African Scientist Vol. 26, No. 1 March 31, 2025
Printed in Nigeria

1595-6881/2025 $80.00 + 0.00

https://africansciientistjournal.org

afs2024056/26104

Ameliorative Action of the Extracts of *Vernonia amygdalina* and *Dacryodes edulis* on Alloxan-induced Necrosis of the Islet of Langerhans of Albino Wistar Rats

Emmanuel Killian Akpan and Osarhieme Tinuade Okugbo*

[1]Department of Biochemistry, Faculty of Science, Benson Idahosa University, Benin City.
[2]Department of Medical Biochemistry, Faculty of Basic Medical Sciences, College of Medical Sciences, Benson Idahosa University, Benin City.

*Corresponding author email: ookugbo@biu.edu.ng, Tel: +234 (0) 812 289 8163

(Received December 24, 2024; Accepted in revised form February 21, 2025)

ABSTRACT: The global incidence of diabetes mellitus is increasing despite the availability of synthetic antidiabetic agents. This study evaluated the protective and regenerative effects of *Vernonia amygdalina* and *Dacryodes edulis* aqueous leaf extracts on pancreatic beta-cell damage in alloxan-induced diabetic Wistar rats. Thirty-six male rats were randomized into six groups (n = 6). Group 1 was the normal control, while Groups 2–6 were alloxan-induced (150 mg/kg i.p.). Group 2 was the negative control, Group 3 received metformin (200 mg/kg), Groups 4 and 5 were treated with *V. amygdalina* and *D. edulis* extracts (300 mg/kg each), and Group 6 received a combination of both extracts (500 mg/kg). Treatments lasted 14 days. Body and organ weights were recorded, and pancreatic tissues were subjected to histological analysis. All treatment groups showed improved body and organ weights relative to the diabetic control. Histological findings indicated partial to significant regeneration of islet β-cells, with the most marked restoration observed in the metformin and combined extract-treated groups. These results support the antidiabetic potential of these plants and justify their ethnomedicinal application.

Keywords: Diabetes mellitus, Alloxan, *Vernonia amygdalina*, *Dacryodes edulis*, Pancreatic islets, β-cell regeneration

Introduction

Deficiencies in insulin secretion and/or function may be part of the pathogenesis of diabetes mellitus (DM), a metabolic disease that causes chronic hyperglycemia (Ozougwu *et al.*, 2013; Kim, 2019). A third of American adults are predicted to develop hyperglycemia at some point in their lives (Saelee *et al*., 2023), and about 90 % of DM cases are type 2 diabetes mellitus (T2DM), which is the most prevalent type of the disease. The primary cause of type 2 diabetes is the body's tissues' inability to react positively to insulin or produce sufficient amounts (Yun and Ko, 2021). According to several scientific studies, diabetes lowers the overall quality of life by increasing the risk of serious comorbidities like stroke, amputation, kidney failure and blindness, which can result in high morbidity and early death (Garcia *et al*., 2018).
Experimental models of diabetes, such as alloxan-induced diabetes in albino Wistar rats, are widely employed in studying the pathophysiology of diabetes and evaluating potential antidiabetic agents. Alloxan selectively targets pancreatic β-cells, inducing oxidative stress and apoptosis, thereby mimicking the pathogenesis of type 1 and certain aspects of type 2 diabetes (Lenzen, 2008).
With an estimated 10.5 % prevalence among adults aged 20 – 79 in 2021, diabetes mellitus has reached epidemic proportions worldwide and is expected to continue to rise by 2045 (IDF Diabetes Atlas, 2021). Treatments for diabetes mellitus have advanced over time. However, serious side effects like hypoglycemic coma and liver and kidney issues can be brought on by anti-diabetic drugs. To treat diabetes mellitus, the World Health Organization (WHO) recommends using medicinal plants in food products (Chaudhury *et al.*, 2017). Therefore, essential nutrients, medicinal plants and other essential components with anti-hypoglycemic

properties remain essential for diabetes treatment. It has been shown in preclinical and clinical studies that vitamins, essential elements and medicinal plants can effectively lower blood sugar levels (da Rocha *et al.,* 2016).

Plants like the bitter leaf, *Vernonia amygdalina,* and the African pear *Dacryodes edulis* have natural extracts demonstrating encouraging antidiabetic potential (Jayaweera *et al.,* 2022; Idaguko and Adeniyi, 2023) Traditional African medicine extensively uses *Vernonia amygdalina*, which is rich in bioactive substances like flavonoids, alkaloids, tannins, and saponins. These substances have been shown to have anti-inflammatory, hypoglycemic, and antioxidant properties (Asante and Wiafe, 2023). In diabetic animal models, prior research has demonstrated its capacity to reduce blood glucose levels, enhance lipid profiles, and guard against oxidative damage **(**Okugbo and Killian, 2022)**.**

Similarly, *Dacryodes edulis,* possess strong phenolic, alkaloidal, and essential oil components that support its antidiabetic and antioxidant properties (Ononamadu *et al.,* 2019). Its extracts have been demonstrated to improve insulin sensitivity, control glucose metabolism, and lessen the harmful effects of diabetes on the body, including oxidative stress and lipid dysregulation.

While many studies have independently demonstrated the anti-diabetic qualities of *Dacryodes edulis* and *Vernonia amygdalina* (Kumar *et al*., 2013; Kupchan *et al.*, 1969; Agbor *et al.*, 2007; Johns, 2017), little research has compared the combined effect of these plants in diabetic studies (Okugbo and Killian.2022). Previous studies have documented their individual antidiabetic, antioxidant, and anti-inflammatory effects. However, limited information exists on their combined efficacy in pancreatic protection.

This study investigates the histological and physiological effects of these extracts on alloxan-induced diabetic rats to explore their potential synergistic roles in restoring pancreatic function.

Materials and methods

Collection and preparation of plant extracts: Leaf extracts of *V. amygdalina* and *D. edulis* were prepared using the method of Akah *et al*. (2009). The leaves were collected from the main campus of the University of Benin, Benin City, Edo State, Nigeria. Each plant's newly picked leaves were cleansed with distilled water. After being allowed to air dry in the shade, the leaves were manually ground into a powder. The ground powders of *D. edulis* and *V. amygdalina* were macerated separately in distilled water for a whole day. A rotary evaporator was used to evaporate and concentrate the clear filtrate produced after it had been filtered using double muslin cloth and Whatman No. 1 filter paper. The 78 g of *V. amygdalina* and 65 g of *D. edulis* semi-solid leftovers were stored in a plastic container that was sealed and kept at 4 °C.

Experimental animals and induction of Diabetes mellitus: In this study, 36 male Albino Wistar rats were used. Six groups of six rats were established.

Before alloxan monohydrate was used to induce diabetes in any of the experimental animals, they were all fasted for 12 hours. Diabetes was induced by a single intraperitoneal injection of alloxan monohydrate (150 mg/kg body weight) dissolved in 0.9% saline. Rats with fasting blood glucose ≥250 mg/dL after 72 hours were considered diabetic.

Experimental design

- Group 1: Normal control (distilled water)
- Group 2: Diabetic control (alloxan only)
- Group 3: Diabetic + Metformin (200 mg/kg)
- Group 4: Diabetic + V. amygdalina extract (300 mg/kg)
- Group 5: Diabetic + D. edulis extract (300 mg/kg)
- Group 6: Diabetic + Combined extract (500 mg/kg)

Histopathological examination: After the rats were sacrificed, the pancreas was harvested, the blood was extracted for biochemical analysis, the pancreas was cleansed with saline solution, and it was fixed in formalin for 24 h. Tissues were periodically removed and dehydrated by embedding them in paraffin wax. Using a microtome, a 5 µm-thick section of the pancreas was prepared and mounted on a slide. Thereafter, the pancreas was deparaffinized twice in xylene for five minutes each, alcohol was used to dehydrate it, and hematoxylin and eosin dye were used to stain it. Sections were examined under a light microscope for islet integrity and β-cell morphology.

Results

Effect of metformin and the aqueous leaf extracts of V. amygdalina and D. edulis on body and organ weight of Albino Wistar rats: Alloxan administration significantly reduced body and organ weights compared to normal controls. Treatment with metformin and plant extracts improved weight parameters, with the combined extract showing a comparable effect to metformin.

As shown in Tables 1 and 2. The administration of the extracts and metformin resulted in significant improvement in the body and organ weight of the treated animals compared to the untreated group ($P < 0.05$).

Table 1: Effects of metformin, aqueous leaf extracts of *V. amygdalina*, *D. edulis* and their combination on body weight of alloxan-induced diabetic rats

Groups	Duration (Days)			
	0	**4**	**8**	**14**
NC	176±4.49^{aa}	180.17±3.66^{aa}	185.6±4.52^{aa}	188.67±4.71^{aa}
Neg. C	180.17±6.72^{aa}	152.33±3.68	128.67±2.35	119.83±0.31
DC + M	237.5±6.99^{a}	242.67±7.11^{a}	253.83±3.89^{a}	260.33±3.67
DC + DE	189.17±3.75^{aa}	194.33±4.10^{aa}	202.83±5.17^{aa}	211.17±4.91
DC +VA	185.5±9.45^{a}	198.5±8.92^{aa}	207.17±7.90^{a}	220.00±5.17
DC + DE + VA	176.2±54.39^{a}	186.2±5.70^{aa}	203.00±4.35^{a}	218.00±6.76

Results are expressed as Mean ± SEM. Mean that do not share the same letters as superscript in a column are significantly different ($p<0.05$).

Mean values that do not share letters as superscript in a row are significantly different ($p < 0.05$).

NC = normal control, DC =Diabetic control, DC + M = diabetic rats treated with metformin, DC + DE = diabetic rats treated with *Dacryodes edulis*, DC + VA = diabetic rats treated with *Vernonia amygdalina*, and DC + DE +VA = diabetic rats treated with combined extracts of *Dacryodes edulis* and *Vernonia amygdalina.*

Table 2: Effects of metformin, aqueous extracts of *D. edulis* and *V. amygdalina* and their combination on organ weight of alloxan-induced diabetic rats

Groups	Duration (Days)				
	P	**L**	**K**	**H**	**T**
NC	0.88±0.02^{aa}	6.72±0.11^{a}	0.66±0.03^{a}	0.73±0.02^{aa}	1.25±0.02^{a}
Neg. C	0.66±0.07^{a}	5.42±0.03	0.46±0.01^{c}	0.53±0.01	0.64±0.02^{c}
DC + M	0.89±0.06^{aa}	6.80±0.03^{a}	0.65±0.01^{ab}	0.64±0.004^{a}	1.23±0.02^{a}
DC + DE	0.89±0.03^{aa}	6.77±0.01^{a}	0.64±0.01^{ab}	0.61±0.005^{a}	1.19±0.03^{b}
DC +VA	0.89±0.07^{aa}	6.80±0.04^{a}	0.63±0.01^{ab}	0.61±0.007^{a}	1.23±0.02^{a}
DC + DE + VA	0.89±0.03^{aa}	6.81±0.03^{a}	0.62±0.01^{b}	0.60±0.01^{a}	1.19±0.01^{b}

Results are expressed as Mean ± SEM. Mean values that do not share letters as superscripts in a column significantly differ from normal control ($P < 0.05$).

P = Pancreas, L = Liver, K = Kidney, H = Heart, T = Testes.

NC = normal control, DC = Diabetic control, DC + M = diabetic rats treated with metformin, DC + DE = diabetic rats treated with *Dacryodes edulis*, DC + VA = diabetic rats treated with *Vernonia amygdalina*, and DC + DE +VA = diabetic rats treated with combined extracts of *Dacryodes edulis* and *Vernonia amygdalina*

Histopathological findings: Figure 1 (plates A—F) shows the histopathological analysis of the β cell of the pancreas of alloxanized rats treated with *V. amygdalina and D. edulis*.

In the normal control group (Group 1), the pancreatic sections exhibited intact islets of Langerhans with well-preserved β-cell architecture (Plate A). The diabetic control group (Group 2), which received alloxan but no treatment, showed marked degeneration and necrosis of the β-cells, characterized by cellular disruption and loss of islet integrity (Plate B).

Treatment with metformin (Group 3) resulted in marked regenerative changes in the islets, with significant restoration of β-cell mass and architecture (Plate C). Rats treated with *Vernonia amygdalina* extract alone (Group 4) showed moderate recovery of islet cell structure, with visible β-cell clusters and reduced cellular damage (Plate D).

Similarly, the group treated with *Dacryodes edulis* extract (Group 5) showed mild-to-moderate β-cell regeneration with improved cellular density compared to the diabetic control group (Plate E). Rats treated with the combined extract of *V. amygdalina* and *D. edulis* (Group 6) exhibited significant restoration of islet architecture, with densely packed β-cells and normal histological appearance (Plate F).

These observations suggest a progressive ameliorative action of the plant extracts, with metformin and the combined extracts demonstrating the highest efficacy.

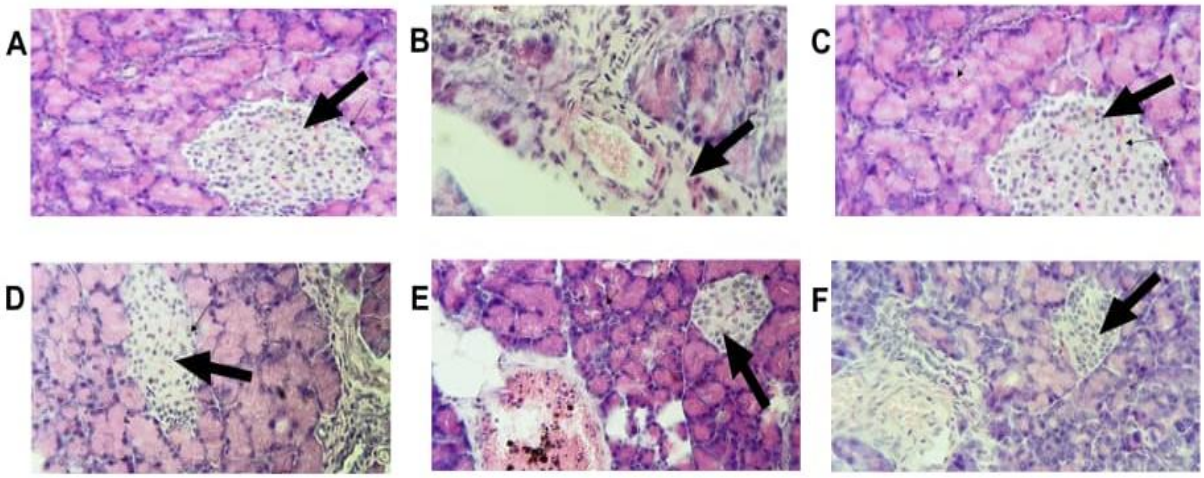

Figure 1: Histopathological sections of the pancreas (Hematoxylin & Eosin stain, ×400 magnification)

Plate A (Group 1 – Normal Control): Normal pancreatic architecture showing well-organized and intact islets of Langerhans with abundant β-cells.

Plate B (Group 2 – Diabetic Control): Severe degeneration and necrosis of islets of Langerhans. Marked reduction in β-cell population with disorganized architecture.

Plate C (Group 3 – Metformin Treated): complete regeneration of islet cells. Densely populated β-cells and normal islet morphology comparable to control.

Plate D (Group 4 – *Vernonia amygdalina* Treated): Moderate restoration of β-cell mass. Regenerating islets with some preserved architecture.

Plate E (Group 5 – *Dacryodes edulis* Treated**):** moderate β-cell regeneration. Islets appeared partially organized.

Plate F (Group 6 – Combined Extract Treated): significant restoration of islets of Langerhans.

Discussion

Weight loss is one of the characteristic features of diabetes mellitus. This is attributed to high depletion of body adiposity occasioned by hypoinsulinemia (Pardhan, 2023). The present study shows the effects of treatment on the body weight of diabetic rats. From the study, it is observed that there was a significant improvement in the body weight of the animals following treatment with the extracts and metformin. This is in agreement with Kim *et al*. (2023), whose study indicated that weight loss within the first two years of a type 2 diabetes diagnosis increased the likelihood of achieving diabetes remission. The reduction in body weight seen in untreated rats could be attributed to the excessive breakdown of fatty acids and protein due to insufficient glucose in the cells. Similarly, glycosuria, one of the symptoms of diabetes mellitus, results in excessive excretion (loss) of glucose, resulting in weight loss in spite of the concomitant increase in appetite (Nguyen *et al.,* 2024). Hence, uncontrolled weight loss was prevented following the administration of the drug (metformin) and the extracts.

Diabetes mellitus, particularly type 2 diabetes mellitus (T2DM), induces metabolic and physiological alterations in multiple organs, often resulting in changes in organ weight**.** These changes are largely due to insulin resistance**,** chronic inflammation**,** lipid accumulation, and vascular complications **(**Daryabor *et al*., 2020). In the present study, there was excessive organ weight reduction following alloxan exposure. The result reveals the varying degree of restoration of weight in the pancreas, liver, kidneys, testes and heart following treatment with metformin and the aqueous extracts of *V. amygdalina* and *D. edulis.* The alteration in organ weight agrees with the study conducted by Hu *et al*., (2023) who observed that in early stages of T2DM, kidney hypertrophy may occur due to hyperfiltration and increased metabolic demands which progressively leads to kidney atrophy and loss of weight. Similarly, Yamaghishi *et al*. (2012) reported that diabetes can lead to cardiac hypertrophy and remodeling due to persistent high blood pressure, oxidative stress, and advanced glycation end-products (AGEs).

The observed histopathological changes confirm the potential of *Vernonia amygdalina* and *Dacryodes edulis* extracts to mitigate alloxan-induced pancreatic damage. The β-cell necrosis seen in the diabetic control group aligns with known effects of alloxan, which selectively targets pancreatic β-cells, causing oxidative stress and DNA damage (Lenzen, 2008). This leads to significant loss of β-cell function and structural integrity, mirroring the pathophysiology of diabetes mellitus. In the present study, after 14 days of alloxan injection, the histology of the β cells of the pancreas showed necrosis and complete loss of structure and function. This is in consonant with similar studies where animals' exposure to alloxan caused their β cells to necrotize (Elsner *et al.,* 2008).

According to previous findings, the GLUT-2 transporter mediates the uptake of alloxan into β cells (Jalal *et al.,* 2007). By the end of the experiment, the group that received the plant extracts and metformin had much lower blood glucose levels than the negative control group.

Studies on type 1 diabetes has long used alloxan as a model since it specifically affects pancreatic β cells. According to Obeten *et al*. (2014), an alloxan injection raises insulin secretion regardless of the presence of glucose, resulting in hyperinsulinemia, or elevated insulin circulation in the plasma. A full suppression of the islet response to glucose occurs shortly after the commencement of alloxan-induced hyperinsulinemia. Furthermore, it has been proposed that one of the main reasons impacting alloxan's diabetogenicity is the rapid absorption of the drug by pancreatic β cells, which results in β cell necrosis (Lenzen, 2008). According to reports, ROS's impact on the DNA of the pancreatic islets is another possible explanation of alloxan's diabetogenic effect. Alloxan exposure in β cells has been shown to result in DNA fragmentation, which harms DNA. Consequently, poly ADP-ribosylation, a DNA repair step, is triggered (Ankur and Shahjad, 2012).

The present study is a continuation of the report by Okugbo and Killian (2022). In the study, the effect of the leaf extracts of *V. amygdalina* and *D. edulis* on alloxan-induced diabetic rats was investigated. Hyperglycemia was confirmed following injection of 150 mg/kg of alloxan. Dyslipidemia, renal and hepatic disorders were also confirmed following the administration of 150 mg/kg of alloxan. Treatment with metformin, *V. amygdalina* and *D. edulis* showed a remarkable drop in the blood glucose levels as well as normalization of lipid profile, as well as kidneys and liver functions. The decrease in the groups that received the plant extracts could have resulted from either the extracts' stimulation of insulin release or the potential regeneration of the β cells in the pancreas. *Vernonia amygdalina* extracts have the ability to regenerate pancreatic β cells that have been damaged by streptozocin, according to a previous study conducted by Ugoanyanwu *et al.* (2015).

The treatment groups demonstrated a clear trend in ameliorative effects. Metformin, a well-established antidiabetic agent, showed the highest degree of β-cell restoration, as expected. This supports its known ability to preserve pancreatic function and enhance insulin sensitivity. This study agrees with the report of Salem (2022), who in a study involving alloxan-induced diabetic rats, treatment with metformin nanoparticles resulted in significant improvements in liver and kidney function markers. Histopathological analyses revealed alleviation of damage in the pancreas, liver and kidneys, indicating a protective role of metformin at the organ level.

*Vernonia amygdalina'*s moderate restoration of islet structure aligns with previous studies highlighting its hypoglycemic and antioxidant properties. The bioactive compounds, including flavonoids and saponins, may help counteract oxidative stress and promote β-cell regeneration. This finding aligns with that of Ong *et al*. (2011), who demonstrated that *V. amygdalina* extract improved glucose tolerance, decreased fasting blood glucose, and exhibited protective effects on pancreatic β-cells against streptozotocin-induced damage. These benefits were attributed to the extract's antioxidant properties and ability to enhance GLUT4 expression in skeletal muscle. Similarly, Akpaso *et al*. (2017) reported the full restoration of the streptozotocin-induced damaged β cells following treatment with the methanol extract of *Vernonia amygdalina*. Saponins derived from *Vernonia amygdalina* were found to have antioxidant and hypolipidemic properties. Asanta & Wiafe (2023) reported that saponins extracted from *Vernonia amygdalina* were found to have antioxidant and hypolipidemic properties. Some significant phytochemicals in the leaf extracts of the plant were identified (Alara *et al.,* 2017; Atangwho *et al.,* 2013). Previous research has demonstrated that the presence of saponin lowers blood glucose levels by reducing oxidative stress and has anti-diabetic properties that promote insulin secretion, action and β-cell regeneration in the pancreas (El Barky *et al.,* 2016).

Dacryodes edulis, rich in phenolics and essential oils, exhibited mild-to-moderate improvement in islet histology, suggesting a complementary antioxidant effect. This validates the study by Okolo *et al*. (2016), which examined the hexane extract of *Dacryodes edulis* in alloxan-induced diabetic rats and found that the extract decreased blood glucose levels and improved lipid profiles. Histopathological analysis revealed that the extract restored pancreatic β-cell architecture, suggesting a protective effect on pancreatic tissues.

The study confirms the antidiabetic and regenerative effects of *V. amygdalina* and *D. edulis*, individually and in combination. The observed histological improvements suggest the extracts may protect and promote recovery of pancreatic β-cells, likely through antioxidant and anti-inflammatory mechanisms. The combination therapy appeared synergistic, warranting further investigation.

These findings underscore the potential of these plant extracts, individually and in combination, as candidates for managing diabetes-induced pancreatic damage. However, further studies are needed to isolate the active compounds responsible for the observed effects, establish optimal dosages, and evaluate long-term safety and efficacy.

Conclusion

Aqueous extracts of *V. amygdalina* and *D. edulis* demonstrated protective effects against alloxan-induced pancreatic damage. These findings support their ethnomedicinal use and highlight the potential for combined phytotherapy in diabetes management.

Acknowledgments

The authors would like to acknowledge the technical support of the laboratory technologists at Benson Idahosa University's Department of Biochemistry.

Ethical Approval

The Institutional Animal Ethics Committee approved all procedures involving animals and conformed to national guidelines for laboratory animal care and use.

Conflict of Interest

The authors declare no conflict of interest

References

Akah P, Alemji J, Salawu O: Effects of *Vernonia amygdalina* on biochemical and haematological parameters in diabetic rats. Asian J Med Sci, 1(3):108-113. 2009.

Alara OR, Nour A, Olalere OA: Phytochemical and pharmacological properties of *Vernonia amygdalina*: A review. J Chem Eng Ind Biotechnol, 2: 80–96. 2017.

Akpaso MI, Igiri AO, Odey PA: A comparative study on the effect of combined methanolic leaf extracts of *Vernonia amygdalina* and *Gongronema latifolium* and metformin on the pancreatic β cells of streptozotocin-induced diabetic Wistar rats. Asian J Pharm Nurs Med Sci, 5(2): 1–8. 2017.

Agbor A, Kuate D, Oben JE: Medicinal plants can be good source of antioxidants: Case study in Cameroon. Park J Biol Sci, 10(4):537-544. 2007.

Ankur R, Shahjad A: Alloxan induced diabetes: mechanisms and effects. Int J Res Pharm Biomed Sci, 3(2):819-823. 2012.

Atangwho IJ, Egbung GE, Ahmad M, Yam MF, Asmawi M.Z: Antioxidant versus anti-diabetic properties of leaves from *Vernonia amygdalina* del. growing in Malaysia. Food Chem 141(4): 3428–3434. 2013.

Asante DB, Wiafe GA: Therapeutic benefit of *Vernonia amygdalina* in the treatment of diabetes and its associated complications in preclinical studies. J Diabetes Res, 22: 1155. 2023.

Chaudhury A, Duvoor C, Reddy Dendi VS, Kraleti S, Chada A, Ravilla R, Marco A, Shekhawat N.S, Montales MT Kuriakose K.: Clinical review of antidiabetic drugs: implications for type 2 diabetes mellitus management. Front Endocrinol, 8(6). 2017.

Choudhury H, Pandey M, Hua CK, Mun CS, Jing JK, Kong L, Ern LY, Ashraf NA, Kit SW, Yee TS: An update on natural compounds in the remedy of diabetes mellitus: A systematic review. J Tradit Complement Med, 8(3): 361–376. 2018.

da Rocha Fernandes J, Ogurtsova K, Linnenkamp U, Guariguata L, Seuring T, Zhang P, Cavan D, Makaroff LE: IDF diabetes atlas estimates of 2014 global health expenditures on diabetes. Diab Res Clin Pract, 117: 48–54. 2016.

Daryabor G, Atashzar MR, Kabelitz D, Meri S, Kalantar K: The effects of type 2 diabetes mellitus on organ metabolism and the immune system. Front Immunol, 11: 1582. 2020.

El Barky AR, Hussein SA, Alm-Eldeen AA, Hafez YA, Mohamed, TM: Anti-diabetic activity of Holothuria thomasi saponin. Biomed Pharmacother, 84: 1472–1487. 2016.

Elsner M, Gurgul-Convey E, Lenzen S: Relation between triketone structure, generation of reactive oxygen species and selective toxicity of the diabetogenic agent alloxan. Antioxid Redox Signal, 67: 7-9. 2017.

Garcia DE, Narvaez-Mendez M, Morgan S, Coronado-Malagon M, Arce-Salinas CA, Barajas A, Arenas I, Svarch A: Biomarkers through the development, progression, and chronic complications of diabetes mellitus: A mini-review. J Endocrinol Diabetes, 5(1): 1–7. 2018.

Hu Q, Chen Y, Deng X, Li Y, Ma X, Zeng J, Zhao Y: Diabetic nephropathy: Focusing on pathological signals, clinical treatment, and dietary regulation. Biomed. Pharmacother, 159: 114252. 2023.

Idaguko CA, Adeniyi MJ: Indigenous antidiabetic medicinal plants used in Nigeria: A review. *Asian* P*lant Res J*, 11(6): 81-97. 2023.

Jalal R, Bagberi S, Moghimi A, Rasuli M: Hypoglycemic effect of aqueous shallot and garlic extracts in rats with fructose induced insulin resistance. J Clin Biochem Nutr, 41 (3): 218-223. 2007.

Jayaweera U, Akowuah GA, Ling CY, Kumar PV, Herapathdeniya S: Diabetes and *Vernonia amygdalina* Delile (Asteraceae). Biointerface Res Appl Chem, 12 (4): 4496–4517. 2022.

Johns T: Dietary, diversity, global change and human health. Proceedings of the Symposium Managing Biodiversity in Agricultural Ecosystems, Nov 8–10, Montreal, Canada. 1–11. 2017.

Kim H.G: Cognitive dysfunctions in individuals with diabetes mellitus. Yeungnam Univ J Med, 36(3):183–191. 2019.

Kim J, Kim B, Kim MK, Baek KH, Song KH, Han K, Kwon HS: Weight change in patients with new onset type 2 diabetes mellitus and its association with remission: Comprehensive real-world data. Diabet Obes Metab, 26(2): 567–575. 2023.

Kupchan SM, Hemingway RJ, karim A, Wermer D: tumour inhibitors xlvii vernodalin and vernomygdin, two new cytotoxic sesquiterpene lactones from *Vernonia amygdalina* Del. J Org Chem, 34(12): 3908-3911. 1969.

Kumar S, Pandey AK: Chemistry and biological activities of flavonoids: an overview. Sci World J, 16: 750-760. 2013.

Lenzen S: The mechanisms of alloxan- and streptozotocin-induced diabetes. Diabetologia, 51(2):216-226. 2008.

Nguyen AT, Amigo Z, McDuffie K, MacQueen VC, Bell LD, Truong LK, Batchi G, McMillin SM: Effects of empagliflozin-induced glycosuria on weight gain, food intake and metabolic indicators in mice fed a high-fat diet. Endocrinol Diabetes Metab, 7(2):e00475. 2024.

Obeten KE, Ubom KS, Charles CM: Some histological changes in the intestines of alloxan induced diabetic mellitus albino rats. J Biol Agric Healthcare, 4:81-84. 2014.

Okolo CA, Ejere VC, Chukwuka CO, Ezeigbo II, Nwibo DD, Okorie AN: Hexane extract of *Dacryodes edulis* fruits possesses anti-diabetic and hypolipidaemic potentials in alloxan diabetes of rats. Afr J Tradit Complement Altern Med, 13(4):132–144. 2016.

Okugbo OT, Killian AE: Antidiabetic effect of aqueous extracts of *Vernonia amygdalina* an *Dacryodes edulis* leaves and their combination in alloxan-induced diabetic rats. BIU J Basic Appl Sci, 7(1):105-118. 2022.

Ong KW, Hsu A, Song L, Huang D, Tan BKH: Polyphenols-rich Vernonia amygdalina shows anti-diabetic streptozotocin-induced diabetic rats. J Ethnopharmacol, 133(2): 598–607. 2011.

Ononamadu CJ, Alhassan AJ, Ibrahim A, Imam AA, Ihegboro GO, Owolarafe TA, Sule MS: Methanol-extract/fractions of *Dacryodes edulis* leaves ameliorate hyperglycemia and associated oxidative stress in streptozotocin-induced diabetic Wistar rats. J Evid Based Integr Med, 24: 1–12. 2019.

Ozougwu JC, Obimba KC, Belonwu CD, Unakalamba CB: The pathogenesis and pathophysiology of type 1 and type 2 diabetes mellitus. J Physiol Pathophysiol 4(4): 46–57. 2013.

Pardhan S: Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. Lancet, 402(10397):203-234. 2023.

Roglic G: WHO global report on diabetes: A summary. Int J Noncommun Dis, 1(1): 3-8. 2016.

Saelee R, Hora IA, Pavkov ME, Imperatore G, Chen Y, Benoit SR, Holliday CS, Bullard KM: Diabetes prevalence and incidence inequality trends among US adults, 2008–2021. Am J Prevent Med, 65(6):973-82. 2023.

Salem AA: The superiority of the nanoparticle form of metformin over its conventional form on glucose levels and SIRT-1 gene expression in diabetic male rats. Benha Vet Med J, 42(2):120-7. 2022.

Ugoanyanwu FO, Mgbeje BI, Igile GO, Ebong PE: The flavonoid-rich fraction *Vernonia amygdalina* leaf extract reversed diabetes-induced hyperglycemia and pancreatic B cell damage in albino Wistar rats. World J Pharm Pharm Sci, 4(10):1788–1802. 2015.

Yamagishi SI, Maeda S, Matsui T, Ueda S, Fukami K, Okuda S: Role of advanced glycation end products (AGEs) and oxidative stress in vascular complications in diabetes. Biochimica et Biophysica Acta (BBA)-General Subjects, 1820(5):663-671. 2012.

Yun JS, Ko SH: Current trends in epidemiology of cardiovascular disease and cardiovascular risk management in type 2 diabetes. Metabolism: Clin Exp, 123: 154838. 2021.