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Research Article

Evaluation of Oral Administration of Lauric Acid Supplement on Fasting Blood Glucose Level and Pancreatic Histomorphological Studies in High Fat Diet/ Streptozotocin-Induced Type 2 Diabetic Male Wistar Rats

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ABSTRACT

Background: Diabetes mellitus is the most common serious metabolic disease in human with a hall-mark of an elevated blood glucose concentration caused by a number of biochemical and physiological alterations

Aim: The aim of the study was to evaluate the effect oral administration of lauric acid supplement on fasting blood glucose level and pancreatic histomorphological studies in high fat diet/streptozotocin (STZ)-induced type 2 diabetic male Wistar rats.

Study Design: Thirty-five apparently healthy male Wistar rats of 6-8 weeks, weighing between 70 g-90 g were grouped into seven groups of five animals each (n=5) and treated for a period of twenty-one days (21) with graded doses of lauric acid supplement after validation of diabetes. Group 1 and 3 were fed with normal rat feed while group 2, 4, 5, 6, 7 were fed with high fat diet for eight weeks after which low dose STZ was given to same groups.

Methodology: Group 1: (Normal control), Group 2: (Diabetic control untreated), Groups 3: (Normoglycemic) received 125 mg/kg Lauric acid, Group 4, 5 and 6 were administered 125, 250 and 500 mg/kg body weight of lauric acid, Group 7: (Standard control) received metformin 100 mg/kg. Blood glucose level was determined at weekly intervals using glucose test strips and digital glucometer (Accu-Chek Advantage, Roche Diagnostic, Germany). At the end of twenty-one (21) days, rats were anaesthetized using ketamine and xylazine at 75 and 25 (mg/kg) respectively. The Pancreatic tissues were excised and subjected to routine histological investigation for histo-pathological changes.

Result: The results showed that lauric acid at all doses significantly ($P<0.05$) decreased the fasting blood glucose level from (32.45 ± 0.54, 28.85 ± 1.81, 28.85 ± 2.52 mmo/L) to (7.9 ± 1.07, 5.27 ± 0.39 and 4.45 ± 0.48 mmol/L) after three weeks of treatment. And also, Subsequent histomorphological evaluation also showed necrosis and vacuolization of islet β -cells to be reasonably reduced in the diabetic treated rats

Conclusion: This study has been able to demonstrate the Antidiabetic potential of graded doses of lauric acid supplementations for 21 days of administration and it has found out that it possesses strong Antihyperglycemic potencies and induced β -cell regeneration in high fat diet/streptozotocin induced type 2 diabetic rat models.

Keywords: Hyperglycemia; High fat diet; Streptozotocin; Pancreas; Lauric acid

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INTRODUCTION

Diabetes Mellitus (DM) is a muster of metabolic diseases manifested as the presence of higher concentrations of glucose in the blood because of improper production of insulin from pancreas or insensitivity of cells to the produced insulin. It is characterized by periodic or persistent hyperglycemia, which produces classical symptoms such as polyuria, polydipsia and polyphagia [1]. It is a threat to the entire human race without any cogent cure except management over some decades now.

Diabetes mellitus accounts for about 1.6 million deaths each year globally and this condition is worst in developing countries where the number of people afflicted is expected to increase by 150% by the year 2030 [2]. Nigeria has the highest number of people with diabetes in Africa with 3,921,500 cases reported on a prevalence rate of 4.99% [3]. Type 2 diabetes (T2D) accounts for 95% of all cases reported [4,5].

Lauric acid (LA) or a dodecanoic acid is saturated fatty acids with a 12-carbon atom chain thus falling into the group of medium chain fatty acids (C6-C12) [6]. LA is the primary fatty acid of coconut oil which is present at approximately 45%-53% and its metabolic and physiological properties account for many of the healing miracles revealed by coconut oil. It is found in a wide variety of fruits, seeds [7] and as a human milk component [8]. Because of the significant differences in the properties of lauric acid relative to longer chain fatty acids, they are typically differentiated as medium-chain fatty acids covering C6-C12, and long-chain fatty acids covering C14 and longer [9].

Therefore this study was designed to evaluate the effect of oral administration of lauric acid supplement on fasting blood glucose level and pancreatic histomorphological studies in high fat diet/streptozotocin (STZ)-induced type 2 diabetic male Wistar rats.

MATERIALS AND METHODS

Experimental site

This study was carried out in the Physiology Laboratory of the Department of Human Physiology, Faculty of Basic Medical Sciences, College of Health Sciences, Ahmadu Bello University Zaria, Kaduna state Nigeria. Zaria is located between latitudes 110 and 3 ´ N, and between 70 and 42 ´ E, at an altitude of 670 m above the sea level and 664 km away from the sea, in the Northern Guinea Savanna zone [10].

Chemicals and reagents

Lauric acid (white crystalline powder with CAS No-143-07-7, malaysia), Streptozotocin (Bristol sigma, Lagos a subsidiary of sigma Aldrich MO, ST. Louis, U.S.A), Metformin, Chloroform, (Zayo sigma company, Jos, Nigeria: a subsidiary of sigma Aldrich MO, ST. Louis, U.S.A) Normal saline (0.9% w/v), Methylated spirit, Tween 80, Citrate buffer, fructose solution (Kem Light Laboratories PVT Ltd, India), Simas Margarine (PT Salim Ivomas Pratama Tbk, Indonesia), Groundnut mill, and ground nut oil were purchased in Samaru-Zaria market, Kaduna Nigeria.

All chemicals will be obtained commercially and were of analytical grade.

Experimental animals

Thirty-five (35) wistar rats of 5-8 weeks weighing 70 g-100 g were used for this study. The Wistar rats were purchased from Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria, Nigeria. The animals were housed in plastic cages with bedding material (saw dust), in animal house of department of Human Physiology, Faculty of Medicine, Ahmadu Bello University, Zaria, and were provided with food (pelletized growers mash) and water *ad libitum* for a period of two (2) weeks to acclimatize before the study began.

Experimental design

Animal grouping: Thirty-five (35) wistar rats were divided into seven (7) groups containing 5 wistar rats each (n=5) as follows:

Group 1: Normoglycemic administered 1 ml/kg Distilled water via intragastric intubation once daily for three weeks.

Group 2: Diabetic administered 1 ml/kg Tween 80 via intragastric intubation once daily for three weeks.

Group 3: Normoglycemic administered 125 mg/kg of Lauric Acid via intragastric intubation once daily for three weeks.

Group 4: Diabetic administered 125 mg/kg of Lauric Acid via intragastric intubation once daily for three weeks.

Group 5: Diabetic administered 250 mg/kg of Lauric Acid via intragastric intubation once daily for three weeks.

Group 6: Diabetic administered 500 mg/kg of Lauric Acid via intragastric intubation once daily for three weeks.

Group 7: Diabetic administered 100 mg/kg Metformin via intragastric intubation once daily for three weeks [11].

Preparation of high fat diet

Composition of the high fat diet was 25% margarine, 25% groundnut meal, 15% ground nut oil with 35% of the animal feed which was a modification of the composition described by Okoduwa et al. [12] and Tanko et al., [13].

Induction and confirmation of hyperglycaemia

Insulin resistance was induced by feeding the animals with high fat diet (25% margarine which is made up of (fat 99.9%, Emulsifiant E471, E322, E306, Beta Carotene C175130, Vitamin D 30,000 IU/kg), 25% ground nut mill, 15% ground nut oil with 35% of the animal feed which contains crude protein 13%, fat 8%, crude fibre 15%, calcium 0.90%, available phosphorus 0.35%, methionine 0.37%, lysine 0.70%, metabolizable energy 2600 kcal/kg orally for a period of eight weeks) with 10% fructose solution as drinking water. On the 8th week, a single intraperitoneal dose (30 mg/kg) of streptozotocin (STZ) dissolved in 0.1M fresh cold citrate buffer pH 4.5 was injected into overnight fasted rats. The rats were provided 5% glucose solution as drinking water in the first 24 hrs after STZ induction [14-17] as modified. After three (3) days, the blood

glucose level of the rats was measured, and after two weeks, it was measured again and only animals with fasting blood glucose level greater than 11.1 mmol/L were considered diabetic [18].

Determination of blood glucose level

Blood glucose level was determined at weekly intervals from blood obtained from the tail vein of the animals using glucose test strips and digital glucometer (Accu-Chek Advantage, Roche Diagnostic, Germany). The result was expressed in mmol/l of blood [19].

Tissue harvest and histopathological procedures

At the end of twenty-one (21) days, rats were anaesthetized using ketamine and xylazine at 75 and 25 mg/kg respectively. The Pancreatic tissues were excised and subjected to routine histological investigation for histo-pathological changes. Excised pancreas tissues from all the groups were fixed in 10% neutral buffered formalin (JALLICA Scientific, Nigeria) at the end of 21 days treatment period and used for histological study in the department of Histopathology Ahmadu Bello University Teaching Hospital (ABUTH), Zaria. The method of Haematoxylin and Eosin (H&E) was used. The tissues were processed with an automatic tissue processor (Leica ATP 1020). Embedding was done in paraffin wax with the aid of an embedding machine bearing an embedding center (Leica EG1160) and sectioned at 5 µ on a rotatory microtome (Leica RM2125RT). The sections were stained with hematoxylin and eosin staining technique which involved hydrating the tissue sections in descending grades of alcohol from 100%, 95%, 90% and finally 70%. Each of these steps lasted for three (3) minutes and the tissues were then washed in running tap water. The tissues were stained with haematoxylin for twenty-five (25) minutes, washed with water and then differentiated in acid alcohol. The tissues were then counter stained with eosin and blued in Scott water. The tissues were hydrated in ascending grades of alcohol and cleared in xylene for three (3) changes in five (5) minutes each. The tissues were then mounted with cover slips using a mounting media.and mounted on distyrene plasticizer xylene. Photomicrographs at magnifications of ×250 were taken from all the groups with the aid of a digital microscope camera (ScopePhoto ® DCM 510 megapixels) and a Leitz Wetzlar light microscope. (Bancroft and Stevens, 1990).

Statistical analysis

Data collected on weekly changes in blood glucose level were analyzed using repeated measures analysis of variance (ANOVA) and *Tukey's post-hoc* test was used to compare the level of significance between the controls and treatment groups, using SPSS version 22.0. Values of $p<0.05$ was considered significant.

RESULT

Effect of three weeks oral administration of lauric acid on fasting blood glucose level (FBGL) in high fat diet/ streptozotocin-induced type 2 diabetes mellitus in male wistar rats.

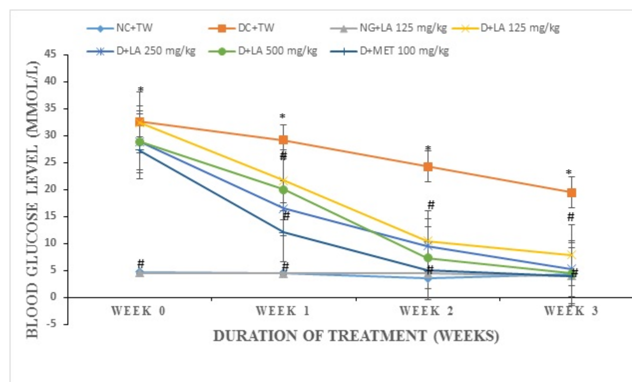

Figure 1: Fasting Plasma Glucose Level in HFD/STZ-Induced Type 2 Diabetes Mellitus in Male Wistar Rats Treated with Lauric acid and Metformin for 21days. Values are presented as mean ± SEM; n=5: P< 0.05=significant; Superscripts: *=significant different when compared to NC group, and ;#=significant different when compared to DC group; DC= Diabetic control, NC= Normal (Non-diabetic) control, NG=Normoglycemic, D=Diabetic, LA=Lauric acid, MET=Metformin, TW=Tween 80.

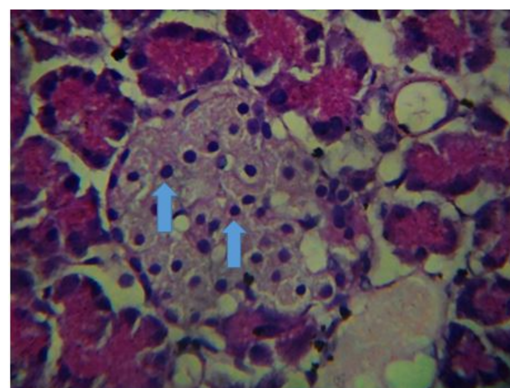

Figure 2: Plate I: Photomicrograph sections of the pancreas for male wistar rats given distilled water (*Normoglycaemic control*) characterized by an organized pattern and showed normal histo-architecture of islets of Langerhans with normal round nuclei of the beta cells with abundant granular cytoplasm (Blue Arrow), H and E, x250.

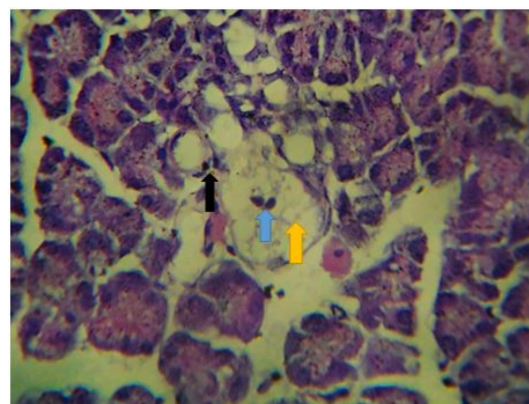

Figure 3: Plate II- Photomicrograph sections of the pancreas Diabetic untreated male Wistar rats (DC+TW) demonstrated damaged islets of Langerhans (Black Arrow), atrophy of beta cells, and reduced beta cell mass (Blue Arrow) with fat infiltration as compared to NC. (Yellow Arrow), H and E, x250.

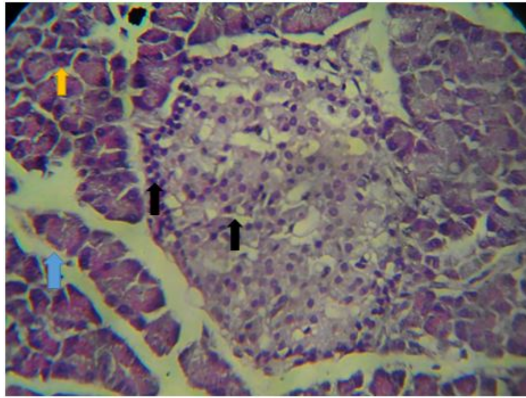

Figure 4: Plate II: Photomicrograph sections of the pancreas for male Wistar rats treated orally with 125 mg/kg Lauric acid (NG+LA 125 mg/kg) characterized by an organized pattern and showed normal histo-architecture of islets of Langerhans with normal round nuclei of the beta cells with abundant granular cytoplasm (Black Arrow), H and E, x250.

Figure 1 shows the effect of a three weeks oral administration of graded doses of lauric acid on fasting blood glucose level in HFD/STZ-induced type 2 diabetes mellitus. Treatment of diabetic animals with graded doses of lauric acid (125, 250 and 500 mg/kg) and metformin (100 mg/kg) resulted in a significant ($P<0.05$) steady decrease in blood glucose level and in a dose dependent manner from week 1 of treatment (21.65 ± 2.55, 16.50 ± 1.84, 20.00 ± 1.47 and 12.07 ± 2.11 mmol/l) and week 2 (10.45 ± 1.17, 9.50 ± 0.25, 7.35 ± 0.96 and 5.00 ± 0.35 mmol/l) to week 3 (7.90 ± 1.07, 5.27 ± 0.39, 4.45 ± 0.48 and 3.85 ± 0.23 mmol/l) when compared with corresponding diabetic control group (29.17 ± 1.56, 24.25 ± 1.33, 19.42 ± 0.77 mmol/l).

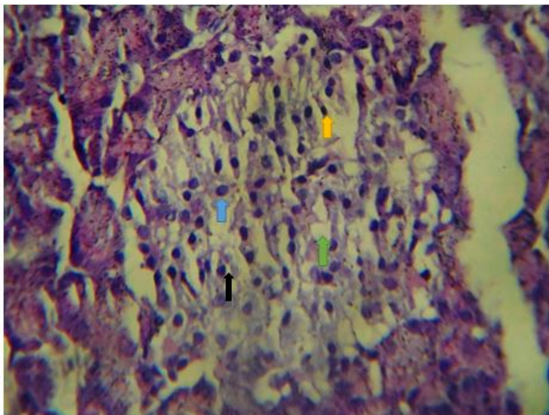

Figure 5: Plate IV: Photomicrograph sections of the pancreas of Diabetic Treated with Lauric Acid 125 mg/kg male Wistar rats (DC +LA 125 mg/kg) demonstrated the presence of more viable cells (Blue Arrow) as compared to diabetic control. However, there is evidence of focal necrosis with pyknotic nuclei (Yellow Arrow) and some vacuolated (Black Arrow), with fat infiltration (Green Arrow), H and E, x250.

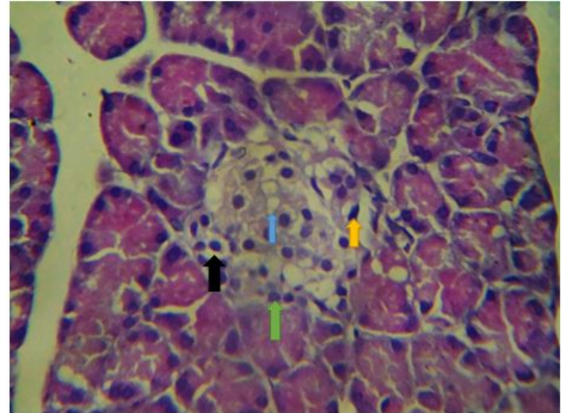

Figure 6: Plate V: Photomicrograph sections of the pancreas of Diabetic Treated with Lauric Acid 250 mg/kg male Wistar rats (DC +LA 250 mg/kg) demonstrated the presence of more viable cells (Green Arrow) as compared to diabetic control and DC+LA 125 mg/kg. However, there is still evidence of focal necrosis with pyknotic nuclei (Yellow Arrow) and some vacuolated cells (Black Arrow), with reduced fat infiltration (Blue Arrow), H and E, x250.

Effect of Three (3) Weeks Oral Administration of Lauric Acid on the Histomorphology of the Pancreas in HFD/STZ-Induced Type 2 Diabetes Mellitus in Male Wistar Rat.

Photomicrograph sections of the pancreas after 21 days of oral administration of 1 ml/kg Distilled water (Normal Control), 1 ml/kg Tween 80 (Diabetic control untreated), Normoglycemic rats treated with 125 mg/kg lauric acid, Diabetic rats treated with 125 mg/kg of Lauric acid, Diabetic rats treated with 250 mg/kg of Lauric acid, Diabetic rats treated with 500 mg/kg of Lauric acid and Diabetic rats treated with Metformin 100 mg/kg are represented in plate I, II, III, IV, V, VI, VII respectively. The lauric acid and metformin treated groups showed increase proliferation of islet cells (Figures 2-8).

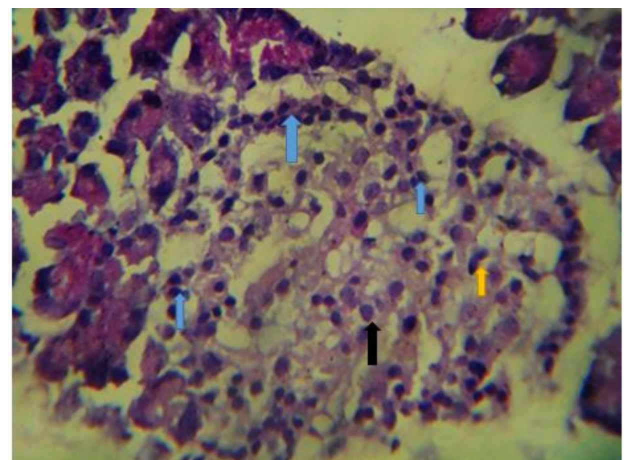

Figure 7: Plate VI: Photomicrograph sections of the pancreas of Diabetic Treated with Lauric Acid 500 mg/kg male Wistar rats (DC +LA 500 mg/kg) demonstrated the presence of more viable cells (Blue Arrow) as compared to diabetic control and DC+LA 250 mg/kg. However, there is still slight evidence of some vacuolated cells (Black Arrow), with reduced fat infiltration (Yellow Arrow), H and E, x250.

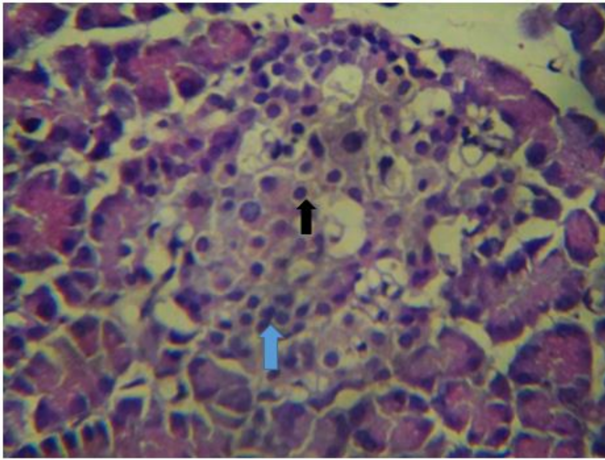

Figure 8: Plate VII: Photomicrograph sections of the pancreas of Diabetic Treated with Metformin 100 mg/kg male Wistar rats (DC +MET 100 mg/kg) demonstrated the presence of more viable beta cells (Blue Arrow) as compared to diabetic control and DC+LA 500 mg/kg. However, there is still slight evidence of some vacuolated cells (Black Arrow), with almost no fat infiltration, H and E, x250.

DISCUSSION

Weekly fasting blood glucose (FBG) level of the present study revealed that oral administration of graded doses of lauric acid (125 mg/kg, 250 mg/kg, and 500 mg/kg) significantly reduced the blood glucose level steadily for the period of three weeks and in a dose dependent manner in hyperglycemic rats when compared to diabetic untreated rats. There was no significant difference between the treated groups and standard control group (metformin) across the weeks and also no significant difference between normoglycemic group that received 125 mg/kg lauric acid and normal control group (1 ml/kg distilled water). The mechanism by which lauric acid exert its antihyperglycemic action could probably involves direct or indirect stimulation of insulin secretion from the remnant of β-cells or regenerated β-cells. Furthermore, it is also suggested that lauric acid treatment interventions might have enhanced glucose utilization by restoring delayed insulin response at the level of the insulin receptors or along the insulin signaling pathway up to the glucose transporter in insulin sensitive cells. It could also be due to the ability of lauric acid to bind to, and activate peroxisome proliferator activated-receptor-Y (PPAR-Y) which is predominantly found in adipose tissue and is an essential regulator of adipocyte differentiation and thus, an indirect regulator of glucose and lipid homeostasis [20,21]. Upon activation, PPAR-Y facilitates normal insulin sensitivity by directly modulating the activation of specific insulin signaling molecules [20,22] and also increase the number of small adipocytes while it decreases the number of large, dysfunctional adipocytes commonly associated with obesity and insulin resistance. Both actions will contribute towards alleviating insulin resistance [23,21]. The reduced fasting blood glucose level by lauric acid could probably be due to the ability of LA to inhibit tyrosine phosphorylation of CCAAT Enhancer Binding Protein-beta (C/EBPβ), and activating adenosine monophosphate-activated protein kinase (AMPK) pathways [24,25]. These actions produce anti-adipogenic effects that improve insulin resistance. The activation of AMPK may also be a key mechanism of action for lauric acid. Studies have shown that activation of AMPK could cause increase in GLUT4 translocation leading to increased glucose uptake and improved insulin sensitivity [21,26,27].

Recently, many studies have shown that pro-inflammatory macrophage accumulation in the liver could trigger chronic low-grade inflammation that promoted the development of insulin resistance via the mitogen activated protein kinase (MAPK) signaling pathway [28,29]. Since MAPK signaling pathway is implicated in the pathogenesis of insulin resistance [30], lauric acid could have significantly reduced the serum levels of key proinflammatory cytokines like C-reaction protein (CRP), interferon gamma (IFN-γ), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-1β (IL-1β), resistin, nitric oxide (NO) and suppressor of cytokine signaling 3 (SOCS3) in the treated groups via its ability to regulate key targets in MAPK signaling pathway (c-jun N-terminal kinase (JNK), p38 mitogen-activated protein kinases (P38), extracellular regulated protein kinases (ERK), c-fos, c-jun, Inhibitor of nuclear factor kappa-B kinase (IKK) and P65) which is a known pathway also regulated by insulin sensitizers like thiazolindinediones like pioglitazone and biguanides like metformin and it's in line with some studies that showed glucose lowering effects of specific TNF-α or IL-1β inhibitors [17,31,32].

This pathway could be a key target for lauric acid in ameliorating the insulin resistance seen in the diabetic treated groups. Lauric acid could have also improved insulin signaling by increasing mRNA expressions of insulin receptor substrate 1(IRS1), Phosphatidylinositol-3-kinase (PI3K), Protein kinase B (Akt2) and Glucose transporter 2 (Glut2) in the liver while protein expressions of p-PI3K, p-Akt, and Glut2 were also enhanced thereby contributing to the improvement of glucose disposal seen in T2DM treated rats [17].

The liver is crucial for the maintenance of normal glucose homeostasis-it produces glucose during fasting and stores glucose postprandially. Insulin could inhibit glycogenolysis, stimulate glycogen synthesis, reduce gluconeogenesis, and increase glucose metabolism. However, these hepatic processes were dysregulated in T2DM because the liver became insulin resistant.

Gluconeogenesis and glycogenolysis are two major pathways for endogenous glucose production. Phosphoenolpyruvate carboxykinase (PEPCK), fructose-1,6-bisphosphatase (FBPase), glucose 6-phosphatase (G6Pase) and glycogen phosphorylase (GP) are the rate-limiting enzymes controlling gluconeogenesis and glycogenolysis in the liver, respectively, while glucokinase (GK), phosphofructokinase (PFK), pyruvate kinase (PK) and glycogen synthase (GS) are the rate-limiting enzymes controlling glycolysis and glycogenesis in the liver, respectively [33,34]

Lauric acid could have reduced fasting blood glucose level of the treated groups by either directly acting on the liver to decrease the activities of the rate limiting enzymes in gluconeogenesis and glycogenolysis, decreasing the transcription of their genes as well and at the same time increase the activity of the rate limiting enzymes in glycolysis and glycogenesis, increasing the

transcription of their genes as well or it activates insulin signaling in the liver which may lead to inhibition of hepatic gluconeogenesis and glycogenolysis as well as increasing hepatic glycogenesis via the action of insulin on the liver [35-39]. This is in agreement with previous study which also found that the ability of glucose metabolism in T2DM was reduced when the synthesis and activity of PFK, PK, GK and GS were decreased and after increasing the synthesis and activity of these enzymes, glucose metabolism was improved [17,36,39,40].

The histological observation of pancreatic tissues provided additional support to the antidiabetic potential of lauric acid. The induced type 2 diabetes mellitus produced noticeable pancreatic injury culminating in a decrease in the pancreatic islets total surface area that was perhaps due to decrease in the number of β-cells. STZ is highly specific to β-cell toxicity. It enters the beta cells via the glucose transporter (GLUT2) and causes alkylation of DNA. DNA damage induces establishment of poly ADP-ribosylation, a progression that is more important for the diabetogenecity. Improved ATP dephosphorylation after streptozotocin induction supplies a substrate for xanthine oxidase resulting in the formation of super oxide radicals, hydrogen peroxide and hydroxyl radicals. In addition streptozotocin liberates toxic amounts of nitric oxide that inhibits aconitase activity and participates in DNA damage and finally destruction of the beta cells by necrosis [41] and consequently causes diabetes mellitus; hence, it is widely used to study β-cell damage *in vivo* in animal experiments [14,42,43].

In the present study, necrosis and vacuolization of pancreatic islet β-cells was observed in the pancreas of the diabetic control (untreated) rats. However, oral administration of graded doses of lauric acid to the diabetic rats ameliorated the pancreatic islet injuries and preserve the remaining β-cells and perhaps cause a regeneration of some β-cells in the islets and subsequently an increase in the total surface area of the islets. Histomorphologically, lauric acid 250 mg/kg and 500 mg/kg reduced significantly the vacuolization and necrosis of pancreatic islets β-cells as compared to the lauric acid 125 mg/kg treated rats. Lauric acid could have ameliorated the pancreatic islets from free radicals and hyperglycemic-mediated oxidative stress and thus preserve the integrity of the remaining pancreatic β-cells and stimulate the cells to synthesize and secrete insulin to maintain glucose homeostasis. These histomorphological observations in the diabetic rats treated with LA in the present study appear to correlate with the biochemical analysis, which would have brought about the lowered levels of blood glucose in the treated rats. These findings suggest the antidiabetic potential of lauric acid in restoring and preserving the structural and functional integrity of pancreatic β-cells especially at higher doses.

CONCLUSION

This study has been able to demonstrate the Antidiabetic potential of graded doses of lauric acid supplementations for 21 days of administration and it has found out that it possesses strong Anti-hyperglycemic potencies and induced β-cell regeneration in high fat diet/streptozotocin induced type 2 diabetic rat models.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this paper.

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