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Ethanol leaf extract of *Alchornea cordifolia* (Euphorbiaceae) effects on reproductive dysfunctions in streptozotocin-induced diabetic male Wistar rats

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Abstract. *Ejeh SA, Abu HA, Onyeyili PA, Abenga JN, Abalaka SE, Enefe NG, Eugiene I. 2024. Ethanol leaf extract of* Alchornea cordifolia *(Euphorbiaceae) effects on reproductive dysfunctions in streptozotocin-induced diabetic male Wistar rats. Asian J Nat Prod Biochem 22: 35-42.* Diabetes and some of its treatment agents reportedly induce male reproductive dysfunction in male Wistar rats. Therefore, the study investigated the therapeutic effects of ethanol leaf extract of *Alchornea cordifolia* (Schumach. & Thonn.) Müll. Arg. on diabetic male Wistar rats. Twenty-five male Wistar rats were used, and 50 mg/kg freshly prepared streptozotocin in cool citrate buffer single intraperitoneal injection was used to induce diabetes mellitus. The rats were grouped into 5 of 5 rats each. Group 1 was normal + distilled water; group II was diabetic untreated; group III was diabetic + 100 mg/kg metformin HCl; and IV and V rats were diabetic and received 100 and 200 mg/kg of the extract orally, respectively. Treatment was done for 28 days; after that, reproductive parameters such as extrapyramidal sperm parameters (sperm motility, count, concentrations, viability, morphology, and acrosome integrity) and hormonal assay (FSH, LH, and Testosterone) were evaluated using a standard protocol. Testicular and epididymal histopathological changes were analyzed using standard procedure. The results revealed a marked impairment in all the parameters evaluated in the untreated diabetic group. However, groups exposed to the ethanol leaf extract of *A. cordifolia* recorded a significant ($p < 0.05$) improvement in the above-mentioned reproductive parameters, including the restorations of the collapsed epididymal tubules observed in the diabetic untreated group. Therefore, the ethanol leaf extract of *A. cordifolia* can potentially facilitate and restore reproductive dysfunctions associated with diabetes mellitus complications, hence a possible alternative to synthetic antidiabetic agents.

Keywords: *Alchornea cordifolia*, diabetes mellitus, histopathology, morphometry, sperm parameters

INTRODUCTION

Diabetes mellitus is a non-infectious endocrine, metabolic condition with persistent hyperglycemia resulting from deficient insulin secretion or the inability of insulin receptors to function effectively or both. The global estimate of people affected with diabetes mellitus stood at 463 million, with about 1.5 million deaths annually (American Diabetes Association (ADA 2022)). Diabetes mellitus is a highly devastating disease with increased morbidity and mortality (Lotti and Maggi 2023) if not properly managed and could lead to increased complications such as retinopathy, neuropathy, and foot ulceration (ADA 2021) and macrovascular complications and several other systemic disorders (Zawada et al. 2018). Studies have shown that diabetes mellitus affects the health status of an individual, leading to poor quality of life by enhancing and modulating several risk factors associated with the condition and a consequential increase in several complications such as microangiopathy and macrovascular diseases, resulting in higher morbidity and mortality (E-Garcia et al. 2018; Yun and Ko 2021). Besides the various complications recorded in diabetes, the recent rise in cases of infertility among diabetic patients has increased the awareness of many researchers regarding the role of diabetes in reproductive failure (Ventimiglia et al. 2017). According to He et al. (2021), there is a growing incidence of diabetes mellitus among male couples worldwide compared to their female counterpart, prompting an insinuation that most infertility in couples may be caused by male factor-induced infertility. Investigations into the possible mechanisms of diabetes-induced reproductive dysfunctions revealed a serious change in semen/sperm quality owing to an increase in mitochondria DNA fragmentation, apoptosis, and DNA integrity decrease (Shi et al. 2017). Oxidative stress induced by hyperglycemia has been implicated in the pathophysiology of diabetes reproductive dysfunctions (Shoorei et al. 2019), resulting in

increased DNA sperm damage and decreased sperm motility, viability, and count. Increased oxidative stress-induced reproductive dysfunction in diabetic patients has also been attributed to the impairment of the hypothalamic-pituitary-gonadal axis, leading to hormonal disorders (Temidayo and du Plessis 2018). Several treatment protocols have been used in the management of diabetes and its complications, including the use of oral antidiabetic agents such as Metformin, which is considered the first-line drug of choice (Fatima et al. 2018). However, exposure of diabetes patients to these agents has been shown to exert a negative effect on the reproductive system, resulting in reduced testosterone levels, sexual motivation, libido, and erectile dysfunctions (Al-Kuraishy and Al-Gareeb 2016).

Recent scientific improvement has led to the development of several treatment protocols for managing diabetes and its complications. However, side effects such as hepatic and gastrointestinal disorders, hypoglycemic coma, and lactic acidosis have been associated with the use of current antidiabetic agents (Chaudhury et al. 2017). Interestingly, the World Health Organization recommends alternative plant-based medicine to treat the disease (da Rocha Fernandes et al. 2016). Therefore, there is a need for a search for alternative remedies for the therapeutic management of diabetes and its reproductive complications that will be readily accessible, available, and potent.

The use of plants as alternatives to synthetic antidiabetic agents has continued to attract researchers' concerns, given the presence of important bioactive molecules with therapeutic properties (Solati et al. 2021). It has become a major source of disease management among the rural population in sub-Saharan Africa (Solati et al. 2021). *Alchornea cordifolia* (Schumach. & Thonn.) Müll. Arg. is a dioecious evergreen plant belonging to the family Euphorbiaceae. It is a widely used plant in both tropical and sub-Saharan African traditional medicine for managing diverse disease conditions ranging from respiratory, gastrointestinal, wound healing, infectious diseases, and inflammatory conditions (Noundou et al. 2016). Several reports have attributed *A. cordifolia* medicinal actions to the presence of vital phytochemical compounds such as flavonoids, polyphenols, alchornedine, triterpenes, quercetin, steroids, and protocatechnic acids (Kouakou-Siransy et al. 2010; Osadebe et al. 2012) Pharmacological activities associated with *A. cordifolia* have also been reported, including; antimicrobial, anti-inflammatory, antidiarrheal, antidiabetic, and antioxidant activity (Agbor et al. 2004; Manga et al. 2004; Effo et al. 2017).

Although the antidiabetic and reproductive enhancing potentials of *A. cordifolia* have been investigated (Mohammed et al. 2013; Ngaha-Njile et al. 2019), its ameliorative activity on reproductive dysfunctions associated with diabetic complications remains poorly understood. Hence, this work aimed to evaluate the therapeutic effects of *A. cordifolia* on reproductive dysfunctions in streptozotocin-induced diabetic Wistar rats.

MATERIALS AND METHODS

Ethical clearance was sought and received from the University of Abuja Ethics Committee on Animal Use (UAECAU), Nigeria with approval number UAECAU/2022/005. It was performed according to national guidelines on the use of animals for scientific investigation.

Plant collection

The *A. cordifolia* leaf was collected from a farm in Alkpali, Ugbokolo, Okpokwu Local Government Area, Benue State, Nigeria during the dry season. Dr Okoh Thomas identified and authenticated the leaf at the herbarium of the Department of Botany, Faculty of Biological Sciences, Joseph Sarwuan Tarka University Makurdi, Nigeria, where the voucher's number (FUAM/BOT/HERB/02781) was deposited for future reference.

Extract preparation

The harvested leaves were washed in running tap water to remove sand and other solid particles/impurities and dried under laboratory conditions before pulverization into a fine powder using an electric blender. Next, 500 g of the leaves powder was loaded into the thimble and extracted in 1000 mL ethanol using the Soxhlet apparatus and concentrated at 40°C for three (3) hours in a rotary evaporator (Shanghai Yarong Re-52aa/52CS, China) before evaporating it to dryness using a water bath at 40°C to obtain a yellow-brown Ethanol Leaf Extract of *A. cordifolia* (ELEAC) residue. The percentage yield recorded was 28.8%.

Induction of diabetes mellitus in male albino Wistar rats

Diabetes mellitus was injected by intraperitoneal injection of 50 mg/kg of streptozotocin in freshly prepared 0.1M cold citrate buffer at a pH of 4.5 after eighteen (18) hours of fasting. The rats were then exposed to clean water and feed before measuring their blood glucose levels using blood from the tail vein on an Accu-chek® glucometer (Accu-chek® GB, Roche Mannheim Germany) after forty-eight (48) hours of treatment. Male Wistar rats with fasting blood glucose above 200 mg/dL concentrations were considered diabetic and selected for the study.

Testicular and epididymal morphometric evaluation

Morphometric parameters such as weight, length, width, and volume of the epididymis and testes were measured using conventional instruments such as a ruler, scientific weighing scale, measuring cylinder, and ropes.

Evaluation of epididymal sperm motility

Sperm motility was determined using the swim-out technique (Veen and Preeti 2017). After exteriorization and trimming of the cauda epididymis to remove fat and tissue debris, a small incision was made through it and then placed in 1 mL of normal saline for a few minutes to allow the spermatozoa to swim into the fluid. After that, a drop of the suspension was placed on a pre-warmed grease-free

glass slide, and a cover slip was placed on it, which was viewed at X400 magnification. Individual sperm motility was assessed by counting progressive motile sperm across different fields per unit area. The values were presented as percentages of motile spermatozoa.

Evaluation of epidydimal sperm viability

Sperm viability was assessed using the method of (Blom 1973). Briefly, about 0.1 mL of sperm suspension was mixed with 0.1 mL of eosin-nigrosin stain on a grease-free microscope slide and allowed to stand for a few seconds. Next, a smear was made, air-dried, and viewed at X400 magnification. After that, 200 spermatozoa were counted across different fields, and the percentage of live spermatozoa was recorded.

Evaluation of epididymal sperm concentration

The method of (Robb et al. 1978) was used to evaluate epididymal sperm concentration. Briefly, a drop of sperm suspension prepared in 0.05% formol-saline was placed on a pre-warmed improved hemocytometer and counted to determine the epididymal sperm concentration.

Evaluation of epididymal sperm morphology

The effect of the extract on sperm morphology was evaluated using sperms from the cauda epididymis, following the method of (Linder et al. 1992). Next, 0.1 mL sperm suspension was placed on a grease-free slide to make a thin smear. The smear was air-dried, fixed in methanol, and stained with Giemsa. After that, the slide was washed in running water, dried, and viewed at X40 magnification. Abnormal spermatozoa were counted in different fields and expressed as a percentage of the normal spermatozoa.

Assessment of the effects of the extract on acrosome integrity of spermatozoa of streptozotocin-induced diabetic male albino Wistar rats

In this study, the method of (De-Oliveira et al. 2011) was used to assess the effects of the extract of *A. cordifolia* on the acrosome integrity of spermatozoa in Streptozotocin-induced diabetic rats. Briefly, 0.1 mL of sperm suspension was placed on a pre-warmed glass slide, and a smear was made on it. The smear slides were fixed in methanol for 10 minutes and rinsed for a few minutes in running tap water. After that, the slides were stained in buffer Giemsa for three hours, rinsed in running water, dried, and examined at X400 magnification. Next, 200 cells were counted under the microscope, and the number of intact acrosome, which is characterized by purple head, was calculated by dividing its number by the total number of spermatozoa multiplied by 100%

Evaluation of the effects of ethanol leaves extract of *A. cordifolia* on male hormones of streptozotocin-induced diabetic Wistar rat

Male hormones [testosterone, luteinizing hormone (LH), and Follicle-Stimulating Hormone (FSH)] were evaluated using commercial ELISA kits obtained from Monobind Inc. (Lake Forest, CA 92630, USA) following the manufacturer's instructions. The values were extracted from the plotted absorbance curve versus the concentrations and recorded accordingly.

Histopathological analysis

The testis and the epididymis were harvested after the last day of treatment following the humane sacrifice of the experimental Wistar rats. For histopathological preparation according to standard procedures (Bancroft and Cook 1994), combined ketamine (0.1 mg/kg)/xylazine (0.5 mg/kg) was administered after fixation in 10% formalin for histopathological evaluations.

Statistical analysis

Data obtained from this study were analyzed and represented as mean ± standard error of the mean (Mean ± SEM). Data were subjected to a One-way analysis of variance, and tests of significance between treated groups and control were evaluated using Dunnett's multiple post hoc test. All statistical analyses were done using GraphPad Prism version 7 software (Graph Pad Prism Inc., San Diego, CA, USA), and values of $P < 0.05$ were considered significant.

RESULTS AND DISCUSSION

Testicular and epidydimal morphometry

The results of testicular and epididymal morphometry revealed a significant ($p < 0.05$) increase in the weight of the epididymis compared with the diabetic untreated group. However, no significant changes in the other parameters were measured (Table 1).

Table 1 The effects of ethanol leaf extract of *Alchornea cordifolia* on testicular and epidydimal morphometry of streptozotocin-induced diabetic male albino Wistar rats

Groups	Testes weight (g)	Testes length (cm)	Testes width (cm)	Testes volume (cm)	Epididymal weight (g)	Epididymal length (cm)
Control	1.31±0.21	1.81±0.13	1.08±0.25	1.21±0.21	0.33±0.03[a]	4.10±0.14
Diabetic contr.	1.22±0.13	2.03±0.02	1.09±0.03	1.28±0.12	0.36±0.02	4.47±0.18
Extract (100 mg/kg)	1.21±0.13	1.88±0.12	1.08±0.06	1.28±0.11	0.38±0.06	3.84±0.36
Extract (200 mg/kg)	1.24±0.04	1.89±0.05	1.03±0.01	1.31±0.06	0.51±0.02[b]	4.54±0.10
Metformin (5 mg/kg)	1.33±0.04	1.98±0.02	1.13±0.04	1.27±0.07	0.39±0.01	4.60±0.10

Note: Different superscripts within columns are statistically significant ($p<0.05$) compared to the control after post hoc Dunnett's multiple comparison test

Table 2. Effects of ethanol leaf extract of *A. cordifolia* on sperm parameters of streptozotocin-induced diabetic male albino Wistar rats

Groups	Epididymal sperm count (x10^6)	Percent sperm motility	Percent sperm viability	Percent abnormal sperm	Percent acrosome integrity
Control	84.63±12.62^a	80.60±3.37	85.00±2.20^a	1.88±0.43^a	72.50±4.47^a
Diabetic control	44.44±16.31	59.00±5.10	64.25±2.78	6.00±0.96	22.90±3.83
Extract (100 mg/kg)	66.50±11.52	72.00±11.25	83.80±4.74^b	4.10±1.16	36.00±4.09
Extract (200 mg/kg)	111.6±9.27^b	85.60±7.13	90.20±2.35c	3.70±0.56^b	40.80±4.03^b
Metformin (5 mg/kg)	74.15±16.81	79.00±5.34	87.20±2.52^d	2.90±0.29^c	30.50±3.66

Note: Different superscripts within columns are statistically significant ($p<0.05$) compared to the control after post hoc Dunnett's multiple comparison test

Table 3. Effects of ethanol leaf extract of *A. cordifolia* on male hormones of Streptozotocin-induced diabetic Wistar rats

Groups	LH (ng/mL)	FSH (ng/mL)	Testosterone (ng/mL)
Control	8.96±3.12	4.90±1.12	62.10±16.63^a
Diabetic control	6.22±1.90	3.30±1.16	42.50±16.22
Extract (100 mg/kg)	7.16±2.64	5.14±1.76	61.20±3.46
Extract (200 mg/kg)	7.52±1.96	3.50±1.18	63.96±6.07^b
Metformin (5 mg/kg)	8.72±3.56	3.0±0.52	68.10±5.14^c

Note: Different superscripts within columns are statistically significant ($p<0.05$) compared to the control after post hoc Dunnett's multiple comparison test

Effects of ethanol leaf extract of *A. cordifolia* on sperm parameters of streptozotocin-induced diabetic male albino Wistar rats.

The results of the ethanol leaf extract of *A. cordifolia* on sperm parameters such as epididymal sperm count, percentage viability, motility, percentage acrosome integrity, and morphological abnormality percentage were presented in Table 2. Diabetes was observed to induce marked acrosome damage and increased morphological abnormality. However, treatment with the extract of *A. cordifolia* at 200 mg/kg significantly ($p<0.05$) improved the integrity of the acrosome (40.80±4.03^b). It markedly decreased (3.70±0.56^b) the percentage of sperm damage observed in the diabetic control group (6.00±0.96). Though no significant ($p>0.05$) changes were noted in the groups treated with 100 mg/kg (36.00±4.09) and standard antidiabetic drug (30.50±3.66) (Metformin hydrochloride), there was an improvement in the level of acrosome damage compared with the diabetic control (22.90±3.83). There were also no significant ($p>0.05$) changes in the morphological abnormality of the treated groups compared to the diabetic untreated group. However, a non-significant ($p>0.05$) reduction in the percentage morphological abnormality was observed in the 200 mg/kg treated group and standard antidiabetic drug (Metformin hydrochloride). There was also a significant ($p<0.05$) increase in the percentage viability of the sperm cells of extract-treated groups compared to the diabetic control. Decreased epididymal sperm count induced by diabetes was significantly ($p<0.05$) increased at 200 mg/kg exposure. However, there was no significant change in the other treatment groups compared to the diabetic untreated group.

Effects of ethanol leaves extract of *A. cordifolia* on hormones male reproductive in streptozotocin-induced diabetic male albino Wistar rats.

The results of the effects of the extract of *A. cordifolia* on male hormones are presented in Table 3. The results showed a significant ($p<0.05$) increase in serum testosterone level at 200 mg/kg extract treated groups compared to the diabetic control. Despite Luteinizing hormone (7.16±2.64; 7.52±1.96) and follicle-stimulating hormone (5.14±1.76; 3.50±1.18) levels elevations in the study, the values were not statistically significant ($p>0.05$) when compared to the diabetic control.

Histopathological findings

There were no obvious cellular changes in the testes of male Wistar rats exposed to streptozotocin alone (45 mg/kg) (Figure 1. B) and in conjunction with either 5 mg/kg, 100 mg/kg, or 200 mg/kg (Figure 1. C, 1.D, and 1. E, respectively) of the ethanol extract of *A. cordifolia* by gavage. However, there were collapsed epididymal tubules within a fibrous stroma (33%) in the diabetic untreated group (Figure 2. B), which was greatly ameliorated by the extract-treated groups (100 and 200 mg/kg) (Figure 2c and 2d) and the standard antidiabetic drug used in this study (Figure 2. E).

Discussion

The presence of numerous bioactive compounds and the array of natural plant communities (Ezeonu and Ejikeme 2016) across sub-Saharan Africa has enhanced the herbal medicine use as an undisputable alternative to synthetic antidiabetic agents in diabetes management and its complications, especially those associated with male functions and fertility. Diabetes mellitus, a disease associated with disorders of carbohydrates, proteins, and lipids metabolism, is known to greatly impair reproductive functions, including male fertility (Jangir and Jain 2014). The use of streptozotocin as a chemical model for the induction of experimental diabetes mellitus in animal species continues to be relevant in diabetology due to its ability to destroy pancreatic beta cells selectively (Shi et al. 2017).

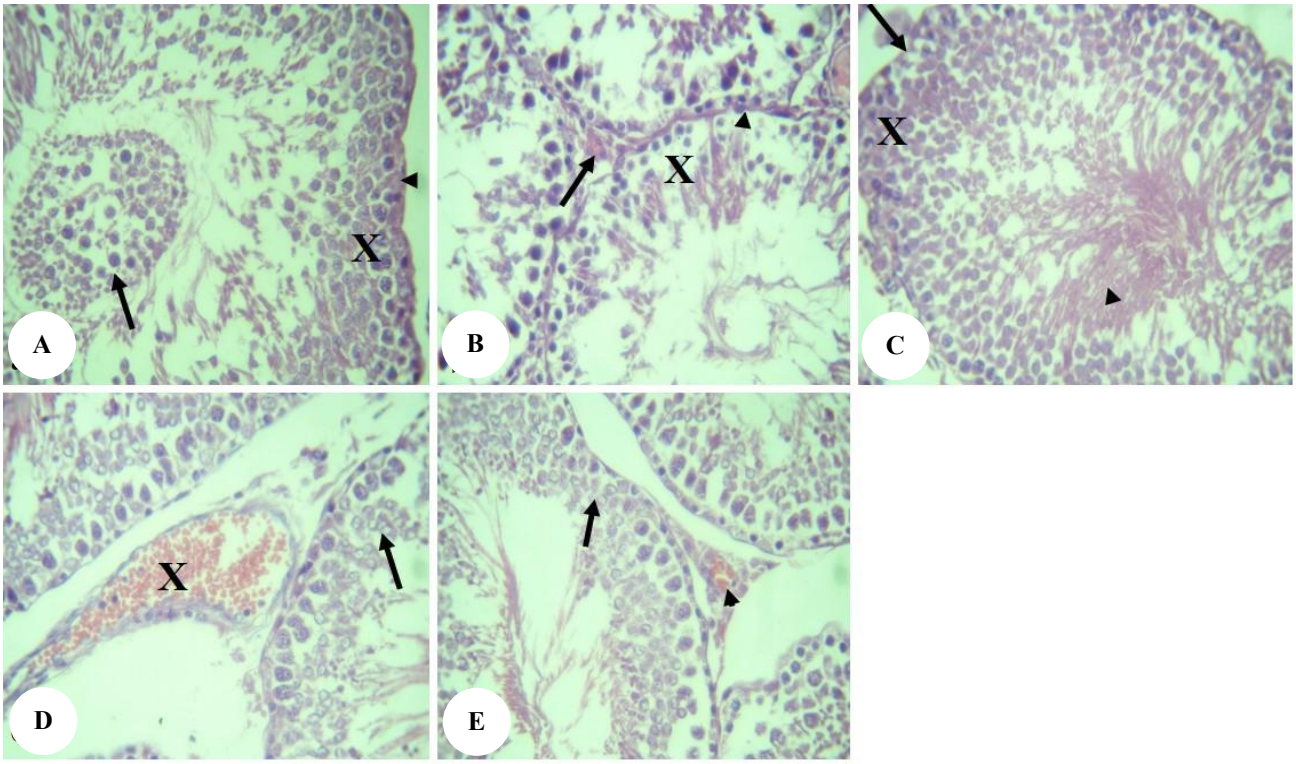

Figure 1. A-D: Photomicrograph of a section of the testis of streptozotocin-induced diabetic male Wistar rats exposed to various ethanol leaf extracts of *A. cordifolia* (100 mg/kg, 200 mg/kg) and Metformin (5 mg/kg). A: Control; note the intact basement membrane of the seminiferous tubule (arrowhead) with the spermatogonia spermatocytes (X) and spermatozoa (arrow). B: Diabetic untreated. Note the inter-tubular congestion (arrow) and intact basement membrane (arrowhead) with necrosis of the spermatogonia, primary spermatocytes, secondary spermatocytes, and the spermatids C: Diabetic + drug; note the seminiferous tubule with intact basement membrane (arrow) containing spermatogonia and spermatocytes (X) and spermatids (arrowheads) D: Diabetic + 100 mg/kg extract. E: Diabetic + 200 mg/kg. Note the inter-tubular congestion (arrowhead) with the necrosis of the primary spermatocyte (arrow) and secondary spermatocyte (double arrowheads). H and E: x 400

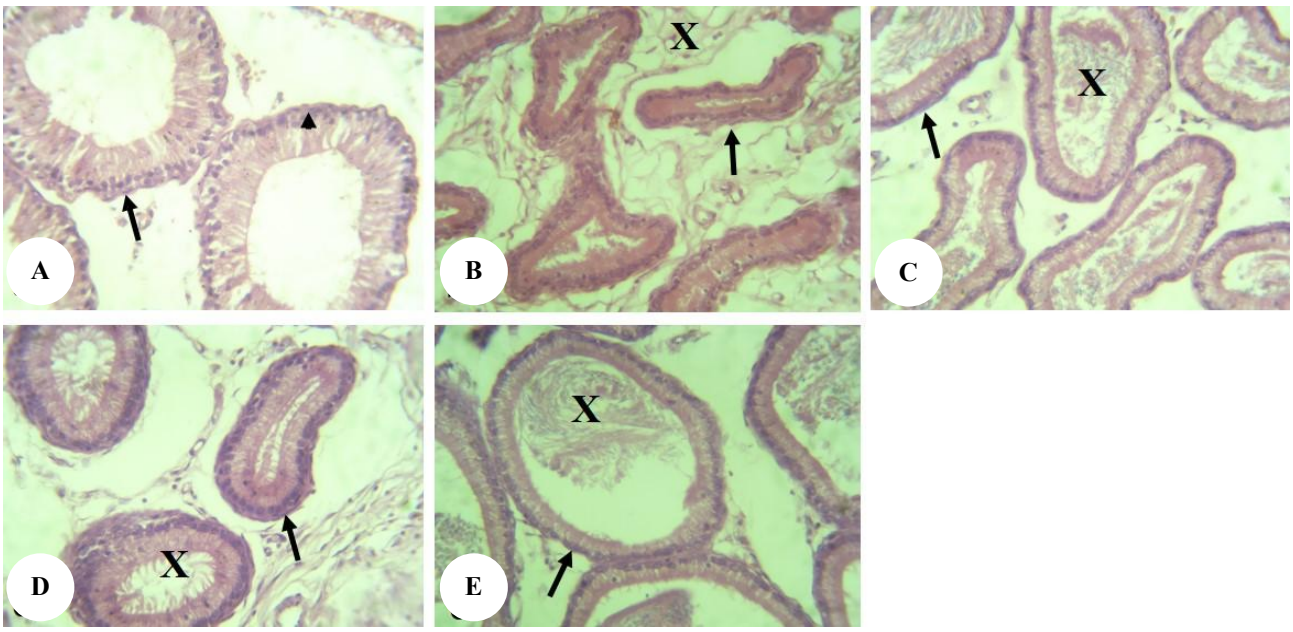

Figure 2. A-D: Photomicrograph of a section of the epididymis of streptozotocin-induced diabetic male Wistar rats exposed to various ethanol leaf extracts of *A. cordifolia* (100 mg/kg, 200 mg/kg) and Metformin (5 mg/kg). A: Note the epididymal tubules (arrows) with pseudostratified columnar epithelial cells (arrowheads). B: Diabetic untreated. Note the collapsed epididymal tubules (arrows) within a fibrous stroma (X), C: Diabetic + drug, Note the epididymal tubules (arrows) containing spermatozoa, D: Diabetic + 100 mg/kg extract, Note the epididymal tubules (arrows) containing spermatozoa. E: Diabetic + 200 mg/kg. Note the epididymal tubules (arrows) containing spermatozoa (X). H and E: x 400

This study evaluated the effects of ethanol leaf extract of *A. cordifolia* on male reproductive dysfunctions induced by diabetes. Although the morphometric analysis of the testes and the epididymis revealed diabetes-induced organ weight reduction (1.22±0.13; 0.36±0.02), significant ($p<0.05$) increases were recorded in groups exposed to the various doses of the extract as well as in the epididymis weight ($0.51±0.02^b$) compared to the diabetic untreated group. The increased epididymal weight could be attributable to the presence of more spermatozoa in the epididymal tubular lumen, as evidenced in the photomicrographs (Figure 2. C-D). The finding was consistent with the report of Allassane et al. (2021), who associated the gain in epididymal weight with the androgenic activity of the plant extract since testicular growth and secretions are strictly under the influence of androgens (Bakloul et al. 2016). Allassane et al. (2021) also reported significantly ($p<0.05$) increased testicular weight and volume in streptozotocin-induced diabetic rats coadministered with hydroalcoholic extract of *Alpinia officinarum* leaf extract (Heidari et al. 2021).

The significantly ($p<0.05$) increased extrapyramidal sperm count and enhanced sperm motility and viability suggested that the exposure of those diabetic rats to ethanol leaf extract of *A. cordifolia* greatly improved the hyperglycemia-induced damages. The ability of the ethanol leaf extract of *A. cordifolia* to enhance the evaluated reproductive parameters could be linked to the presence of their inherent important bioactive phytoconstituents, according to Solati et al. (2021). Several studies have demonstrated that important phytochemicals such as polyphenols and flavonoids could restore damaged sperm parameters and hormonal disturbances associated with disease conditions because of their potent antioxidant activity (Jangir and Jain 2014).

Oxidative stress damage has been implicated as the main instigator of complications in diabetes (Nna et al. 2019), including male infertility (Alsenosy et al. 2019). This is because increased oxidative stress induced by hyperglycemia could disrupt the hypothalamic-pituitary-gonadal system to trigger hormonal disorder with a consequential decrease in male fertility as a result of lower gonadotropins, sperm motility, count, and viability (Abbasihormozi et al. 2019). The positive impact of this plant extract could be attributed to the presence of vital phytochemical constituents such as phenol and flavonoids earlier reported by Ejeh et al. (2023), which possess strong radical scavenging abilities (Kaushik et al. 2011).

This study revealed that streptozotocin diabetes induction lowered serum gonadotropins (6.22±1.90; 3.30±1.16) and testosterone levels (42.50±16.22), which agreed with the findings of Arikawe et al. (2012), Jangir and Jain (2014), and Soliman et al. (2019), who recorded similarly decreased hormonal values. The findings showed the ability of diabetes to disrupt the synthesis of these hormones and cause Leydig and Sertoli cell functional alterations with subsequent impairment of spermatogenesis (Jangir and Jain 2014). However, the exposure of diabetic male Wistar rats to ethanol leaf extract of *A. cordifolia* in this study significantly ($p<0.05$) elevated serum testosterone levels (63.96±1.96) and insignificantly ($p>0.05$) increased FSH (5.14±1.76) and LH levels (7.52±1.96). Although the LH and FSH values were not statistically significant ($p>0.05$), they might be clinically relevant as both hormones influence Leydig and Sertoli's cellular functions. The finding was consistent with the work of (Ngaha-Njile et al. 2019), who reported an increased testosterone concentration in male Wistar rats exposed to various doses of *A. cordifolia*. The elevated testosterone level might be responsible for the improved sperm motility, viability, counts, and acrosome integrity recorded in the present study.

According to Tian et al. (2020), testicular and epididymal damage resulting in defective spermatozoa production and maturation has occurred in diabetes-induced oxidative stress. Histopathological findings in the present study revealed complete epididymal tubular collapse with seminiferous cellular damage. Heidari et al. (2021) have reported testicular damage with a manifested tubular atrophy, reduction in seminiferous tubular diameter, and thickness of the seminiferous epithelium in streptozotocin-induced diabetic animals. The reported testicular damage could probably be due to elevated oxidative stress damage.

In conclusion, the study has demonstrated that streptozotocin-induced diabetes causes serious damage to male reproductive structures and parameters. However, the exposure of diabetes-induced Wistar rats to various doses of the ethanol leaf extract of *A. cordifolia* improved the evaluated reproductive structure and profile of the exposed Wistar rats. Therefore, the ethanol leaf extract of *A. cordifolia* could be employed as an alternative to synthetic antidiabetic agents in managing male reproductive dysfunctions associated with diabetic complications.

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