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Investigation of the Modulatory Effect of Aqueous Extract of *Dialium guineense* Stem Bark on Oxidative Status of Diabetic Rat Kidneys

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ABSTRACT: Streptozotocin (STZ) is a chemical compound known to damage pancreatic β-cells and cause hyperglycemia. Hyperglycemia plays a key role in glomerular, mesangial cell, and tubular damage in kidneys. Metabolic dysregulation, including hyperglycemia, initiates cellular damage in the kidneys. The present study investigated the modulatory effect of aqueous extract of *Dialium guineense* (AEDG) stem bark on oxidative status of diabetic rat kidneys. Male rats (Wistar strain, n = 20, mean weight = 165 ± 15 g) were randomly allocated to four groups (5 rats/group): control, diabetic, metformin, and extract groups. Diabetes mellitus (DM) was induced in the rats via intraperitoneal injection of STZ (50 mg/kg body weight, bwt). The diabetic rats were subsequently treated for 21 days with either 50 mg/kg bwt metformin or 1000 mg/kg bwt AEDG. Body weight and blood glucose data were collected on weekly basis. Markers of oxidative stress were measured in rat renal tissue using standard methods. The results showed that STZ-induced DM significantly increased plasma blood glucose concentration, while reducing antioxidant status of the rats. However, treatment of the diabetic rats with 1000 mg/kg bwt aqueous extract of *D. guineense* stem bark significantly reduced their fasting blood glucose, malondialdehyde (MDA) and nitric oxide (NO) concentrations, but it significantly increased activities of the antioxidant enzymes, and concentrations of total protein, reduced glutathione (GSH), and redox status (GSH/GSSG), in renal tissue ($p < 0.05$). These results indicate that AEDG stem bark can mitigate against STZ-induced oxidative stress in rat kidneys.

Keywords: Reduced glutathione, Renal tissue, Lipid peroxidation index, Nephropathy, Oxidative stress.

Introduction

Kidney is one of the organs affected by microvascular complications of diabetes mellitus (DM). Microvascular changes caused by chronic hyperglycemia lead to imbalance in cell metabolism, with progressive lesions in several organs (kidneys, eyes, nerves, liver, and the vascular, immunological and gastrointestinal systems) (Sheetz and King, 2002). Diabetic nephropathy is a progressive disease that involves several mechanisms, with changes in glomerular hemodynamics, causing renal lesions, oxidative stress, inflammatory response, and fibrosis. Chronic hyperglycemia causes glomerular hyperfiltration through vasodilation of afferent arteriole in relation to the efferent arteriole, leading to increased hydrostatic pressure and greater passage of fluids through the glomerulus (Forbes and Cooper, 2013). Glomerular dysfunction is observed as microalbuminuria caused by changes in renal structure, such as thickening of the basal membrane, podocyte lesions, expansion of the mesangial matrix, which progress to glomerular sclerosis and tubule-interstitial fibrosis associated with reduced glomerular filtration rates (GFR) (Gonzales-Suarez *et al.*, 2013). The cumulative results of these transformations are caused by excess production of reactive oxygen species (ROS) mediated by chronic hyperglycemia. The generation of ROS in diabetic kidneys is caused by enzymatic and non-enzymatic systems that include glucose auto-oxidation, Fenton reaction catalyzed by unbound iron, and depletion of endogenous antioxidants reserve.

Examples of ROS are free radicals, such as superoxide anion ($O_2^{\cdot-}$) and hydroxyl radical ($OH^{\cdot}$), and non-radicals such as hydrogen peroxide (H_2O_2). Also important is the production of reactive nitrogen species (RNS), such as nitric oxide radicals (NO) (Forbes *et al*., 2008).
The pathogenesis of diabetic complications has been linked to ROS production, mainly $O_2^{\cdot-}$, which causes cell dysfunction and oxidative lesion via protein denaturation, lipid peroxidation, and mitochondrial DNA damage (Nath and Norby, 2000). These changes in renal cells, including glomerular endothelial cells, mesangial cells, and renal epithelial cells, lead to changes in ATP synthesis, intracellular calcium imbalance, and changes in cell membrane permeability that contribute to cell death by apoptosis or necrosis (Vallon and Thomson, 2012). Studies have shown that control of glycaemia with plant-based resources or herbal formulations can greatly reduce microvascular complications in diabetic patients (Hassani *et al.,* 2017; Okpiabhele *et al.,* 2018; Abu *et al*., 2020a; Abu *et al.,* 2020b).
Dialium guineense is a medicinal plant that is used in parts of Africa for the treatment of various ailments (Dalziel and Hutchison, 1973). The medicinal plant contains bioactive substances such as alkaloids, tannins, saponins and phenolics with proven pharmacological/biological activities (Abu *et al.,* 2022a; Abu *et al.,* 2022b). The aim of this study was to investigate the modulatory effect of aqueous extract of *Dialium guineense* (AEDG) stem bark on oxidative status of diabetic rat kidneys.

Materials and methods

Chemicals and reagents: All chemicals and reagents used in this study were of analytical grade, and they were products of Sigma-Aldrich Ltd. (USA).
Plant sample collection and extract preparation: The stem barks of *D. guineense* were collected from Auchi, Edo State, Nigeria, and authenticated at the herbarium of the Department of Plant Biology and Biotechnology, University of Benin, Benin City, Nigeria (No. UBH_D330). The plant's stem bark was washed and shade-dried for 1 month at room temperature, and subsequently pulverized using an electrical blender. Exactly 500 g of the powdered plant material was steeped in 5 L of distilled water. The resulting extract was filtered through muslin cloth and freeze-dried via lyophilization (Abu *et al.,* 2017a; Omoregie *et al.,* 2017; Obayuwana *et al.,* 2020).
Experimental rats: Adult male albino rats (Wistar strain, n = 20, mean weight = 165 ± 15 g) were purchased from the Department of Anatomy, University of Benin, Nigeria and housed in wooden cages. They were acclimatized for 14 days just before commencement of the study, and had free access to feed (rat chow) and water.
Experimental design: The rats were divided into four groups (5 rats/group): control, diabetic, metformin, and extract groups. With the exception of control group, DM was induced in the rats using a single intraperitoneal injection of STZ (50 mg/kg bwt). Rats in the extract group received 1000 mg/kg bwt AEDG orally. Another group was administered the standard antidiabetic drug, metformin, at a dose of 50 mg/kg bwt. Treatment lasted twenty-one days.
Blood sample collection and preparation: At the end of day 21 of treatment, the rats were euthanized under mild chloroform anaesthesia after an overnight fast. Blood samples collected via cardiac puncture in heparin containers were centrifuged at 2000 rpm for 10 min to obtain plasma.
Determination of oxidative status in rats renal tissues: The activities of catalase, superoxide dismutase (SOD), glutathione peroxidase (GPx) and glutathione reductase (GR) were determined in renal tissue using standard methods (Cohen *et al*., 1970; Misra and Fridovich, 1972; Rotruck *et al*., 1973; Dubler and Anderson, 1981). Levels of renal total protein, MDA, GSH, and NO were also measured (Henry *et al*., 1957; Ellman, 1959; Guttridge and Wilkins, 1982; Marcocci *et al*., 1994).
Data analysis: Data are expressed as mean ± standard error of mean (SEM, n = 5). Statistical analysis was performed using SPSS version 21. Statistical differences between means of the different groups were compared using Duncan multiple range test. Statistical significance was assumed at $p < 0.05$.

Results

Effect of AEDG stem bark on body and organ weights: Induction of DM in the rats caused significant reductions in their body weights, but extract treatment significantly and time-dependently increased the body weighs of rats ($p < 0.05$). Streptozotocin-induced DM caused significant increases in the weights of rat kidneys as well as the corresponding relative organ weight ($p < 0.05$). However, treatment of the diabetic rats with AEDG/metformin

markedly reduced kidney weight and the corresponding relative organ weight ($p < 0.05$). These results are shown in Figures 1 – 4.

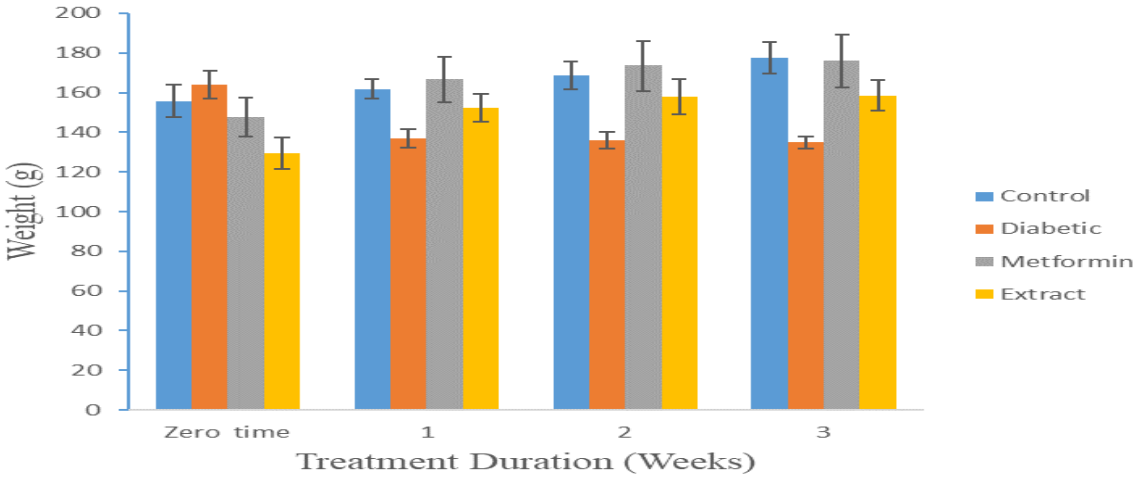

Figure 1: Body weights of rats

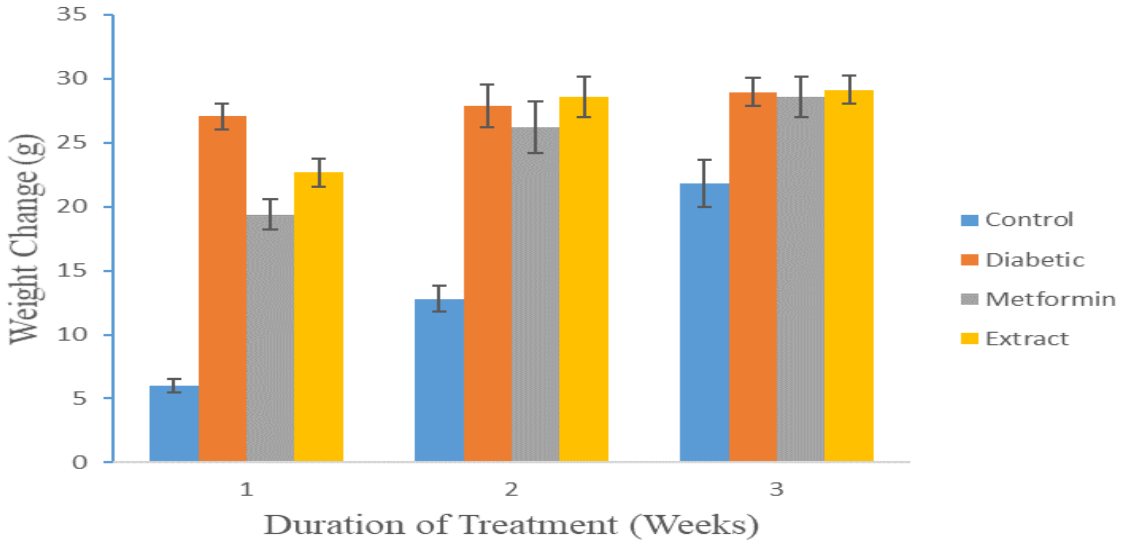

Figure 2: Body weight changes

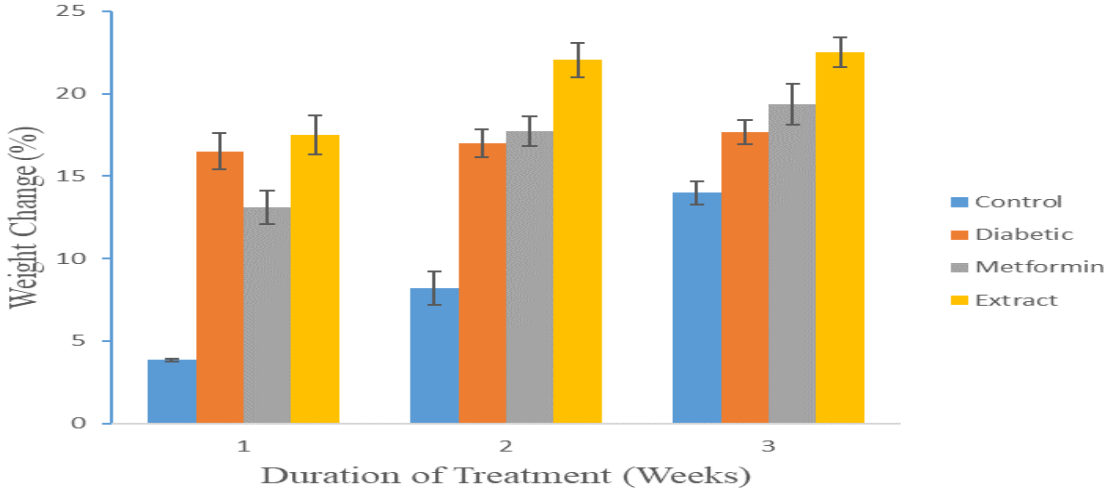

Figure 3: Percentage body weight changes

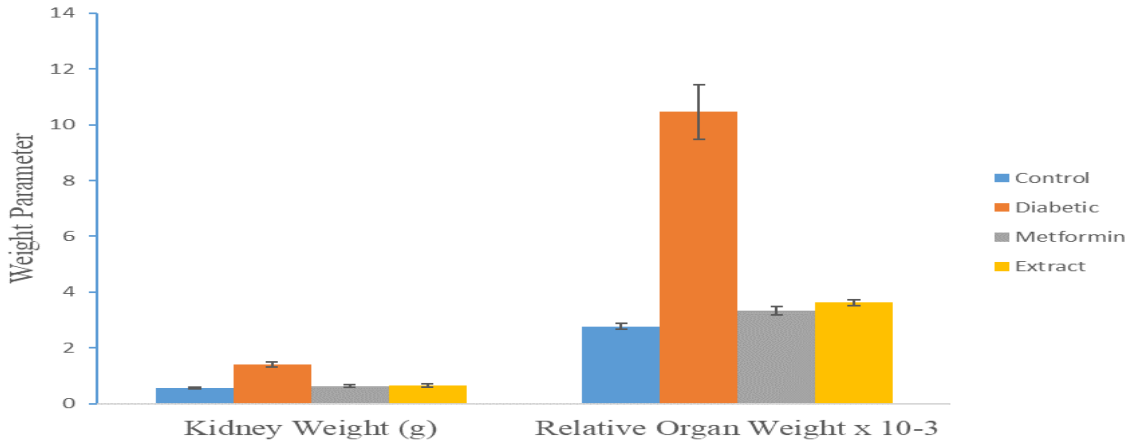

Figure 4: Weight of kidney and relative organ weight

Effect of AEDG stem bark on blood glucose concentration: As shown in Figure 5, treatment of diabetic rats with 1000 mg/kg bwt aqueous extract of *D. guineense* stem bark significantly and time-dependently reduced their fasting blood glucose concentrations ($p < 0.05$).

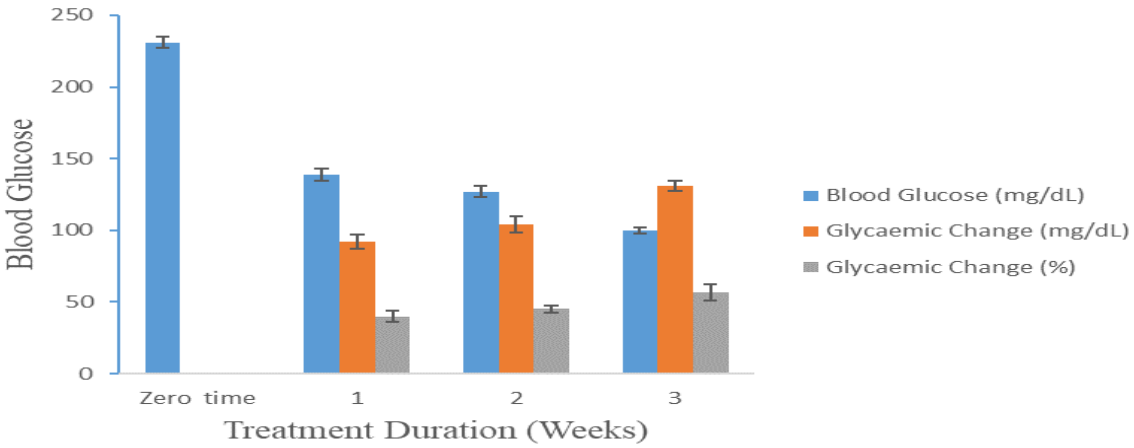

Figure 5: Blood glucose of rats

Effect of AEDG stem bark on renal oxidative status: Treatment of diabetic rats with 1000 mg/kg bwt aqueous extract of *D. guineense* stem bark significantly reduced the renal concentrations of MDA and nitric oxide, but it significantly increased the activities of the antioxidant enzymes, and concentration of total protein, GSH, and redox status ($p < 0.05$). These results are presented in Figures 6 - 11.

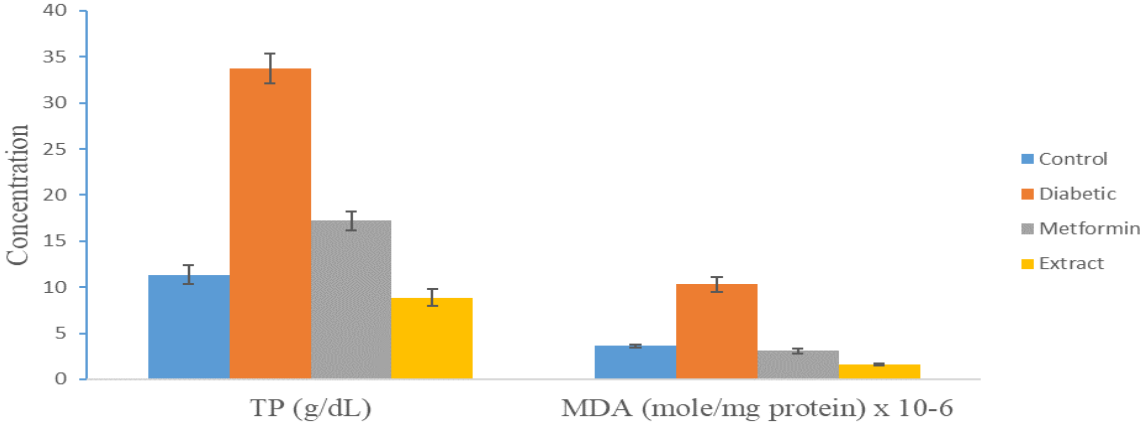

Figure 6: Concentrations of total protein and malondialdehyde in renal tissue

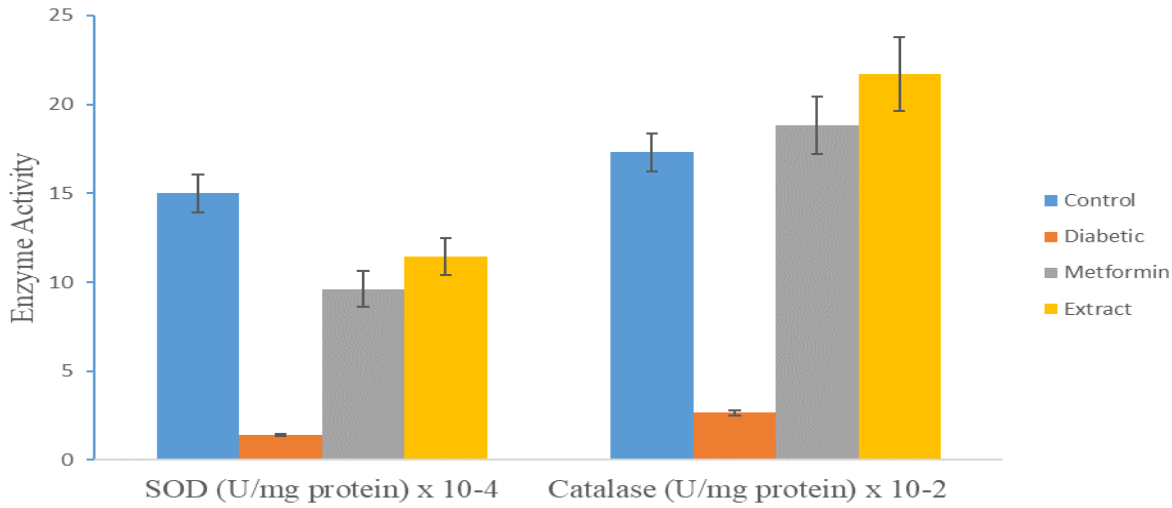

Figure 7: Renal activities of superoxide dismutase and catalase

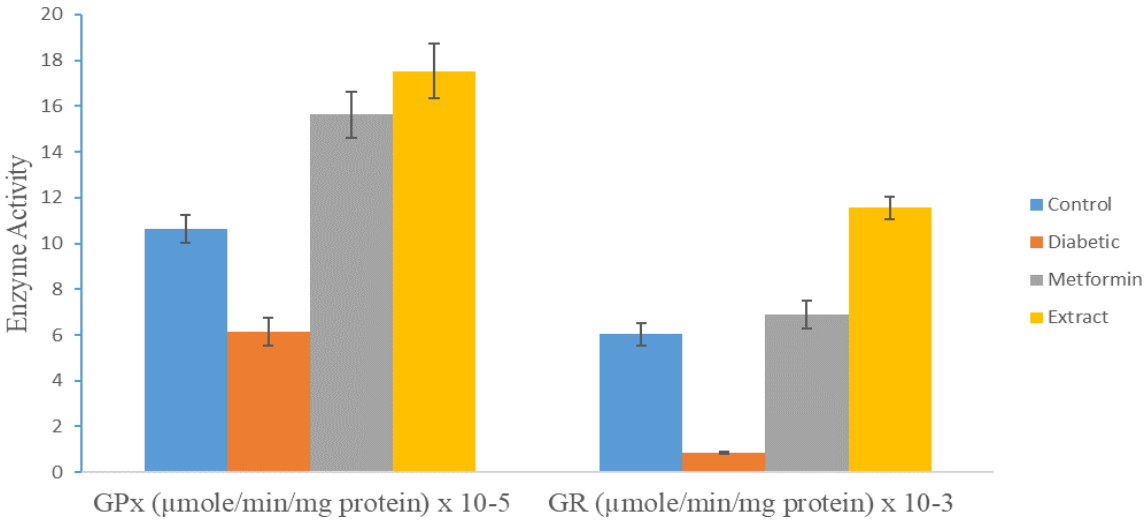

Figure 8: Activities of glutathione enzymes in renal tissue

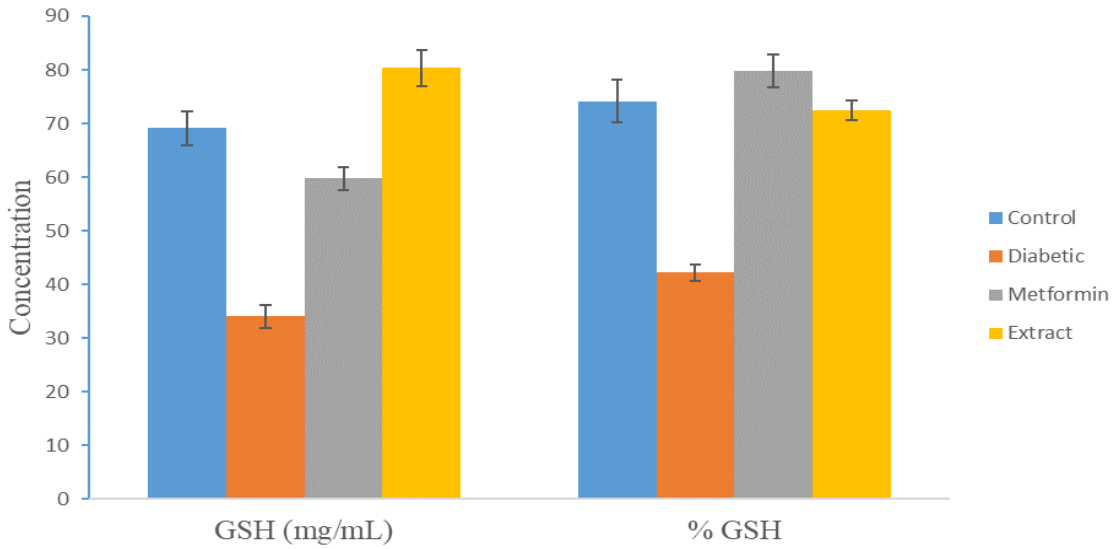

Figure 9: Concentration of glutathione in renal tissue

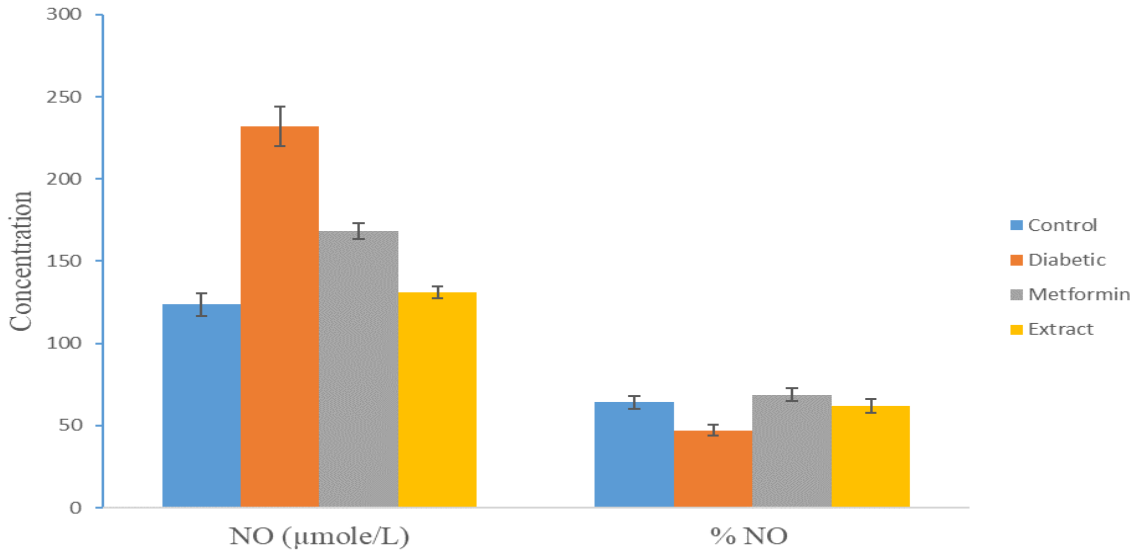

Figure 10: Concentration of nitric oxide in renal tissue

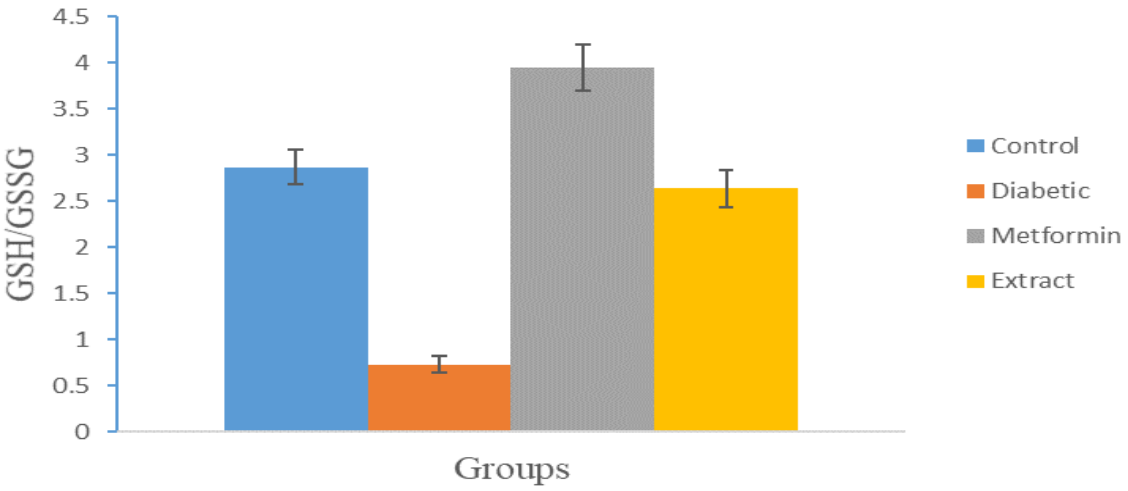

Figure 11: Effect of AEDG stem bark on renal redox status

Discussion

The degenerative nature of the complications of DM leads to high mortality and morbidity. As the prevalence of DM increase worldwide, the probability is there that complications, such as microvascular, macrovascular, and nervous system disorders, will also increase (Nagata, 2016). One of the organs affected by microvascular complications caused by DM is the kidney. Chronic kidney disease is a potential direct impact of DM. In addition, DM is the single most common cause of end-stage chronic kidney disease. About 20 – 40 % of diabetic patients develop diabetic nephropathy, which is the cause of end-stage chronic kidney disease (Bayrasheva *et al*., 2016). Hyperglycemia is an important factor in the development of glomerular, mesangial, and tubular damage in the kidney. Kidney cellular damage is initiated by metabolic dysregulation (hyperglycemia, hyperlipidemia, and insulin resistance). Increased ROS production due to mitochondrial dysfunction in DM is a primary event in the development of complications (Reidy *et al.,* 2014). Mesangial cells function in the maintenance of the structure of glomerular capillaries and regulation of glomerular filtration through smooth muscle activity. Hyperglycemia enhances the proliferation and hypertrophy of mesangial cells via increment in ROS generation in the cells. This in turn can lead to increase in matrix production as well as thickening of the basement membrane. Hyperglycemia can also cause an upregulation in the expression of vascular endothelial growth factor, which results in increased vascular permeability (Moonen *et al*., 2018).

Damage to the glomerulus due to prolonged hyperglycemia can lead to reduced kidney function. In the event that glomerular filtration function is compromised, large molecules, such as proteins and glucose, leak through the filtration process. Furthermore, fluid reabsorption in renal tubules is also impaired in chronic hyperglycemia. Prolonged hyperglycemia causes hypoxia, resulting in the formation of scar tissue. Fibroblasts in renal interstitium differentiate into fibrocytes and fill most of the kidney tissue. Hyperglycemia, in conjunction with transforming growth factor beta (TGF-β), angiotensin II, and advanced glycation end products (AGEs), induce epithelial-mesenchymal transition (EMT). Additionally, it increases alpha smooth muscle actin (α-SMA) and vimentin expressions, downregulates E-cadherin, damages the epithelial layer, and alters the phenotype of mesenchymal cells, thereby resulting in the formation of scar tissue (Braga *et al*., 2022). These conditions clearly worsen kidney function. In the late stages, renal interstitial space becomes filled with scar tissue. A recent study showed that intermittent or chronic hyperglycemia plays an important role in the initiation and persistence of DM complications, including kidney disease (Ameh *et al.*, 2019). Kidney enlargement (renal hypertrophy) is a common early pathological change in DM. It reflects several metabolic and structural alterations associated with DM, especially the development of diabetic nephropathy. Hyperglycemia stimulates increased glomerular filtration rate as well as increased workload on nephrons. In this study, STZ-induced pancreatic beta cell damage caused chronic hyperglycemia which directly impacted the kidney negatively, evident in the enlarged kidneys observed in the diabetic group compared to the control and treatment groups. However, treatment with the medicinal plant extract was able to reduce it close to values observed in the control group. These results are consistent with findings of previous reports (Abu *et al.*, 2023a; Abu *et al*., 2023b; Abu *et al*., 2023c; Abu *et al.*, 2023d). Similarly, treatment of diabetic rats with 1000 mg/kg bwt aqueous extract of *D. guineense* stem bark significantly reduced the renal concentrations of MDA and nitric oxide, but it significantly increased the activities of the antioxidant enzymes, and concentration of total protein, GSH, and redox status. These results are in agreement with those reported in earlier studies (Abu *et al*., 2022c; Abu *et al.*, 2022d; Abu *et al*., 2023e). Therefore, the beneficial action of aqueous extract of *D. guineense* stem bark on renal tissue oxidative damage in STZ-induced diabetic rats might not be unconnected to antioxidant effects conferred mainly by the bioactive compounds (Abu *et al.*, 2017b; Abu *et al*., 2023f; Abu *et al*., 2023g; Abu *et al.*, 2023h; Abu *et al*., 2023i). These results indicate that AEDG stem bark can mitigate against STZ-induced oxidative stress in rat kidneys.

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