Methanol Fraction of Ethanol Extract of *Dialium guineense* Stem Bark May Alter the Activity of Glucose 6-phosphatase/Aminotransferases and Levels of Lipids in Tissues of Diabetic Wistar Rats

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ABSTRACT

The aim of the present study was to investigate the potential of methanol fraction of ethanol extract of *Dialium guineense* (MEDG) stem bark to alter the activity of glucose 6-phosphatase (G6Pase)/aminotransferases and levels of lipids in tissues of streptozotocin (STZ)-induced diabetic Wistar rats. Adult male Wistar rats (n = 25, mean weight = 215 ± 15 g) were randomly assigned to five groups (5 rats/group): normal control, diabetic, metformin, extract (200 mg/kg body weight, bwt) and extract (300 mg/kg bwt) groups. A single intraperitoneal injection of 50 mg/kg bwt STZ was used to induce diabetes mellitus (DM) in the experimental rats. The diabetic rats were subsequently treated for 21 days with 50 mg/kg bwt metformin (standard antidiabetic agent) or MEDG stem bark. Activities of G6Pase, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) and levels of total cholesterol (TC), triacylglycerol (TG), very low-density lipoprotein cholesterol (VLDL-C), and nitric oxide (NO) were measured in plasma or hepatic/cardiac/renal tissues. The results showed that the G6Pase activity that was significantly increased in the plasma and hepatic/renal tissues of rats were markedly reduced after treatment with MEDG stem bark ($p < 0.05$). Similarly, STZ markedly elevated the activities of ALT and ALP in rat hepatic tissue ($p < 0.05$), but it did not alter the activity of AST in hepatic and cardiac tissues ($p > 0.05$). However, treatment of the diabetic Wistar rats with MEDG stem bark significantly reduced the hepatic activities of ALT and ALP ($p < 0.05$). Moreover, STZ-induced DM significantly elevated the levels of hepatic lipids (TC, TG and VLDL-C) and plasma NO, while MEDG administration significantly reversed the effect of the diabetogenic agent STZ by markedly reducing hepatic lipids and plasma NO levels ($p < 0.05$). These results suggest that the medicinal plant extract may alter the activity of G6Pase/aminotransferases and levels of lipids in tissues of STZ-induced diabetic rats.

Keywords: Gluconeogenesis, Glucose 6-phosphatase, Hyperglycemia, Lipids, Medicinal plant.

INTRODUCTION

Characterized by elevated blood glucose level (hyperglycemia) DM is caused by a relative or absolute

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deficiency of insulin [1]. The metabolic abnormalities of type-2 diabetes mellitus (T2DM) (hyperglycemia and hypertriacylglycerolemia) are the result of insulin resistance expressed primarily in liver, muscle, and adipose tissue [2]. Elevated levels of blood glucose and ketones are the hallmarks of untreated DM. Hyperglycemia is caused by increased hepatic production of glucose, combined with diminished peripheral use due to inability of muscle and adipose cells to take up glucose [3, 4]. Ketosis results from increased mobilization of fatty acids from adipose tissue, combined with accelerated hepatic synthesis of 3-hydroxybutyrate and acetoacetate [5 – 8]. Diabetic ketoacidosis occurs in 25 to 40 % of those newly diagnosed with type-1 DM (TIDM), and may recur if the patient becomes ill (most commonly with an infection) or does not comply with therapy. Ketoacidosis is treated by fluid/electrolytes replacement, followed by administration of low-dose insulin to gradually correct hyperglycemia without precipitating hypoglycemia [2]. Not all the fatty acids flooding the liver can be disposed of through oxidation or ketone body synthesis. The excess fatty acids are converted to triacylglycerols, which are packaged and secreted in VLDL-C [3]. Chylomicrons are synthesized from dietary lipids by intestinal mucosal cells following a meal. Because lipoprotein degradation catalyzed by lipoprotein lipase in adipose tissue is low in diabetics, plasma chylomicron and VLDL-C levels are elevated, resulting in hypertriacylglycerolemia [9].

Medicinal plants have long been recognized as important sources of therapeutically active compounds [11]. With special interest in the identification and characterization of bioactive compounds from natural sources, evidence-based research supports the medical and pharmacological uses of plant-derived compounds [12-14]. *Dialium guineense* is a medicinal plant used in Traditional Medicine for the treatment of different disease conditions, such as diarrhea, severe cough, bronchitis, wound, stomachaches, malaria, jaundice, ulcer and hemorrhoids [15-17]. The acute and subchronic toxicity of the plant stem bark have been reported [18, 19]. Extracts of D. guineense have been demonstrated to contain compounds with varied biological/pharmacological effects [20 – 32]. This study investigated the potential of MEDG stem bark to alter the activity of G6Pase/aminotransferases and levels of lipids in tissues of STZ-induced diabetic Wistar rats.

MATERIALS AND METHODS

Chemicals and Reagents

Metformin was a product of Micronova Laboratories (India), and STZ was purchased from British Drug House (BDH) Chemicals Ltd. (England). Solvents (methanol, ethanol and chloroform), and other materials/glass wares were bought from Bell, Sons & Co. (England), while formaldehyde was purchased from Thermo Fisher Scientific Ltd. (USA).

Glucose 6-phosphatase assay kit was obtained from Abcam (UK). All chemicals and solvents used in this study were of analytical grade.

Extract Preparation

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 4 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 absolute ethanol. The resulting extract was filtered through muslin cloth and freeze-dried with a lyophilizer. The ethanol extract was subsequently fractionated with 100% methanol [33 – 35].

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Experimental Rats

Adult male Wistar rats (n = 25) weighing 200 to 230 g (mean weight = 215 ± 15 g) were bought from the Department of Anatomy, University of Benin, Nigeria and housed in wooden cages. They were acclimatized for fourteen (14) days before commencement of the study, and had free access to feed and clean water.

Experimental Design

The experimental design used in this study was a completely randomized block design. The rats were randomly assigned to five groups (5 rats/group): normal control, diabetic, metformin, 200 mg/kg bwt extract and 300 mg/kg bwt extract groups. Diabetes mellitus was induced in the rats using STZ (single intraperitoneal injection of 50 mg/kg bwt). The diabetic rats were then treated with metformin (50 mg/kg bwt) or MEDG stem bark (200 and 300 mg/ kg bwt), for 21 days.

Blood and Tissue Samples Collection and Preparation

At the end of the treatment period, the rats were subjected to mild chloroform anesthesia after an overnight fast. They were euthanized and blood was collected via retro-orbital sinus puncture and centrifuged for 10 min at 3000 rpm to obtain plasma. Rat liver, kidney and heart were excised, blotted dry and used to prepare 20 % tissue homogenate.

Biochemical Analyses

Activities of AST, ALT and ALP as well as levels of TP, TC, TG and VLDL-C were measured in hepatic, renal and cardiac tissues [36 – 41]. Glucose 6-phosphatase activity was determined in plasma, liver and kidney, while NO level was estimated in plasma only [42, 43].

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 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

As shown in Table 1 and Figure 1, STZ-induced DM significantly increased the blood glucose concentrations of the rats, but it reduced the organ/body weight ratio ($p < 0.05$). However, treatment of the diabetic rats with the extract markedly reduced the fasting blood glucose (FBG) concentration and body weights of rats, but it increased the organ/body weight ratio ($p < 0.05$).

Table 1: Effect of MEDG Stem Bark on Weight and Blood Glucose Parameters

Group	Weight Change (g)	% Weight Change	FBG (mg/dL)	Glycemic Change (mg/dL)	% Glycemic Change
Normal Control	–		–	–	–
Diabetic	–		> 800	–	–
Metformin	20.35	12.16	> 800	399	49.88

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Extract (200 mg/kg bwt)	12.26	7.87	> 800	421	52.63
Extract (300 mg/kg bwt)	29.08	17.02	364	227	62.36

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

Organ Weight and Organ/Body Weight Ratio

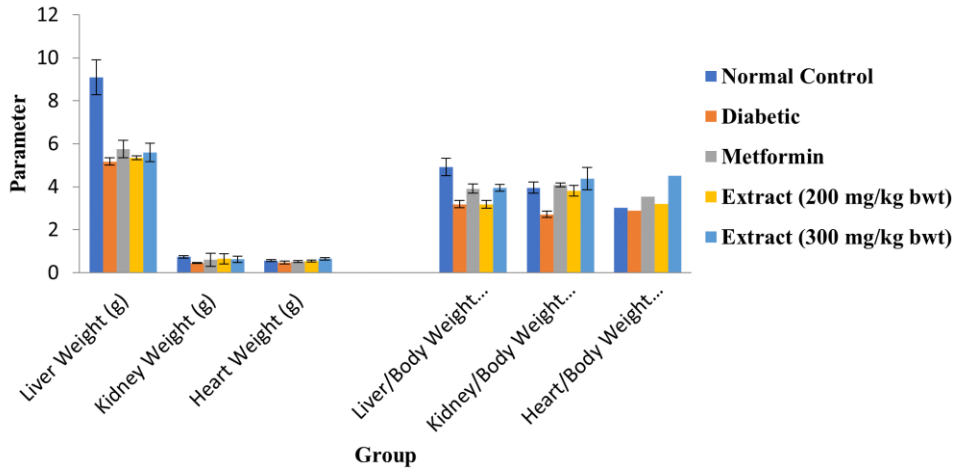

Figure 1: Organ Weight and Organ/Body Weight Ratio

Effect of MEDG Stem Bark on G6Pase Activity

Streptozotocin-induced DM significantly increased G6Pase activity in the plasma as well as hepatic and renal tissues of rats ($p < 0.05$). However, the activity of the enzyme was markedly reduced after treatment with MEDG stem bark ($p < 0.05$; Figure 2).

Activity of G6Pase in Plasma and Rat Hepatic and Renal Tissues

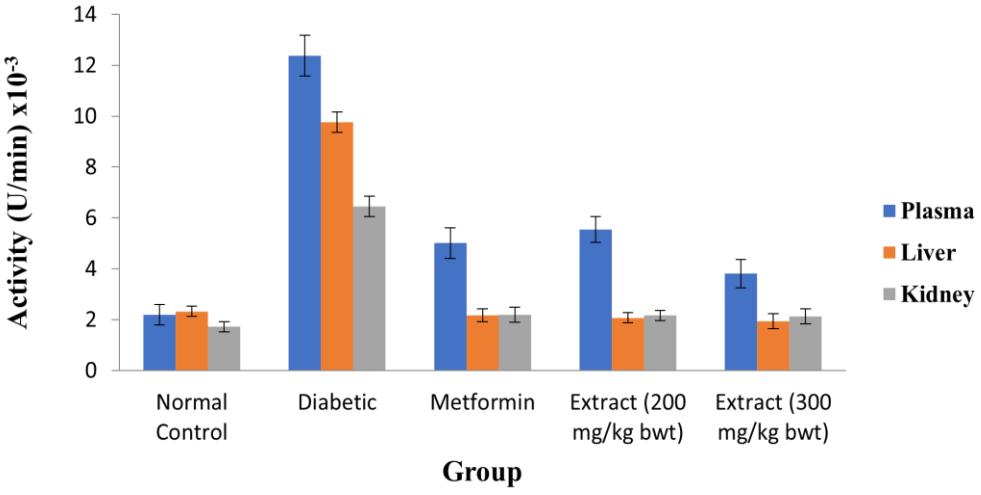

Figure 2: Activity of G6Pase in Plasma and Rat Hepatic and Renal Tissues

Data are plasma and tissue activities of G6Pase and are expressed as mean ± SEM (n = 5).

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Effect of MEDG Stem Bark on Tissue Activity of AST, ALT and ALP

As shown in Figures 3 and 4, STZ markedly elevated the activities of ALT and ALP in rat hepatic tissue ($p < 0.05$), but it did not alter the activity of AST in hepatic and cardiac tissues ($p > 0.05$). On the contrary, treatment of the diabetic rats with MEDG stem bark significantly reduced the hepatic activities of ALT and ALP ($p < 0.05$).

Activity of Cardiac and Hepatic AST

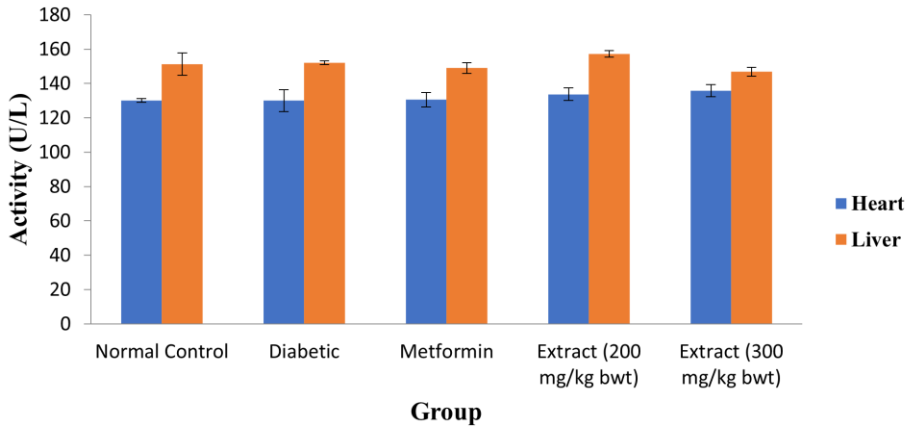

Figure 3: Activity of Cardiac and Hepatic AST

Data are tissue AST, and are expressed as mean ± SEM (n = 5).

Activity of Hepatic ALT and ALP

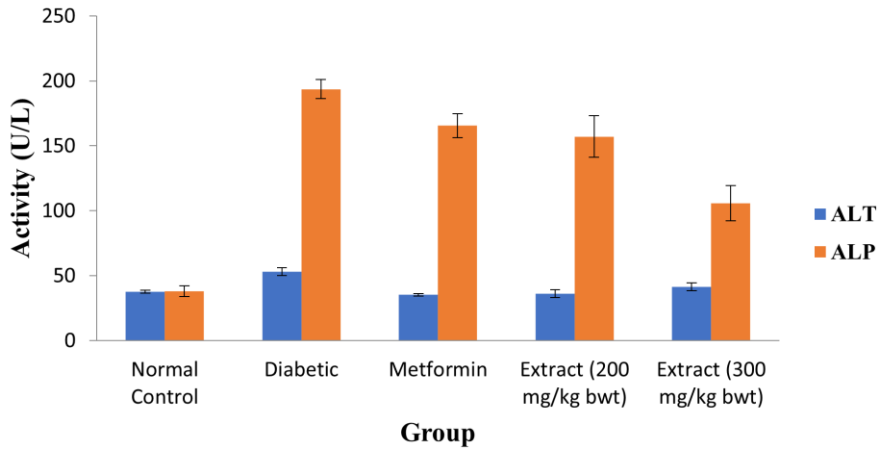

Figure 4: Activity of Hepatic ALT and ALP

Data are tissue ALT and ALP activity, and are expressed as mean ± SEM (n = 5).

Effect of MEDG Stem Bark on Tissue Lipids and NO Level

Induction of DM with STZ led to significant increase in the level of hepatic lipids (TC, TG and VLDL-C) and plasma NO, while treatment of the diabetic Wistar rats significantly reversed the effect of STZ by markedly reducing hepatic lipids and plasma NO levels ($p < 0.05$; Figures 5 and 6).

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume X Issue XII December 2023

Comparison of Levels of Tissue Lipids

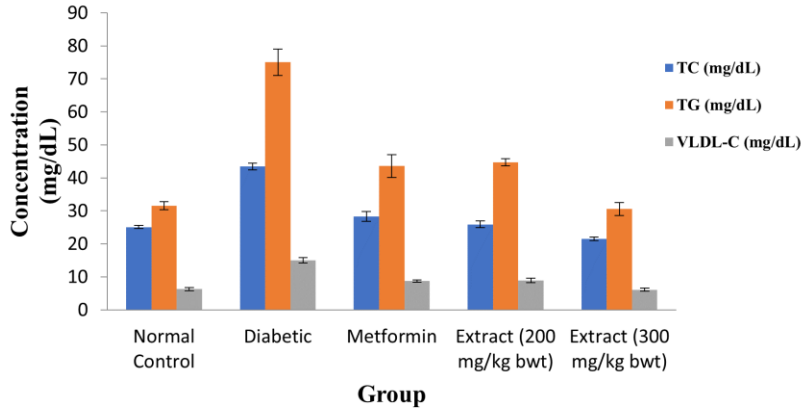

Figure 5: Comparison of Levels of Tissue Lipids

Data are levels of hepatic lipids and are expressed as mean ± SEM (n = 5).

Plasma TP and NO Levels

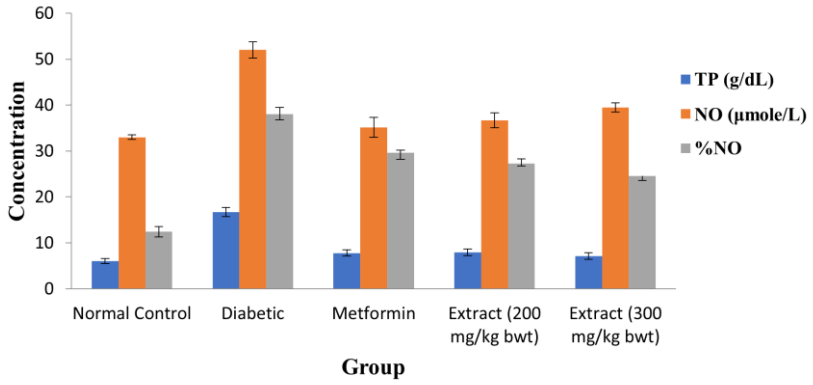

Figure 6: Plasma TP and NO Levels

Data are plasma TP and NO levels, and are expressed as mean ± SEM (n = 5).

DISCUSSION

Plants are at the center of Traditional Medicine. Their use in disease management is as old as man. Medicinal plants serve as cheap alternative to orthodox medicine since they are readily available [44, 45]. A variety of indigenous medicinal plants can effectively manage DM. One of the most significant benefits of medicinal plants is their ready availability and minimal side effects [46, 47].

Dialium guineense is a medicinal plant used locally to treat diverse kinds of diseases [48]. A substantial tropical fruit tree of the family Leguminosae, it bears tiny, frequently grape-sized edible fruits that are coated in brown, inedible shells. At the southernmost border of the Sahel in Africa, it grows in thick woods [15]. The Central African Republic, Sudan, and West Africa are the original home of this plant. In Nigeria, it is referred to by a variety of names, including "*Icheku* (Igbo), *Awin* (Yoruba), *Tsamiyarkurm* (Hausa), and *Amughen* (Bini) [16, 17]. According to reports, the plant's extracts are rich in important phytochemicals [20, 21]. This study investigated the potential of MEDG stem bark to alter the activity of

G6Pase/aminotransferases and levels of lipids in tissues of STZ-induced diabetic Wistar rats.

Hyperglycemia in DM results from increased hepatic gluconeogenesis and reduced glucose uptake in peripheral tissues. The chief and regulatory enzyme of gluconeogenesis is G6Pase. Along with elevated glycogenolysis during fasting, there is increased G6Pase activity in the liver [9]. Thus, glucose 6-phosphate generated from glycogenolysis is released from liver into the circulation for peripheral use. There does not appear to be G6Pase in skeletal muscle; hence, muscle glycogen is not a source of circulating glucose. Glucose-6-phosphatase deficiency (glycogen storage disease, GSD, type Ia) results in hypoglycemia and excessive intracellular accumulation of glucose-6-phosphate [9]. In this study, STZ-induced DM significantly increased G6Pase activity in the plasma as well as rat hepatic and renal tissues. However, the activity of the enzyme was markedly reduced after treatment with MEDG stem bark.

People with T2DM are at risk for both micro- and macrovascular complications [3, 49]. The toxicity produced by STZ impart negatively on organs such as liver, kidneys, heart and lung [50]. The exact molecular mechanism underlying the cytotoxic effect of STZ is not well-understood, however studies suggest that the cytotoxicity could be via production of reactive oxygen species (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 via inhibition of O-linked β -N-acetylglucosaminase (O-GlcNAcase) [51]. In this study, the diabetogenic agent STZ markedly elevated the activities of ALT and ALP in rat hepatic tissue, but it did not alter the activity of AST in hepatic and cardiac tissues. On the contrary, treatment of the diabetic rats with MEDG stem bark significantly reduced the hepatic activities of ALT and ALP. In addition, induction of DM with STZ led to significant increases in the levels of hepatic lipids (TC, TG and VLDL-C) and plasma NO, while treatment of the diabetic Wistar rats markedly reversed the effect of STZ by significantly reducing hepatic lipids and plasma NO levels. These results are similarly to those obtained with ethanol extract of *Cucumis sativus* [52].

CONCLUSION

The results obtained in this study have shown that MEDG stem bark has the capacity to alter the activity of G6Pase/aminotransferases and levels of lipids in tissues of STZ-induced diabetic rats.

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