ECONOMIC SIGNIFICANCE OF MUSA ACUMINATA LEAVES: EVIDENCE OF PROTECTIVE OUTCOME AGAINST ALLOXAN INDUCED DIABETICS MELLITUS IN EXPERIMENTAL MODELS.

ABSTRACT

Context: Musa acuminata is a plant of the tropical and subtropical regions. Over the past few decades, the health benefits of M. acuminata have received much attention. All parts of the plant, including fruits, peel, pseudo stem, corm, flowers, leaves, sap, and roots, have found their use in treating many diseases in traditional medicine.

Aim: This study was conducted to appraise the protective effect of Musa acuminata extract on alloxan-induced Diabetics Mellitus in wistar rats.

Settings and Design: This investigation was carried out using 25 Wistar rats, both males and females. The experimental models were divided into five groups; 5 rats per group.

Materials and methods: The experimental models were divided into five groups; 5 rats per group. Alloxan was intraperitonially injected at a dose of 150 mg/kg body weight for ten days across all groups except the positive control Group (Group A) together with oral administration of the aqueous extract of Musa acuminata (100 mg/kg, 200mg/kg and 300mg/kg b.w for the treatment group). The animals were sacrificed on the 11th day by cervical dislocation, then blood was collected by cardiac puncture, and kidneys were collected for the histological profile.

Statistical Analysis: Kidney oxidative stress markers, including lipid peroxidation(MDA) and antioxidant enzyme activities, namely creatinine and Urea, were all determined.

Result: The alloxan injection elicited a marked elevation concentration on lipid peroxidation, with a concomitant urea and creatinine content depletion compared with the control and a remarkable decrease in antioxidant enzymes. Oxidant/antioxidant imbalance, alloxan-induced diabetic mellitus, and histological changes in the kidneys were successfully reduced to close to normal by the per-administration of Musa acuminata.

Conclusion: Based on the current findings, it can be concluded that Musa acuminata successfully minimizes the harmful effects on kidney function and histological coherence associated with Diabetics Mellitus by strengthening the antioxidant defense system, suppressing oxidative stress, and mitigating apoptosis.

Keywords: Alloxan, *Musa acuminata*, Diabetics Mellitus, Kidney.

INTRODUCTION

According to Choudhury H. et al., 2018 and Thomas D. et al., 2019, Herbal medications have been used to treat various ailments, and a vast number of the population in the world is entirely dependent on

traditional medicines. 80% of the world's population relies on medicinal plants for primary health care. Herbal drugs are readily available, cheaper, time tested, and considered safer than most modern synthetic drugs. The World Health Organization (WHO) believes that the significant population of developing countries rely on traditional medicine for their primary healthcare needs. Therefore, there is an increased demand for medicinal plants in developing and developed countries.

Musa spp (bananas) is a good source of carbohydrates, proteins, vitamins, and minerals. They contain different amino acids like threonine, tryptamine, and tryptophan, as well as flavonoid, dopamine, beta-carotene, and sterols (Choudhury H. et al., 2018). Musa acuminata is a species of banana native to Southern Asia, its range comprising the Indian Subcontinent and Southeast Asia.

Alloxan, chemically known as 5,5-dihydroxyl pyrimidine-2,4,6-trione, is an organic compound, urea derivative, carcinogen, and cytotoxic glucose analog. Alloxan is one of the common diabetic agents often used to assess the antidiabetic potential of pure compounds and plant extracts in studies involving diabetes. Oxidative stress is the principal mechanism of many diabetic complications because of its active role in cellular injury in neuronal and vascular cells (Maiese K., 2015). A hyperglycemic state reduces antioxidant levels, consequently increasing free radical production.(Sonibare M., et al, 2018).

According to Saeedi P. et al., 2020, Diabetics Mellitus is a health crisis in modern society and affects 537 million people worldwide. This number is expected to be increased and become the 7th leading cause of death in the world in 2030 (Ramachandran et al., 2013). Diabetes is a metabolic disorder of carbohydrate, fat, and protein, affecting a large population worldwide. The management of hyperglycemia is of utmost importance to limit the severe complications of Diabetics Mellitus (Viigimaa M., and Sachinidis A., 2020). The conventional treatment of DM includes insulin injections and several anti diabetic drugs such as sulfonylureas (Juan J. and José M. 2016), metformin (Glossmann H.H., and Lutz O. M., 2019), glinides, biguanides, and acarbose (Ma R. 2014).

Despite the success of these drugs in lowering and regulating blood glucose levels, most of these anti diabetic drugs have adverse side effects, including gastrointestinal disorders, anemia, renal failure, weight gain, and hypoglycemia. Therefore, searching for new natural medications with more effective and safer properties is a priority for discovering new anti diabetic drugs (Laurie E. et al., 2020, Dinda B. and Dinda M., 2022, Riaz Z. et al., 2020).

MATERIALS AND METHODOLOGY

MATERIALS:

Acquisition of Plant Materials:

Musa Acuminata were obtained from the modern market in Nigeria and was authenticated by a plant scientist in Nigeria.

Acquisition of Alloxan:

Alloxan was obtained from Ibadan and authenticated by a University chemist in Nigeria.

Extraction of Plant Materials:

The preparation of plant (Musa acuminata leaves) was washed and sun-dried for five days. The dried leaves were ground into flour with a mortar and pestle and sieved. 500mg of the prepared leaf was dissolved in 1L of distilled water and left to stand for 48h; the sample obtained was kept in a container for administration.

Preparation of Alloxan:

1.6g of alloxan was pounded using a laboratory mortar and pestle, dissolved in 50 ml of distilled water, and diluted. The concentration of alloxan obtained was 32mg/ml.

Experimental Animal:

Twenty-five (25) Wistar rats were purchased from Animal House, College of health science, Benue State University Makurdi, Benue, Nigeria. They were housed in the Animal House of the Department of Human Anatomy and allowed to acclimatize for one week before the commencement of the experiments. All the animals were given food (rat chow) and water ad libitum. Experimental groups were given an aqueous extract of Musa Acuminata of various dosages. The experimental rats were weighed at the study's beginning and end.

METHODOLOGY

Experimental Design:

A total number of 25 Wistar rats (male and female) were distributed randomly into five groups (five rats/group). The experiment lasted for ten days, during which alloxan was induced in rats in groups B to E, and after 48h of inducements and the blood glucose level was measured using a glucometer before administration of extract in groups C to E

Group A (negative control group) received distilled water, 5mls per body weight daily for ten days.

Group B (the positive control group) received 150mg/kg of alloxan intraperitonially.

Group C received 100mg/kg of extract orally from day 3 to 10 days and a single dose of Alloxan 150mg intraperitonially on day 1.

Group D received 200mg/kg of extract orally from day 3 to 10 days and a single dose of Alloxan 150mg intraperitonially on day 1.

Group E received 300mg/kg of extract orally from day 3 to 10 days and a single dose of Alloxan 150mg intraperitonially on day 1.

ANIMAL SACRIFICE:

At the end of the experiment (day 15), all the animals were humanely sacrificed. Blood was collected through the animals' left ventricle of the heart in a heparinized centrifuge tube under deep anesthesia with

chloroform. The blood collected was centrifuged using a centrifuge machine at 10,000 rmp for five minutes, and the serum collected was subjected to a kidney function test (Urea and creatinine) and estimation of oxidative stress enzymes (MDA). The kidney tissue was harvested for histological examination.

BIOCHEMICAL ASSAY KIDNEY FUNCTION TEST:

The kidney enzymes analysis, Creatinine, and Blood Urea Nitrogen (BUN) were done using an auto-analyzer.

ESTIMATION OF OXIDATIVE STRESS ENZYMES:

Using the auto-analyzer, the kidney oxidative stress makers analysis was carried out for Lipid Peroxidation (malondialdehyde).

DATA ANALYSIS

Results obtained were analyzed using the statistical software Statistical Package for Social Scientist (SPSS version 18.0), and results were expressed as mean ±SEM. Differences among means of the groups were determined using one-way ANOVA with LSD post hoc test. Paired sample t-test was also used as appropriate, and values were considered statistically significant when $p<0.05$.

RESULTS

PHYSICAL OBSERVATION:

During administration, all the experimental animals (Wistar rats) were observed to have routine physical activity. Weight changes were observed in the experimental animals, **Day 1** before administration and **Day 15** after administration of the experiment, with their weight differences.

During the administration period, **Table 1** shows body weight changes in experimental animals using one-way ANOVA. Weight changes were observed in the groups. An increase in body weights of animals was observed in **Group B, C, D, and E** when compared to **Group A**. However, results revealed a slight decrease in the body weight of **Group D** compared to **Group B**.

There was a significant decrease ($p<0.05$) in the body weight of **Group B, C, D, and E** animals compared to **Group A**. However, results revealed a significant increase ($p<0.05$) in the body weight of **Group C and E** compared to the **Group B**.

Table 1: Showing the mean ± standard deviation of body weight across all groups.

Groups	Initial body weight	Final body weight (g)	Body weight

	(g)		difference (%)
Group A	88.70±12.44	134.82±30.88	46.12±27.30
Group B	112.50±15.90	151.84±23.26	39.34±9.13
Group C	113.10±12.81	154.08±16.90	40.98±11.94
Group D	108.30±19.17	136.04±23.99	27.74±13.93
Group E	117.70±7.54	157.18±18.23	39.48±17.31

BIOCHEMICAL ASSAY

KIDNEY ENZYMES

Creatinine and Blood Urea Nitrogen (BUN):

Table 2 revealed that the Alloxan-treated group **(Group B)** expressed decreased levels of kidney enzymes (Creatinine and Blood Urea Nitrogen (BUN). There was a decrease in kidney enzyme (creatinine) levels in **Groups B, C, D, and E** compared to **Group A** and an increase in **Group C, D, and E** compared to **Group B**. However, in Urea, there was a decrease in **Group B, C, D, and E** when compared to **Group A** and an increase in **Group C, D, and E** when compared to **Group B**

However, there was a significant decrease in both creatinine and Urea in **Group B, C, D, and E.**

Table 2: Showing the mean ± standard deviation of kidney enzymes across all groups.

Groups	Creatinine (mg/dl)	Blood urea nitrogen (mg/dl)
Group A	2.02±0.08	24.12±2.87
Group B	0.77±0.19	18.36±1.52
Group C	0.91±0.27	20.56±2.06
Group D	0.99±0.53	18.81±2.51
Group E	0.97±0.26	20.81±2.59

OXIDATIVE STRESS INDICATOR

Estimation of lipid peroxidation malonaldehyde:

Results depicted in **Table 3** showed that the administration of Musa acuminata aqueous extract caused a significant increase in the levels of MDA compared to the low levels observed in the control group. However, there is also a substantial difference in the decrease of MDA in **Groups C, D, and E** compared to the **Group B**.

In the liver tissue, increased levels of lipid peroxides were recorded in the **Group B, C, D, and E** rats.

Table 3: Showing the mean ± standard deviation of lipid peroxidation malonaldehyde across all groups.

Groups	MDA (nmol/mg pro)
Group A	0.79±0.16
Group B	2.14±0.14
Group C	0.99±0.26
Group D	1.87±0.52
Group E	1.29±0.37

NOTE: *= p>0.05, extract= Musa acuminata

Group 1=negative control (sterile water)

Group 2=positive control (alloxan)

Group 3= extract low dose + alloxan

Group 4= extract medium dose + alloxan

Group 5= extract high dose + alloxan.

HISTOLOGICAL STUDY OF THE KIDNEY

Histological Observations:

Microscopically the kidneys of **Group A** appeared to be expected, as seen in the histological test. The surrounding surfaces were granular, and numerous cortical tissues were present with corticomedullary closure and devoid of vascular markings.

The photomicrograph of this group showed a spherical glomerulus that is composed of superficial endothelial cell capillaries, Bowman's capsules were round shape with simplified squamous cells, proximal convoluted tubules with a cuboid simplex cellular with micro villi, and distal contortus tubules with a rounded cuboid cell with no micro-villi, and the medulla consists of a loop of Henle with spherical simple squamous cell.

Group B, C, D, and E kidney sections appear contracted and have an agranular surface. The cut surface shows a general cortical tissue loss, corticomedullary differentiation, and vascular markings. Their pyramids are small but intact. The parenchyma showed much hemorrhage and vascular congestion. We also observed that there were degenerative changes in the swelling of the epithelium of the proximal.

When you compare **Group B** kidneys to **Group A**, there were varying degrees of relatively cellular interstitial nephritis. A characteristic feature is those areas of dilated tubules alternate with atrophic tubules, rendering a granular appearance to the kidney surface. The histomorphology of **Groups C, D, and E (especially Group E)** is better off than **Group B**, but these were not true for most sections.

Plate 1a and 1b: served as the control group and (sterile water and feed only), Magnification= x40,using H and E.

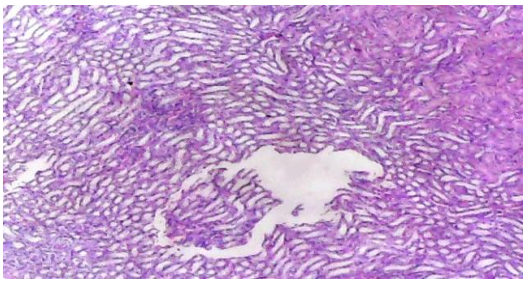


Plate 2a and 2b: served as the alloxan group (positive control), Magnification= x40,using H and E

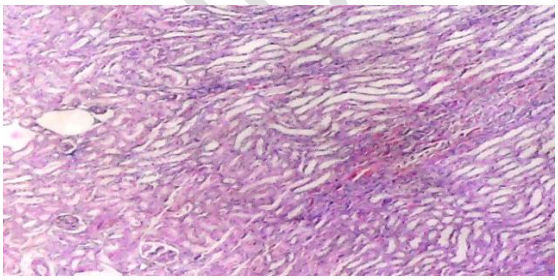


Plate 3a and 3b: served as the extract (low dose) and alloxan. Magnification= x40,using H and E.

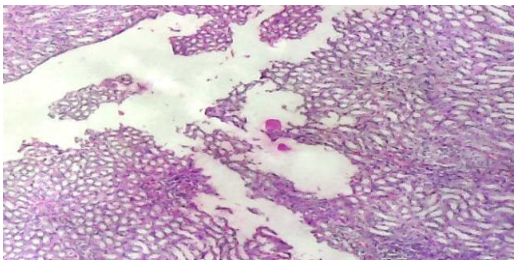


Plate 4a and 4b: served as the extract (medium dose) and alloxan. Magnification= x40,using H and E

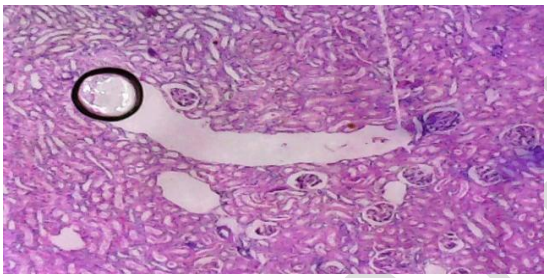
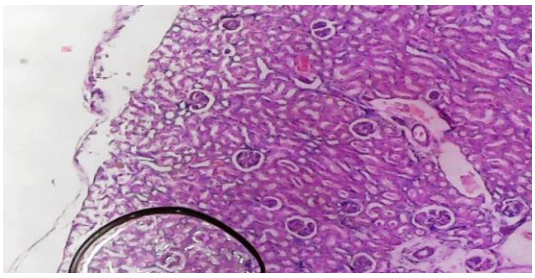


Plate 5a and 5b: served as the extract (highdose) and Alloxan, Magnification = x40 using H and E



DISCUSSION

Glycemic homeostasis refers to glucose balance or control within circulation in living organisms. It usually is compromised mainly in diabetes. The ability of therapeutic compounds, including medicinal plants, to restore glycemic balance or homeostasis in hyperglycemic conditions is an index of their anti diabetic function and relevance. Diabetes was induced by alloxan which aggravates the destruction of beta cells of the pancreas caused by reactive oxygen species (ROS), simulating type-1 and 2 Diabetics Mellitus (Ali, 2018).

PHYSICAL OBSERVATION: The present study evaluated the changes in body weight and organ weight in diabetes mellitus-induced and treated animals for the entire study period as a decrease in body weight is considered a marker for developing Diabetics Mellitus. Our results indicated a considerable change in body and organ weight between alloxan-induced and treated Wistar rats. These results agree with the findings of Miaffo D et al., 2019.

Physical observation of the experimental animals (Wistar rats) revealed changes in the body weights. A marked decrease in body weight was observed in the alloxan-treated group **(Group B)**, which might result from alloxan administration. Changes in body weight have been used to indicate the adverse effects of drugs and chemicals (Miaffo D et al., 2019).

The observed increase in **Group C, D, and E** body weights suggests that the extract might be partially potent against alloxan compared to Group B's weight (Umerah N.N et al., 2023).

KIDNEY ENZYMES: Our results showed that alloxanization caused a significant decrease in creatinine and blood Urea nitrogen. Our results are consistent with those reported by others (Idonije B.O. et al., 2011), who showed that serum urea and creatinine levels were decreased in diabetics mellitus in Wistar rats. The reduced concentrations of Urea and creatinine due to excessive lipolysis in severe diabetes mellitus leads to ketosis and later on to acidosis in **Groups B,C,D and E**, Which as per the studies of (Daisy and Kani, 2013)

A Remarkable decrease of Creatinine and Blood Urea Nitrogen (BUN) enzyme level observed with alloxan administration in **Group B** animals indicates diabetic mellitus.

According to Daisy and Kani, 2013 This suggests that Musa acuminata may be protective against alloxan-induced diabetic mellitus in rats due to its protective nature observed in **Groups C,D and E.**

Groups D and E have a reasonable shielding effect compared to **Group B**, while **Group C** has a small amount. This was ascertained by a comparative analysis of the results obtained in rats pretreated with Musa acuminata.

OXIDATIVE STRESS INDICATOR: Antioxidants enzymes malondialdehyde (MDA) dependently act in the metabolic pathways that involve free radicals. Therefore changes in antioxidant enzyme activity and oxidative stress markers MDA are indicators of Diabetics Mellitus. Extensive lipid peroxidation leads to membrane disorganization by peroxidation of unsaturated fatty acids, which also alters the ratio of poly-unsaturated to other fatty acids. This would lead to a decrease in membrane fluidity and the death of cells. The increase in MDA is due to the toxic effect of alloxan following Joydeep D. et al., 2012.

The increased lipid Peroxidation leads to cellular infiltration and islet cell damage in Diabetics Mellitus (O. Sekiou et al., 2018). This study noticed elevated lipid peroxidation levels in alloxan-treated Wistar rats following Omar Sekiou et al. 2021 investigations. The antioxidant and free radical quenching nature of Musa acuminata may accomplish this normalization.

Increased antioxidant enzyme activity (MDA) observed in alloxan treated group **(Group C)** reflects treatment-related toxicity. This is in agreement with reports from alloxan-related toxicity studies; The increase in the level of MDA in this study toxic effect of alloxan on the kidney by Omar Sekiou et al., 2021.

From the results obtained **(table 3)**, it can be concluded that the extract at a low dose **(Group C)** shows a high-risk case of diabetes mellitus when compared to the high amount **(Group E)** of the extract, as demonstrated in kidney enzyme level and oxidative stress indicators.

HISTOPATHOLOGY OF TREATED EXPERIMENTAL ANIMALS: Histological examination was used to show the severity of toxicity of alloxan-induced Diabetic mellitus. Microscopically the kidneys of Group A appeared to be expected, as seen in histological text. The surrounding surfaces were granular, and numerous cortical tissues were present with corticomedullary closure and devoid of vascular markings. **Group B, C, D, and E** kidney sections appear contracted and have an agranular surface. The cut surface shows a general loss of cortical tissue, corticomedullary differentiation, and vascular markings, which follows Mahmoud and Mahmoud, 2017, Al-Ankily et al., 2020; Elias 2020, Salem et al., 2021 studies.

The recorded alterations verified that diabetes enhanced parenchyma destruction leading to the induction of oxidative stresses (Sadeghinezhad et al., 2016). There was coagulative necrosis (pyknosis) in the epithelium of Henle's loop and the presence of albuminous exudates in the proximal convoluted tubules. In the glomerulus, necrosis in endothelial cells caused a significant gap in the Bowman's space area, and the capsules were seen necrotic in simplex squamous cell wall structure, proximal contortus tubule, and distal contortus tubules were seen to be necrotic, simplex scaly cell wall structure was necrotic and appeared desquamated in its features. Even in the tubular sections, numerous mononuclear inflammatory cells were seen to be necrotic, following the studies of El-Ghazawy et al., 2020.

When you compare **Group B** kidneys to **Group A**, there were varying degrees of relatively cellular interstitial nephritis, areas of dilated tubules alternate with atrophic tubules, rendering a granular

appearance to the kidney surface, a characteristic feature. The histomorphology of **Groups C, D, and E (especially Group E)** seems to be better off than **Group B**, but these were not better than **Group A**

CONCLUSION

Data from the present study indicate that the aqueous extract of Musa acuminata leaves at 200 mg/kg body weight and 300 mg/kg body weight dose exhibited a significant shielding effect of diabetes mellitus than at low dose (100 mg/kg body weight) in the alloxan Induced Wistar rat. From this study, it can be concluded that the aqueous extract of Musa acuminata leaves protects against kidney oxidative damage at high dosages (300mg/kg) and could be used as an effective protector against alloxan-induced diabetic mellitus.

Reference

Al-Ankily, M., Shamel, M., Bakr, M. (2020). Epidermal Growth Factor Improves the Ultrastructure of Submandibular Salivary Glands of Streptozotocin-Induced Diabetic Rats - A Qualitative Study. Int. J. Medi. Dental Sci., 9(1), 1803–1810.

Ali, S. (2018). Stereological and immunohistochemical study on the submandibular gland of diabetic albino rats. J. Am. Sci., 14(12), 24–33.

Choudhury H., Pandey M., Hua C. K., et al. (2018). An update on natural compounds in the remedy of diabetes mellitus: a systematic review. Journal of Traditional and Complementary Medicine, 8(3), 361–376. doi: 10.1016/j.jtcme.2017.08.012.

Daisy, P., & Kani, F.G.J. (2013). Hypolipidemic and hepatoprotective effects of Cassia auriculata Linn bark extracts on streptozotocin-induced diabetics in male Wister albino rats. Asian J. Pharmaceut. Clin. Res., 6(2), 43–48.

Das, J., Parames, C., Sil (2012). Taurine ameliorates alloxan-induced diabetic renal injury, oxidative stress-related signaling pathways, and apoptosis in rats. Amino Acids, 43, 1509–1523.

Dinda B., Dinda M. (2022). Natural Products in Obesity and Diabetes: Therapeutic Potential and Role in Prevention and Treatment. Springer. Natural products, a potential source of new drug discovery to combat obesity and diabetes: their efficacy and multi-target actions in the treatment of these diseases; pp. 101–275.

El-Ghazawy, Y., El-Zainy, M., Hassan, R. (2020). Histological and Immunohistochemical Analysis of Green Coffee Aqueous Extract Effect on Parotid Salivary Gland in Streptozotocin-Induced Diabetic Albino Rats. EJH., 43(3), 748–762.

Elias, W. (2020). The Anti-Diabetic Effect of Hibiscus Cannabinus Extract on the Submandibular Salivary Gland of Alloxan-Induced Diabetic Albino Rats. Int. J. Pharmaceutical Res. Allied Sci., 9(2), 195–202.

Glossmann H. H., Lutz O. M. (2019). Pharmacology of metformin - an update. European Journal of Pharmacology, 865, 172782. doi: 10.1016/j.ejphar.2019.172782.

Idonije, B. O., Festus, O., & Oluba, O. M. (2011). Plasma glucose, creatinine, and urea levels in type 2 diabetic patients attending a Nigerian teaching hospital. Research Journal of Medical Sciences, 5(1), 1-3.

Juan J., José M. (2016). Update on the treatment of type 2 diabetes mellitus. World Journal of Diabetes, 7(17), 354–395. doi: 10.4239/wjd.v7.i17.354.

Lautie E., Russo O., Ducrot P., Boutin J. A. (2020). Unraveling plant natural chemical diversity for drug discovery purposes. Frontiers in Pharmacology, 11, 397. doi: 10.3389/fphar.2020.00397.

Ma R. (2014). Acarbose: an alternative to metformin for first-line treatment in type 2 diabetes. Lancet Diabetes & Endocrinology, 2(1), 6–7. doi: 10.1016/S2213-8587(13)70107-4.

Mahmoud, E., Mahmoud, M. (2017). Effect of Pomegranate Peel Extract on Submandibular Salivary Glands of Streptozotocin-Induced Diabetes in Rats: Histological, Immunohistochemical and Ultrastructural Study. J. Adv. Biol. Biotechnol., 13(3), 1–15.

Maiese K. (2015). New insights for oxidative stress and diabetes mellitus. Oxidative Medicine and Cellular Longevity, 2015, 875961. doi: 10.1155/2015/875961.

Miaffo D, Kamgue OG, Tebou NL, Temhoul CM, Kamanyi A. (2019). Antidiabetic and antioxidant potentials of Vitellaria paradoxa barks in alloxan-induced diabetic rats. Clinical Phytoscience, 5, 44.

Muriach M., Flores-Bellver M., Romero F. J., Barcia J. M. (2014). Diabetes and the brain: oxidative stress, inflammation, and autophagy. Oxidative Medicine and Cellular Longevity, 2014, 102158. doi: 10.1155/2014/102158.

Riaz Z., Ali M. N., Qureshi Z., Mohsin M. (2020). In vitro investigation and evaluation of a novel drug based on polyherbal extract against type 2 diabetes. Journal of Diabetes Research, 2020, 7357482. doi: 10.1155/2020/7357482.

Sadeghinezhad, J., Tootian, Z., Javadi, F. (2016). Anatomical and histological structure of the tongue and histochemical characteristics of the lingual salivary glands in the Persian squirrel (Sciurus anomalus). Anat. Sci. Int., 93(1), 58–68.

Saeedi P., Salpea P., Karuranga S., et al. (2020). Mortality attributable to diabetes in 20-79 years old adults, 2019 estimates: results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Research and Clinical Practice, 162, 108086. doi: 10.1016/j.diabres.2020.108086.

Salem, Z., Kamel, A., AbuBakr, N. (2021). Salivary exosomes as a new therapy to ameliorate diabetes mellitus and combat xerostomia and submandibular salivary gland dysfunction in diabetic rats. J. Mol. Histol., 52(3), 467–477.

Sekiou, O., Boumendjel, M., Taibi, F., Boumendjel, A., Messarah, M. (2018). Mitigating effects of antioxidant properties of Artemisia herba alba aqueous extract on hyperlipidemia and oxidative damage in alloxan-induced diabetic rats. Arch Physiol Biochem, 1–11.

Sekiou, O., Boumendjel, M., Taibi, F., Tichati, L., Boumendjel, A., Messarah, M. (2021). Nephroprotective effect of Artemisia herba alba aqueous extract in alloxan-induced diabetic rats. Arch Physiol Biochem, 1–11.

Sonibare M, et al. (2018). Leaves metabolomic profiling of Musa acuminata accessions using UPLC–QTOF–MS/MS and their antioxidant activity. J. Food Meas. Charact., 12(2), 1093–1106. doi: 10.1007/s11694-018-9725-4.

Thomas D. D., Corkey B. E., Istfan N. W., Apovian C. M. (2019). Hyperinsulinemia: an early indicator of metabolic dysfunction. Journal of the Endocrine Society, 3(9), 1727–1747. doi: 10.1210/js.2019-00065.

Umerah, N. N., & Asouzu, A. I. (2023). Evaluation of Glycemic Index, Hypolipidemic and Hypoglycemic Activities of "osu une" on Alloxan-Induced Diabetic Rats. Retrieved from https://www.sdiarticle5.com/review-history/99372

Viigimaa M., Sachinidis A., Toumpourleka M., Koutsampasopoulos K., Alliksoo S., Titma T. (2020). Macrovascular complications of type 2 diabetes mellitus. Current Vascular Pharmacology, 18(2), 110–116. doi: 10.2174/1570161117666190405165151.