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Methanol fraction of ethanol extract of *Dialium guineense* stem bark reduces oxidative stress in STZ-induced diabetic rat pancreas

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Abstract
The present study investigated the effect of methanol fraction of ethanol extract of *Dialium guineense* (MEDG) stem bark on streptozotocin (STZ)-induced oxidative stress in rat pancreas. Adult male Wistar albino rats (n = 25, mean weight = 215 ± 15 g) were assigned randomly to five groups (5 rats per group): normal control, diabetic control, metformin, MEDG (200 mg/kg body weight, bwt) and MEDG (300 mg/kg bwt) groups. A single intraperitoneal injection of 50 mg/kg bwt STZ was used to induce diabetes mellitus in the experimental rats. Treatment with the extract or standard antidiabetic drug (metformin) lasted 21 days. Activities of catalase, superoxide dismutase (SOD), glutathione peroxidase (GPx) and glutathione reductase (GR) as well as glutathione (GSH), total protein (TP), malondialdehyde (MDA) and nitric oxide (NO) levels were measured in rat pancreas. The results obtained indicated that induction of diabetes mellitus with STZ significantly increased the fasting blood glucose (FBG) levels of the rats, but it decreased the activity/concentration of antioxidants (enzymes/molecules) ($p < 0.05$). However, treatment of the diabetic Wistar albino rats with MEDG (200 and 300 mg/kg bwt, respectively) markedly reduced the FBG level and body weights of rats, but enhanced the activity/concentration of antioxidant enzymes/molecules in pancreatic tissue ($p < 0.05$). The findings from this study have shown that MEDG stem bark has the capacity to enhance antioxidant defense in pancreases of STZ-induced diabetic rats.

Keywords: Catalase, *Dialium guineense,* glutathione, lipid peroxidation, oxidative stress, pancreas

Introduction
Diabetes mellitus (DM) remains a serious health challenge, globally. It is estimated that by the coming decade the number of persons with DM would more than double [1]. Diabetes mellitus is primarily defined by the level of hyperglycemia which causes micro- and macrovascular damage [2]. Strategies currently employed for its treatment are targeted at ameliorating the different metabolic derangement associated with the disease [3-4].
Streptozotocin (STZ) as a diabetogenic agent is a permanent beta cell destroyer. One of its toxicity mechanism involves promotion of oxidative stress in the pancreas thus damaging the organ [5].
It has been asserted that a large population of people in developing countries use herbal medicine for some aspects of their basic health care [6, 7]. Medicinal plants have proven health benefits [8-12]. *Dialium guineense* (Velvet Tamarind) is a medicinal plant used in Traditional Medicine for the treatment of infections [17]. It is a tall, tropical, fruit-bearing tree, belonging to the *Leguminosae* family, and has small, typically grape-sized edible fruits with brown hard inedible shells. In Africa, it is found in dense forests along the southern edge of the Sahel. The plant grows naturally in West African countries, Central African Republic, and Sudan [18]. In Nigeria, it is known by different local names: *Icheku* (Igbo), *Awin* (Yoruba), *Tsamiyarkurm* (Hausa) and *Amughen* (Bini) [19, 20]. The aim of this study was to investigate the effect of MEDG stem bark on STZ-induced oxidative stress in rat pancreas.

Materials and Methods
Chemicals
All chemicals and reagents used in this study were of analytical grade and they were bought from Sigma-Aldrich Ltd. (USA).

Plant Collection and Extraction

Dialium guineense stem barks obtained from Auchi, Edo State, Nigeria, were authenticated at the University of Benin herbarium domiciled in the Department of Plant Biology and Biotechnology, University of Benin, Benin City, Nigeria. The prepared plant specimen was deposited in the herbarium of same department (No. UBHD330).

The plant's stem bark was" washed and shade-dried for 2 weeks at room temperature, and thereafter ground into powder using a blender. A portion (500 g) of powdered plant material was steeped in 5,000 mL of 100% ethanol. The resulting extract was filtered through muslin cloth and freeze-dried with a lyophilizer. The ethanol extract was subsequently fractionated with absolute methanol [13-17].

Experimental Animals

Adult male Wistar albino rats (n = 25, mean weight = 215 ± 15 g) were purchased from the Department of Anatomy, University of Benin, Nigeria and housed in wooden cages. They were acclimatized for two weeks before commencement of the study, and had free access to feed and clean water.

Experimental Design

The rats were divided into five groups (5 rats/group): normal control, diabetic control, metformin, MEDG (200 mg/kg bwt) and MEDG (300 mg/kg bwt) groups. A single intraperitoneal injection of 50 mg/kg bwt STZ was used to induce DM in the experimental rats. Treatment with the extract or standard antidiabetic drug (metformin) lasted 21 days.

Tissue Sample Collection and Preparation

At the end of day 21 of treatment, the rats were euthanized under mild chloroform anaesthesia after an overnight fast. Their pancreases were excised, rinsed in normal saline and blotted dry.

The 20% tissue homogenate prepared from each pancreas was centrifuged at 2000 rpm for 15 min to obtain supernatant which was used for biochemical analysis.

Biochemical Analyses

The activities of catalase, SOD, GPx and α-amylase were determined [18-21]. Levels of pancreatic TP, MDA, GSH, and NO were also measured [22-25]. The activity of GR was determined using a previously described method [26].

Statistical Analysis

Data are presented as mean ± SEM (n = 5). Statistical analysis was performed using SPSS version 21. Statistical differences between means were compared using Duncan multiple range test. Statistical significance was assumed at $p < 0.05$.

Results

Effect of MEDG Stem Bark on Weight and Blood Glucose of Rats

Induction of diabetes mellitus with STZ significantly increased the blood glucose concentrations of the rats ($p < 0.05$). However, treatment of the diabetic rats with MEDG stem bark markedly reduced the FBG concentration and body weights of rats ($p < 0.05$; Table 1 and Figure 1).

Table 1: Weight and Blood glucose parameters of rats

Group	Weight Change (g)	Weight Change (%)	FBG (mg/dL)	Glycemic Change (mg/dL)	Glycemic Change (%)
Normal Control	_	_	_	_	_
Diabetic Control	_	_	> 800	_	_
Metformin	20.35	12.16	> 800	399.00	49.88
MEDG (200 mg/kg bwt)	16.00	11.19	427.00	311.00	71.61
MEDG (300 mg/kg bwt)	27.00	15.68	467.67	394.33	78.19

Data are weight and FBG parameters and are expressed as mean ± SEM (n = 5).

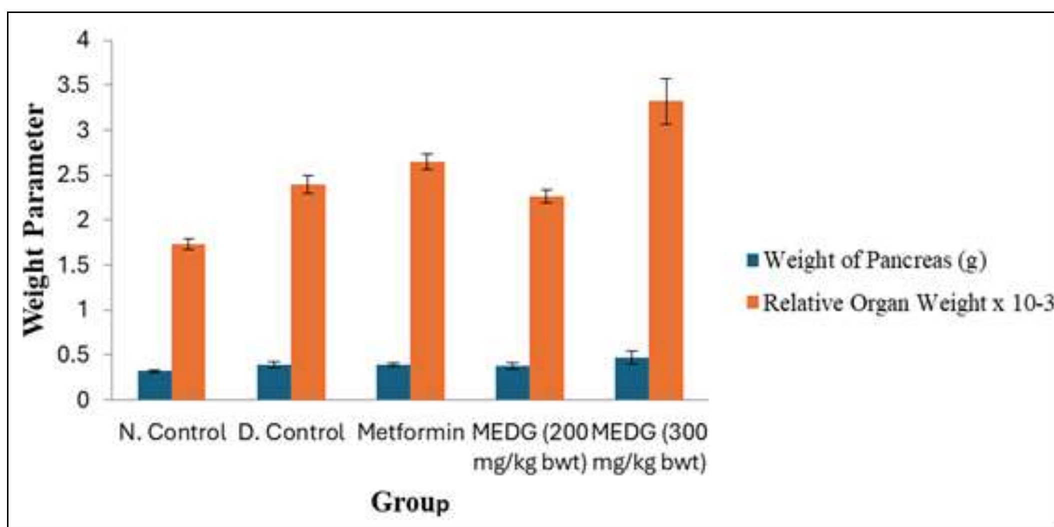

Fig 1: Comparison of Organ and Relative Organ Weights

Oxidative Status in Diabetic Rats Treated with the Medicinal Plant Extract: Treatment of diabetic Wistar rats with MEDG stem bark significantly increased the activities of the antioxidant enzymes as well as concentrations of GSH and NO, but it markedly reduced the concentrations of pancreatic TP and MDA ($p < 0.05$; Figures 2 to 5).

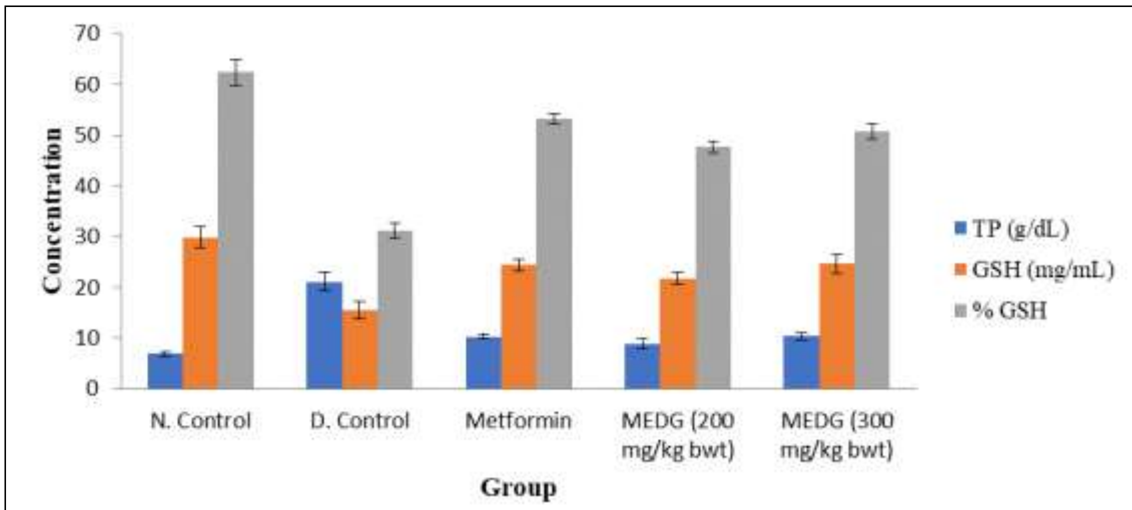

Fig 2: Effect of MEDG stem bark on pancreatic TP and glutathione level

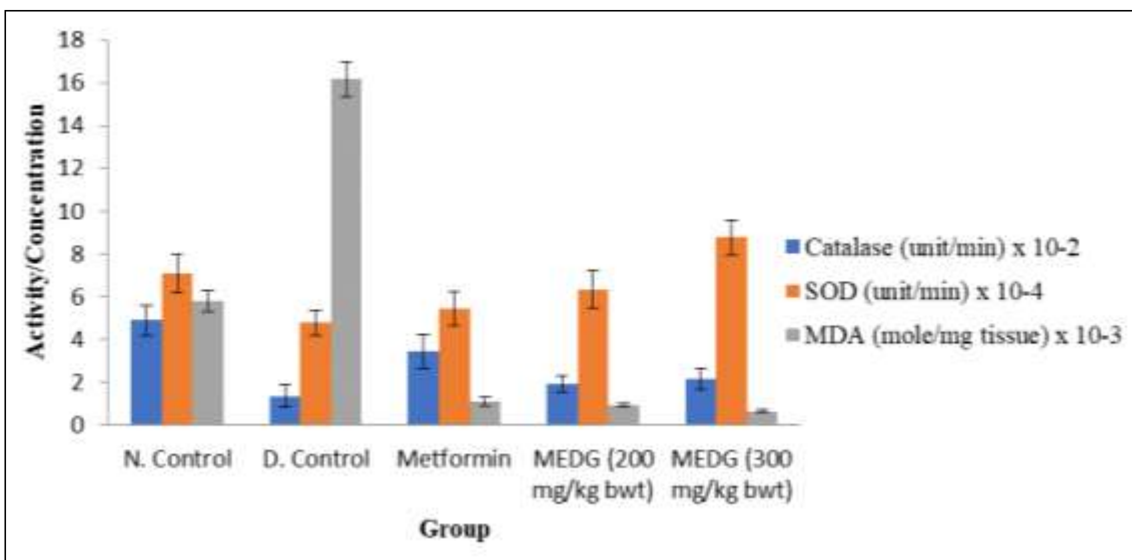

Fig 3: Effect of MEDG stem bark on oxidative status in rat pancreas

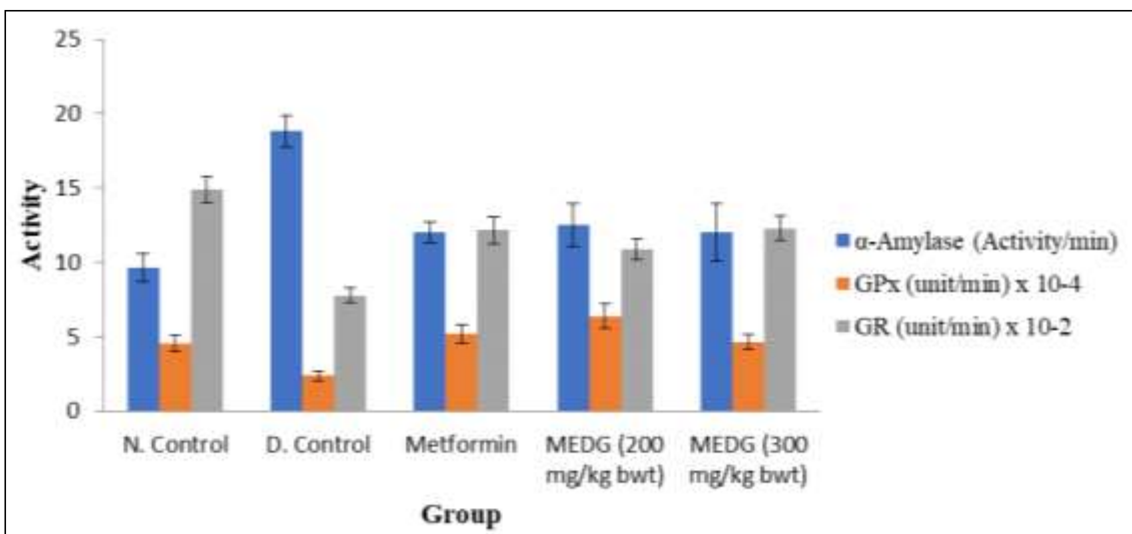

Fig 4: Effect of MEDG stem bark on pancreatic alpha-amylase and glutathione enzyme system

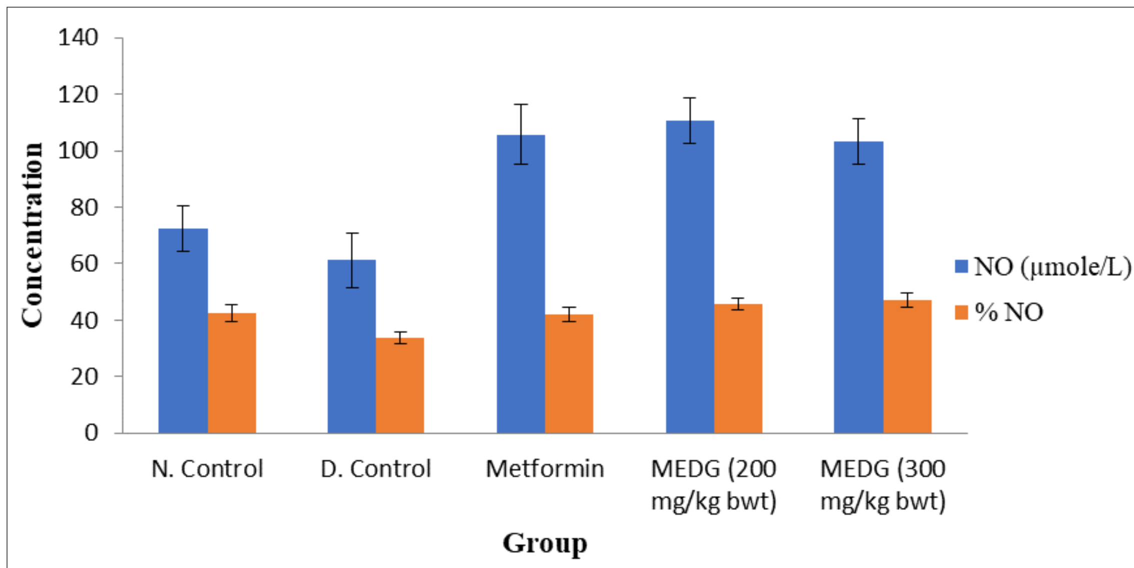

Fig 5: Effect of MEDG stem bark on pancreatic no level

Discussion

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) affect insulin signaling cascade. At lower doses, ROS play a physiological role in insulin signaling. After the stimulation of insulin receptor in adipocytes, hydrogen peroxide (H_2O_2) is produced by the catalytic action of NADPH oxidase, which inhibits PTP1B catalytic activity, thus increasing tyrosine phosphorylation [27]. In DM, oxidative stress caused by hyperglycemia impairs insulin signaling leading to insulin resistance. Hyperglycemia and insulin resistance may also lead to altered mitochondrial function and insulin action impairment by cytokines in response to metabolic stress [28, 29].

Pancreatic β-cells are especially sensitive to ROS and RNS, because their natural enzymatic antioxidant defenses are lower compared to other organs/tissues such as liver. Moreover, they lack the ability to adapt their low enzyme activity in response to stress such as high glucose or high oxygen [30]. Besides the provision of energy, glucose sensing in pancreatic β-cell is crucial for insulin secretion. It has been suggested that hyperglycemia results in chronic oxidative stress via glucose oxidation pathway, leading to an excess in mitochondrial superoxide production, which further activates uncoupling protein-2 (UCP-2) [31]. This protein lowers ATP/ADP through proton leak in β-cell, which reduces insulin secretion [32]. As in other cell types, NO in β-cells has physiological roles. It may regulate glucokinase activity via S-nitrosilation in β-cell, and possibly increase insulin secretion [33]. However, excess NO and concomitant NRS may cause apoptosis through caspase-3 activation and decrease in ATP levels [34].

The precise molecular mechanism underlying the cytotoxic effect of STZ in pancreatic β-cells is not known, but studies have suggested that the cytotoxicity may be by producing ROS thus inducing oxidative stress, causing DNA damage with resultant necrosis due to the DNA methylating activity of the methyl nitroso urea moiety of the drug, release of NO which inhibits aconitase activity resulting in mitochondrial dysfunction, or by inhibition of O-linked β -N-acetylglucosaminase (O-GlcNAcase) [35].

Lipid peroxidation is known to have deleterious effects on structure and functions of cell membrane. Malondialdehyde (MDA) is an important lipid peroxidation index, since individuals affected by several diseases usually have elevated MDA levels. It arises from the breakdown of lipid peroxyl radicals. Increased oxidative stress has been attributed to the formation of reactive metabolites due to biotransformation by cytochrome P450 2E1 (CYP2E1). Once formed, free radicals trigger a cascade of reactions that culminate in lipid peroxidation [36, 37]. Catalase plays an important role in antioxidant defense system. In animals, H_2O_2 is detoxified by catalase and GPx. Catalase protects cells from H_2O_2 generated within them. Even though catalase is not essential for some cell types under normal conditions, it plays an important role in the acquisition of tolerance to oxidative stress in the adaptive response of cells. The increased sensitivity of transfected catalase-enriched cells to some drugs and oxidants is attributed to the property of catalase in cells to prevent drug-induced consumption of O_2 either for converting H_2O_2 to oxygen or for direct interaction with the drug [38]. Suppressed action of this enzyme results in enhanced sensitivity to free radical-induced cellular damage [39]. Superoxide dismutase (SOD) catalyzes the dismutation of the highly reactive superoxide anion (O_2^-) to O_2 and to the less reactive species H_2O_2. This antioxidant enzyme destroys O_2^- by successive oxidation and reduction of the transition metal ion at the active site in a ping-pong type mechanism with remarkably high reaction rates [40]. Glutathione reductase (GR) is a ubiquitous enzyme, which catalyzes the reduction of oxidized glutathione (GSSG) to GSH. It is essential for the glutathione redox cycle that maintains adequate levels of cellular GSH. This homodimeric enzyme is a member of the family of flavoprotein disulfide oxidoreductases [41]. Oxidized glutathione is reduced by a multi-step reaction in which GR is initially reduced by NADPH forming a semiquinone of FAD, a sulfur radical and a thiol. The reduced GR (GR_{red}) reacts with a molecule of GSSG, resulting in a disulfide interchange, which produces a molecule of GSH and the GR_{red}-SG complex. An electron rearrangement in GR_{red}-SG results in a second disulfide interchange, splitting off the second molecule of GSH and restoring the GR to the oxidized form [41]. Redox status is a term used to describe the balance between oxidants (or pro-oxidants) and antioxidants. Reduced glutathione (GSH) is a

major non-protein thiol in living organisms, which acts against xenobiotics and neutralize ROS. Disturbance of GSH status in biological system has been reported to lead to serious consequences [42]. It has been suggested that the possible mechanism underlying the hepatoprotective properties of drugs include the prevention of GSH depletion and destruction of free radicals [43]. The aim of this study was to investigate the effect of MEDG stem bark on STZ-induced oxidative stress in rat pancreas. The results showed that treatment of diabetic Wistar rats with MEDG stem bark significantly increased the activities of the antioxidant enzymes as well as concentrations of GSH and NO, but it markedly reduced the concentrations of pancreatic TP and MDA. These results indicate that oxidative stress plays a key role in STZ-induced DM and that excess ROS production decreases the activity of antioxidant enzymes, while diminishing the levels of antioxidant molecules in pancreatic tissue. The beneficial effect of the medicinal plant may not be unconnected to its bioactive compounds. It has been reported that plants rich in important phytochemicals have varied pharmacological/biological effects [35-86].

Conclusion

This study has demonstrated that methanol fraction of ethanol stem bark extract of *D. guineense* can ameliorate oxidative injury induced by streptozotocin on the pancreas. The effect may not be dose-dependent.

Competing Interests

The authors declare that they have no conflict of interest.

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