leads to the formation of Advanced glycation end products (AGEs). These end products (AGEs) bind to their receptors hence activating it. Its activation leads to the inactivation of antioxidant enzymes (SOD) altering its structure and function hence decreasing its cellular antioxidant effect.

Also in this study, untreated diabetic group showed a significant increase in malondialdehyde (MDA) level when compared with control and diabetic groups treated with *Aloe vera* extracts. This finding is in line with the work done by Betul *et al.,* (2020); Vania *et al.,* (2020) and Lina *et al.,* 2017. Hyperglycemic conditions trigger oxidative stress that can also measured by MDA levels. MDA is a product of lipid peroxidation carried out by the excessive free radical.

On treatment with *Aloe vera* extracts the level of SOD increased significantly when compared to the untreated diabetic group. This coincides with the work done by Wariyah and Riyanto (2015) . But amongst the *Aloe vera* treatment groups, Group D (gel) showed highest SOD levels that is the *Aloe vera* gel had more scavenging ability. This could be as a result of the presence of flavonoid and phenolic compounds hence its antioxidant ability according to Christijanti *et al.,(*2019). Also on treatment with *Aloe vera* extracts MDA levels in diabetic group decreased greatly when compared to untreated

diabetic groups. This finding coincides with the study carried out by Rabab *et al.,* (2019). This is as a result of antioxidant compounds found in *Aloe vera.* Also, Haritha *et al.,* (2014) showed that *Aloe vera* can reduce highly reactive oxygen species that can cause extensive damage to lipid cell membrane thus decreasing MDA levels.

The diabetic group treated with only *Aloe vera* gel extract greatly reduced the MDA levels when compared with other *Aloe vera* treatment groups. This could be as a result of higher flavonoid constituent present in the gel (Ahmed 2024).

4.2. Effect on serum electrolytes

The sodium(Na^+), Potassium(K^+) and Chloride(Cl^-) level in the untreated diabetic group remained unchanged when compared to the control. This contradicts the work carried out by Adeyomoye and Adeola (2017); Rasyid and Muawunah (2019) where they reported that, Na^+, K^+ and Cl^- in diabetes is significantly decreased caused by renal dysfunction, Diabetic nephropathy or dehydration. But the unchanged Na^+, K^+ and Cl^- observed in this study, agrees with the work done by Adesokan *et al.,* (2009). This unchanged electrolyte level especially that of sodium could be as a result of the dilutional effect of hyperosmolar status caused by elevated blood glucose level where water loss from the compartments (intracellularand extracellular space) becomes quantitatively similar which is seen in diabetic ketoacidosis(DKA) one of the complications of type I diabetes.

On treatment with *Aloe vera* extracts (Gel, Rind,Gel +Rind) serum Na^+ and Cl^-level showed no significant change. But the potassium level was significantly decreased when treated with *Aloe vera* rind extract. This could be as a result of the phytochemical constituent present in the rind that is the anthraquinones majorly the "aloin" (Itrat and Zamigor 2013). This phytochemical has a laxative effect which can cause electrolyte imbalance hence its cytotoxic effect. Its mechanism of action include enhancement of fluid retention by osmotic mechanisms leading to fluid retention and hypokalemia.

4.3. Effect on urea and creatinine level

The urea and creatinine concentrations of the diabetic group increased when compared with the control group. This is in accordance with the work carried out by Fedheelah *et al.,* (2020); Bamanikar 2016. The significant elevation in urea and creatinine levels could be as a result of progressive renal damage caused by an elevated blood glucose level beyond its threshold of >180mg/dl. Low clearance of creatinine and urea indicates impaired ability of the kidneys to filter these waste products from the blood and excrete them in urine. As their clearance values decrease, their blood levels increases. When treated with *Aloe vera* extracts(Rind, Gel, Rind+Gel) there was no significant decrease or change in urea and creatinine level though a slight increase in creatinine level was seen when compared to the untreated diabetic group. This contradicts the work carried out by Dangi *et al.,* (2015).This slight increase could be as a result of the nephrotoxic effect of *Aloe vera*

5. Conclusion

Aloe vera extract has a potency of reducing oxidative stress in the diabetic rats by significantly increasing the superoxide(SOD) levels and reducing Malondialdehyde(MDA) levels at the dose of 300mg/kg. But *Aloe vera* gel and *Aloe vera* rind extract administered singly appeared more potent in reducing oxidative stress in diabetic rats when compared to combined extracts of *Aloe vera* rind+gel at lower doses. However, the extracts of *Aloe vera* did not significantly ameliorate the renal injury seen in Diabetes mellitus which was evident in the Renal function test.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

Ethical approval for animal experimentation of this work was obtained from Nnamdi Azikiwe University Animal Research Ethics Committee (NAU-AREC), Nnewi. The Ethical Approval Number is: NAU/CHS/NC/FMBS/675.

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