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Rida Herbal Bitters Attenuates Pancreatic Oxidative Stress, Inflammation and Apoptosis in High-Fat Diet/Streptozotocin-Induced Diabetic Rats

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Ajao Folasade Omobolanle*, Iyedupe Marcus Olaoye, Oluwole Rebecca Promise, Jejeola Martins Olumakinde, Lawal Idris Adebayo, Busari Sheriff Adedamola, Adeseye Damilola Adedoyin, Adegbola Raphael Oneosinina

Department of Physiology, Faculty of Basic Medical Science, Ladoke Akintola University of Technology, P.M.B. 4000, Ogbomoso, Oyo State, Nigeria.

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Keywords: Rida herbal bitters, Diabetes mellitus, Pancreas, Oxidative stress, Inflammation, Apoptosis

ABSTRACT

Background: Diabetes mellitus progression is triggered by oxidative stress, inflammation and pancreatic apoptosis**.** Therefore, this study investigated the effects of Rida herbal bitters (RHB) on oxidative stress, inflammatory response and apoptosis in pancreas of high-fat diet and streptozotocin-induced diabetic rats.
Materials and Methods: Thirty-two (32) male Wistar rats weighing (180 ± 20 g) were used and diabetes was induced by repeated intraperitoneal injection of streptozotocin (35 mg/kgb.wt) after feeding the animals with high-fat diet for six weeks. The rats were randomly assigned into four groups, 8rats each. Group I: control; Group II: diabetic; Group III & IV: diabetic rats received 0.3ml RHB and 200 mg/kgb.wt p.o metformin for 28days. Food and water intake were recorded daily, body weight and fasting blood glucose levels weekly throughout the experiment. The animals were sacrificed on the last day; blood was collected while pancreas was excised for biochemical and histological examinations.
Results: Diabetic rats exhibited significant ($p<0.05$) increases in fasting blood glucose (FBG), serum insulin, pancreatic tumor necrosis factor-alpha (TNF-α), caspase-3, malondialdehyde (MDA), and water intake and reductions in pancreatic interleukin-10 (IL-10), B-cell lymphoma-2 (Bcl-2), reduced glutathione (GSH), superoxide dismutase (SOD), catalase (CAT), body weight and food intake. Rida herbal bitters administration attenuated these changes comparable to metformin in most studied parameters.
Conclusion: In the pancreatic tissue, RHB effectively improved pancreatic cells by reducing hyperglycemia through activating endogenous antioxidants, recovering insulin sensitivity, suppressing inflammation and apoptosis in type II diabetic rat model. RHB could be used as novel therapy for diabetes.

INTRODUCTION

Diabetes mellitus (DM), a non-communicable metabolic disease affecting approximately 415 million people globally and this is forecasted to escalate to 642 million in 2040 and mortality was recorded from diabetes mellitus every 6 seconds according to International Diabetes Federation (IDF) [1].Generally, diabetes mellitus is broadly categories into two, type-1 diabetes mellitus (T1DM) and type-2 diabetes mellitus (T2DM) is the most globally spread diabetes and has enormously cause human morbidity and premature mortality [2].Diabetes mellitus is a metabolic disorder characterized by hyperglycemia affecting metabolism of carbohydrate, protein and fat due to deficit insulin secretion from pancreatic β-cells or ineffective of insulin action at target cells(insulin resistance)[3].

Pancreatic beta-cells (β-cells) in the islets of Langerhans are essential for synthesis and secretion of insulin for regulation of blood glucose levels [4]. Chronic hyperglycemia in diabetes condition causes pancreatic β-cells apoptosis, thereby diminishing the pancreatic β-cells mass, insulin secretion and uptake of glucose [5]. Also, persistence hyperglycemia aggravates oxidative stress generation in pancreatic β-cells with releasing of excessive free radicals through NADPH oxidase, which trigger stimulation of pro-inflammatory cytokines biomarkers [6]. Inflammatory and oxidative stress induced by persistence hyperglycemia plays a critical role in etio-pathogenesis of micro-vascular and macro-vascular diabetes complications [7].

The synthetic oral hypoglycemic drugs for diabetes treatment displayed myriad harmful side effects [8]. In recent times, there has been enormous interest in using herbal medicine as alternative therapy to combat diabetes and its complications as they are free from toxic side effects [9].Rida herbal bitter (RHB) is a polyherbal formulation prepared aqueously from mixture of *Curculigo pilosa, Citrullus colocynthis, Hunteria umbellata, Uvaria chamae,* and *Senna alata*. It's an herbal bitters from Nigeria like other commonly known herbal bitters [10]. Rida herbal bitters was traditionally used for managing and alleviating different ailments and have claimed to possess anti-diabetic, hypoglycemic, antioxidant, anti-hyperlipidemic, anti-inflammatory, analgesic and immuno-modulatory properties. At present, effect of Rida herbal bitters on suppression of oxidative stress, inflammation and apoptosis in pancreas during diabetes condition is still scarce. Therefore, this study investigates the effect of Rida herbal bitter on oxidative stress, inflammatory and apoptosis in pancreas of high-fat diet and streptozotocin (STZ)-induced diabetic rats.

MATERIALS AND METHODS

Chemicals and Drugs: Streptozotocin, glucose, metformin

Experimental Animals

Thirty-two (32) matured male Wistar rats weighing (180 ± 20g) were procured and housed at Physiology Department Animal Research House, Ladoke Akintola University of Technology, Ogbomoso, Oyo State, Nigeria. The animals were kept in a clean ventilated polypropylene cages, 8rats / cage with access to standard feed and water *ad libitum* under pathogen-free hygienic environment of temperature (25 ± 2^{o}C), relatively humidity (45% ± 5%) and natural 12:12hrs light / dark cycle for a week acclimatization prior the initiation of the experiment. All experimental procedures were conducted according to the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals and approved by the Research Ethical Committee of Ladoke Akintola University of Technology.

Diabetes Induction

After acclimatized for a week, animals in groups II-IV were fed with high-fat diet for a period of six weeks. At the end of this period, the animals were fasted overnight (12hrs) and injected intraperitoneally with a repeated doses of freshly prepared streptozotocin (STZ) (35 mg/kgb.wt) dissolved in 0.1 M citrate buffer (pH 4.5) to induce diabetes [11].Fasting blood samples was obtained from the rats tail vein after 72hours of STZ injection to confirm diabetes induction using a digital glucometer (Accu-chek) with test strips and animals with fasting blood glucose levels ≥ 200 mg/dL were considered diabetic and used for the study.

Experimental Design and Treatment

The animals were randomly selected and divided into four (4) groups with 8 each, received treatment as follows;

Group I: Normal control (non-diabetic)

Group II: Diabetic

Group III: Diabetic animals received 0.3ml Rida herbal bitters (RHB)

Group IV: Diabetic animals received 200 mg/kg.bwt Metformin (MET)

Treatment commenced immediately after diabetes confirmation and lasted for 28 consecutive days. Administration of Rida herbal bitters (RHB) and metformin (MET) was done orally with oral cannular. Body weight and blood glucose levels were taken on day 1 of the experiment and weekly throughout the experimental treatment phase, food and water intakes were measured daily.

Biochemical Assay

At the end of 28 days treatment, all the animals were fasted overnight (12hrs) and sacrificed by cervical dislocation. Blood was collected via cardiac puncture into heparinized tube, centrifuged at 3,500 rpm for 5 minutes and supernatant plasma obtained was stored at -20^{o}C for insulin determination.

The pancreas was isolated and homogenized in an ice-cold phosphate buffer saline (PBS) P^{H} 7.4. The homogenate was then centrifuged at 10,000 rpm for 10 minutes at -20^{o}C and the clear supernatant retrieved was stored at -20^{o}C for pancreatic oxidative stress, inflammatory and apoptotic biomarkers evaluation.

Fasting plasma blood glucose level was measured based on the glucose oxidase-peroxidase (GOD-POD) method using rats' tail vein blood and active digital glucometer (Accu-chek). Plasma insulin level was determined by Enzymes-linked immunosorbent assay (ELISA) using rat insulin ELISA Kit and was performed according to manufacturer's protocol.

The pancreatic inflammatory cytokine biomarker, tumors necrosis factors-alpha (TNF-α) and anti-inflammatory cytokine biomarker, interleukin-10 (IL-10) were evaluated by ELISA using rat specific cytokine ELISA kits following manufacturer's guideline.

Pancreatic apoptotic marker, caspase-3 and anti-apoptotic marker, B-cell lymphoma -2 (Bcl-2) were also assayed by a specific ELISA kits.

Marker of oxidative stress, malondialdehyde (MDA) level and antioxidant enzymes, superoxide dismutase (SOD), and catalase (CAT) levels in the pancreas were determined by ELISA methods using Rat MDA, SOD, and CAT commercial ELISA Kits (Elab science, China) in compliance to the manufacturer's instruction. Reduced glutathione (GSH) was measured based on the Gupta and Gupta method. [12]

Statistical Analysis

The data were analysed using statistical package for social science (SPSS version 21.0). Results were presented as mean ± standard error (mean ± SEM). The statistical significant differences between groups were evaluated using analysis of variance (ANOVA), followed by Bonferroni post hoc test. P-value of < 0.05 was considered statistically significant.

RESULTS

Effects of Rida herbal bitters on Body weight, Food and Water Intakes

The diabetic rats demonstrated a significant ($p<0.05$) reductions in food intake and body weight while water intake increase ($p<0.05$) significantly in comparison with the control rats. Rida herbal bitters oral supplementation significantly increases the body weight and food intake and reduced the water intake compared to the diabetic rats (Fig 1. a, b & c).

Effects of Rida herbal bitters on Fasting Blood Glucose Levels, Insulin Concentration and HOMA-IR.

Fasting blood glucose levels, insulin concentration and HOMA-IR of diabetic rats were significantly ($p<0.05$) elevated compared to the control rats. However, Rida herbal bitters significantly reduced the blood glucose levels, insulin concentration and HOMA-IR compared to the diabetic rats (Fig 2. a, b & c).

Effects of Rida herbal bitters on Pancreatic Oxidative Stress Marker and Antioxidant activity

The pancreatic oxidative stress marker malondialdehyde (MDA) level significantly ($p<0.05$) increased in the high-fat diet and STZ-induced diabetic rats compared to control rats while antioxidant enzymes superoxide dismutase (SOD), catalase (CAT) and reduced glutathione (GSH) were significantly ($p<0.05$) reduced in diabetic rats compared to control rats. Treatment with Rida herbal bitters decreased MDA level and improves the antioxidant enzymes activity (SOD, CAT and GSH) in comparison with diabetic rats (table 1).

Effects of Rida herbal bitters on Pancreatic Anti-inflammatory, Pro-inflammatory, Pro-apoptotic and Anti-apoptotic Biomarkers

Biomarker of pancreatic pro-inflammatory cytokine tumor necrosis factor-alpha (TNF-α) significantly ($p<0.05$) increased in diabetic group compared to control rats while biomarker

of pancreatic anti-inflammatory cytokine interleukin-10 (IL-10) significantly ($p<0.05$) reduced in comparison with control rats. Rida herbal bitters administrations attenuates the pro-inflammatory cytokine TNF-α and enhances the anti-inflammatory cytokine IL-10 compared to diabetic rats (Fig 3. a & b).

The pancreatic pro-apoptotic biomarker caspase-3 in diabetic rats elevated ($p<0.05$) significantly in comparison with control rats while anti-apoptotic biomarker B cell lymphoma-2 (Bcl-2) in the pancreas of diabetic rats reduced ($p<0.05$) significantly as compared to control rats. Rida herbal bitter supplementation lessens the pro-apoptotic biomarker caspase-3 and increased the anti-apoptotic biomarker Bcl-2 in comparison with diabetic rats (Fig 3. c & d).

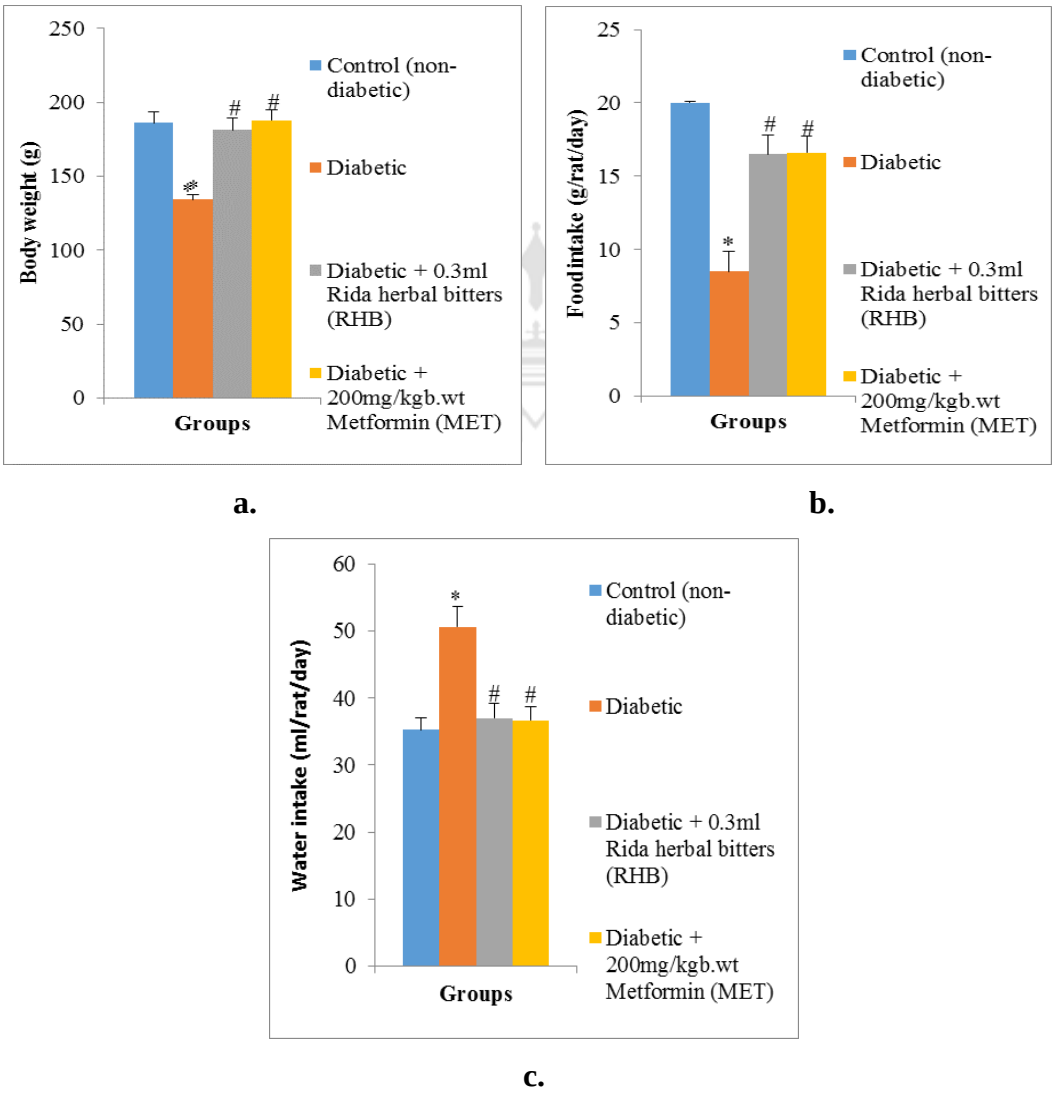
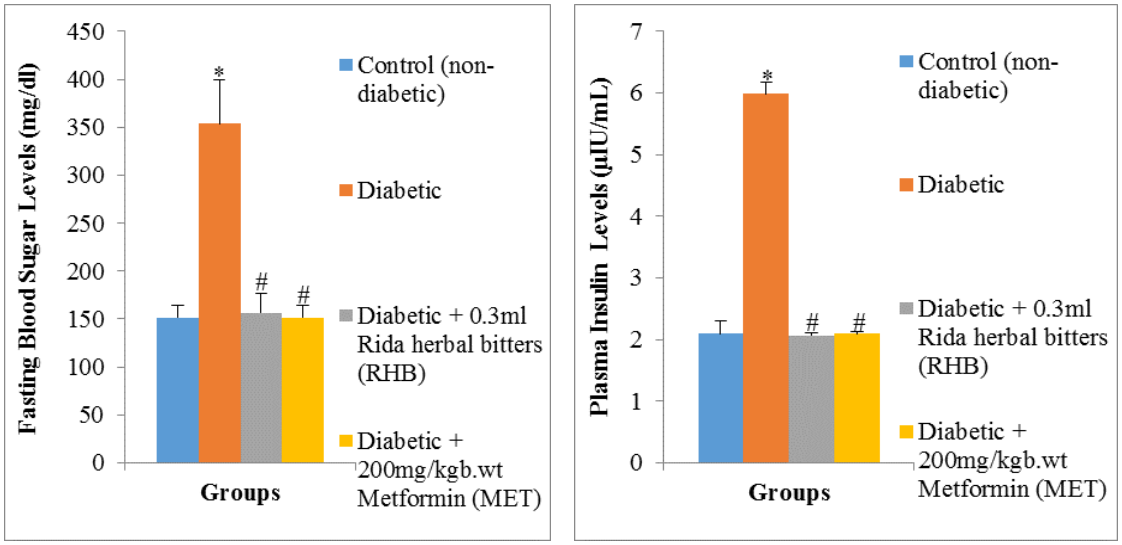


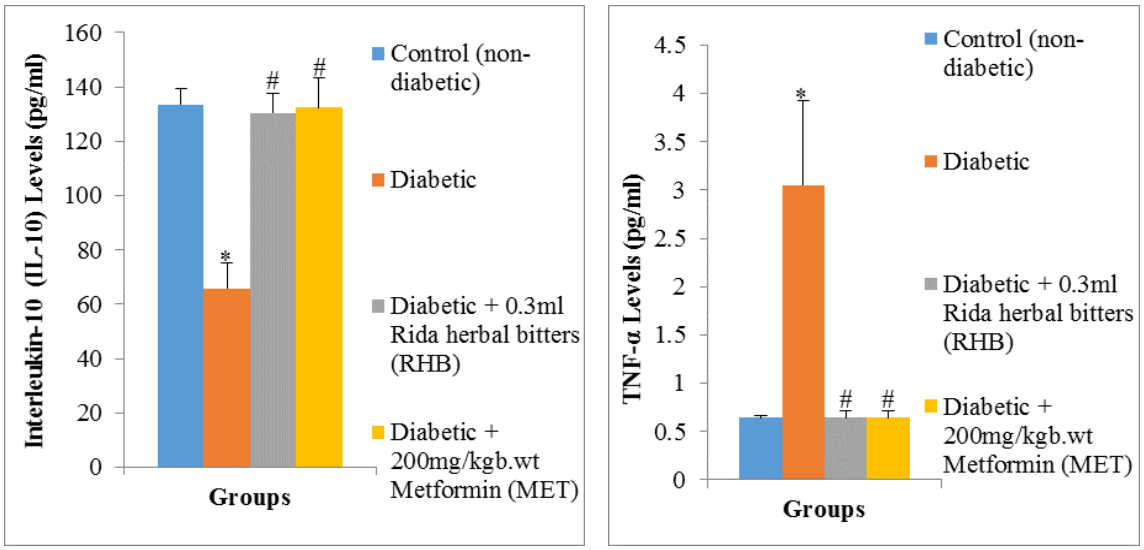
Fig 1: Effects of Rida herbal bitters on (a) body weight, (b) food (c) water intakes in high-fat diet and STZ-induced diabetic rats. *Values are expressed as mean ± SEM (n=8). *significant*

at p<0.05 compared against control; #significant at p<0.05 compared against diabetic group.

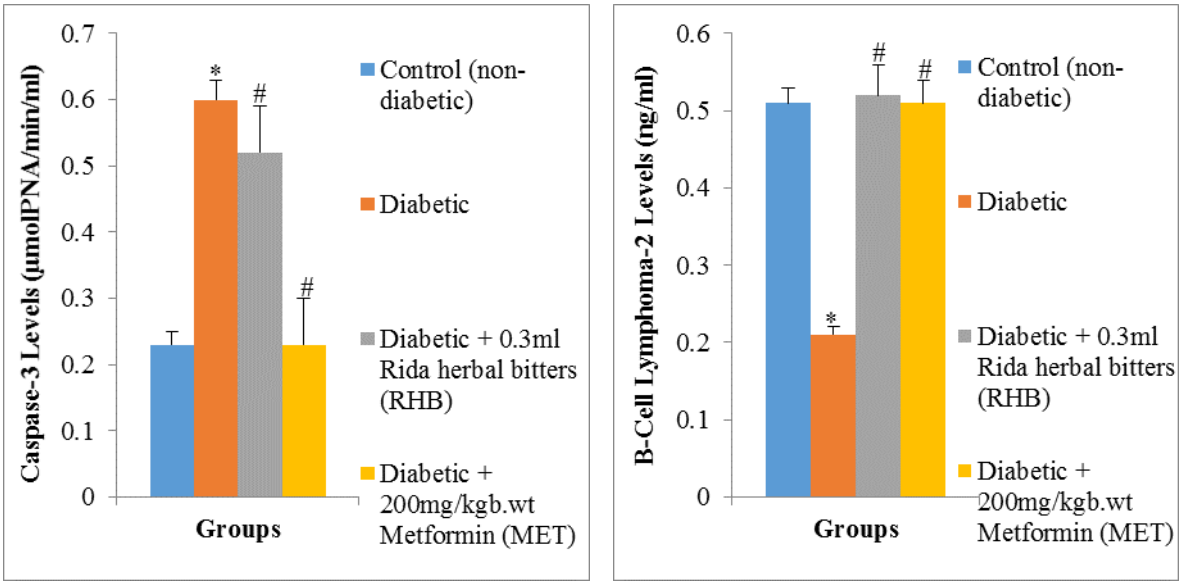


a. **b.**

Fig 2: Effects of Rida herbal bitters on (a) fasting blood glucose levels (b)Insulin concentration in high-fat diet and STZ-induced diabetic rats. *Values are expressed as mean ± SEM (n=8). *significant at p<0.05 compared against control; #significant at p<0.05 compared against diabetic group*



a. **b.**



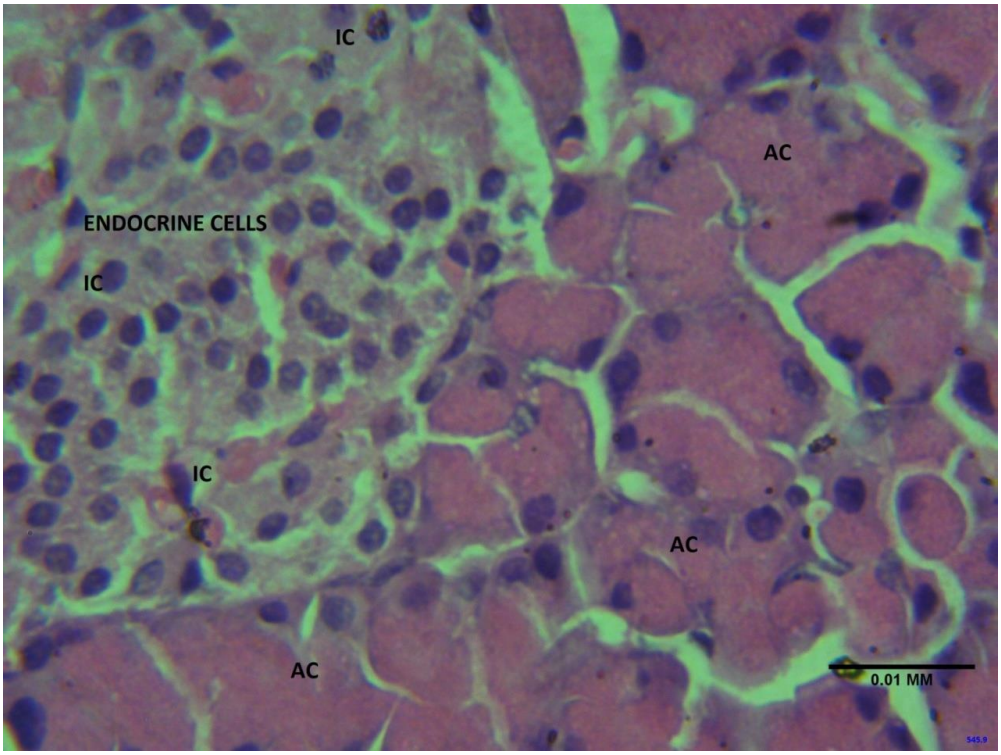
c. **d.**

Fig 3: Effects of Rida herbal bitters on (a) anti-inflammatory cytokine IL-10 (b) pro-inflammatory cytokine TNF-α biomarkers expression (c) apoptotic caspase-3 (d) anti-apoptotic B cell lymphoma-2 (Bcl-2) biomarkers expression in pancreas of high-fat diet and STZ-induced diabetic rats. *Values are expressed as mean ± SEM (n=8). *significant at p<0.05 compared against control; #significant at p<0.05 compared against diabetic group.*

Table 1: Effects of Rida herbal bitters on oxidative stress marker and antioxidants activity in pancreas of high-fat diet and STZ-induced diabetic rats

Groups / Parameters	Control (non-diabetic)	Diabetic	Diabetic + 0.3ml Rida herbal bitters (RHB)	Diabetic + 200mg/kgb.wt Metformin (MET)
Malondialdehyde (MDA) (µM)	3.85 ± 0.08	6.43 ± 0.62*	3.76 ± 0.13#	3.79 ± 0.16#
Catalase (CAT) (µmol/ml/min)	17.89 ± 0.43	13.97 ± 0.22*	17.82 ± 0.70#	17.99 ± 0.43#
Superoxide dismutase (SOD) (U/ml)	1.36 ± 0.04	0.48 ± 0.04*	1.34 ± 0.08#	1.32 ± 0.08#
Reduced glutathione (GSH) (mM)	0.43 ± 0.08	0.19 ± 0.03*	0.42 ± 0.06#	0.42 ± 0.04#

*Values are expressed as mean ± SEM (n=8). *significant at p<0.05 compared against control; #significant at p<0.05 compared against diabetic group.*



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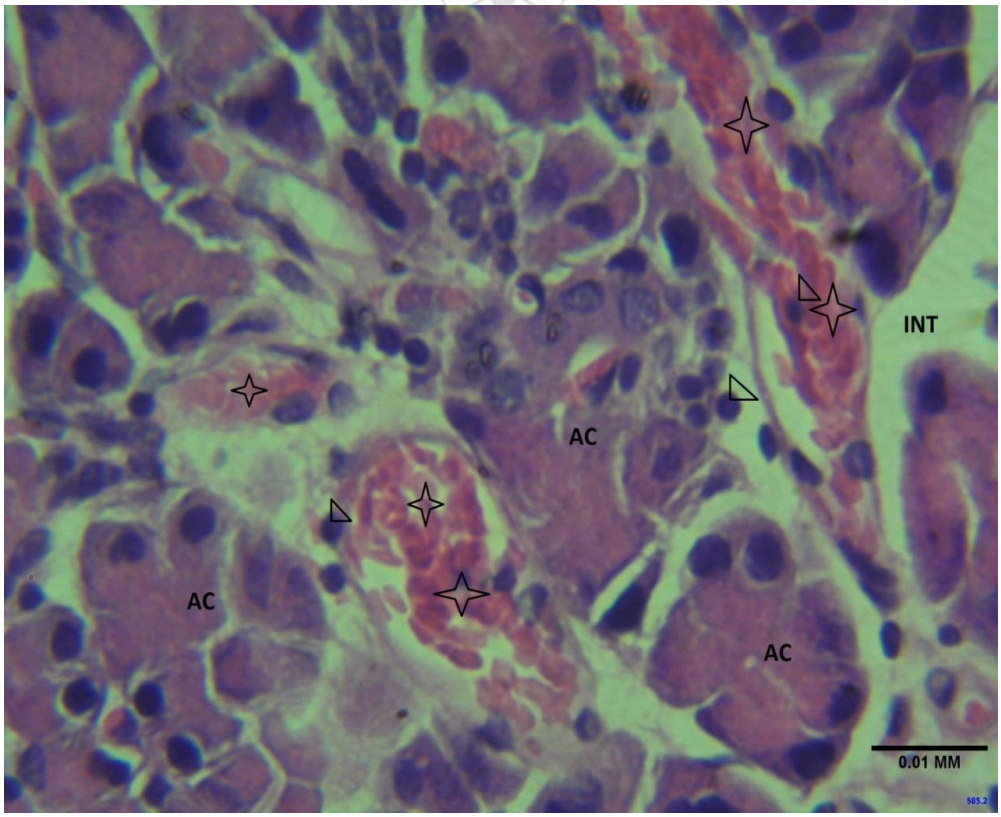

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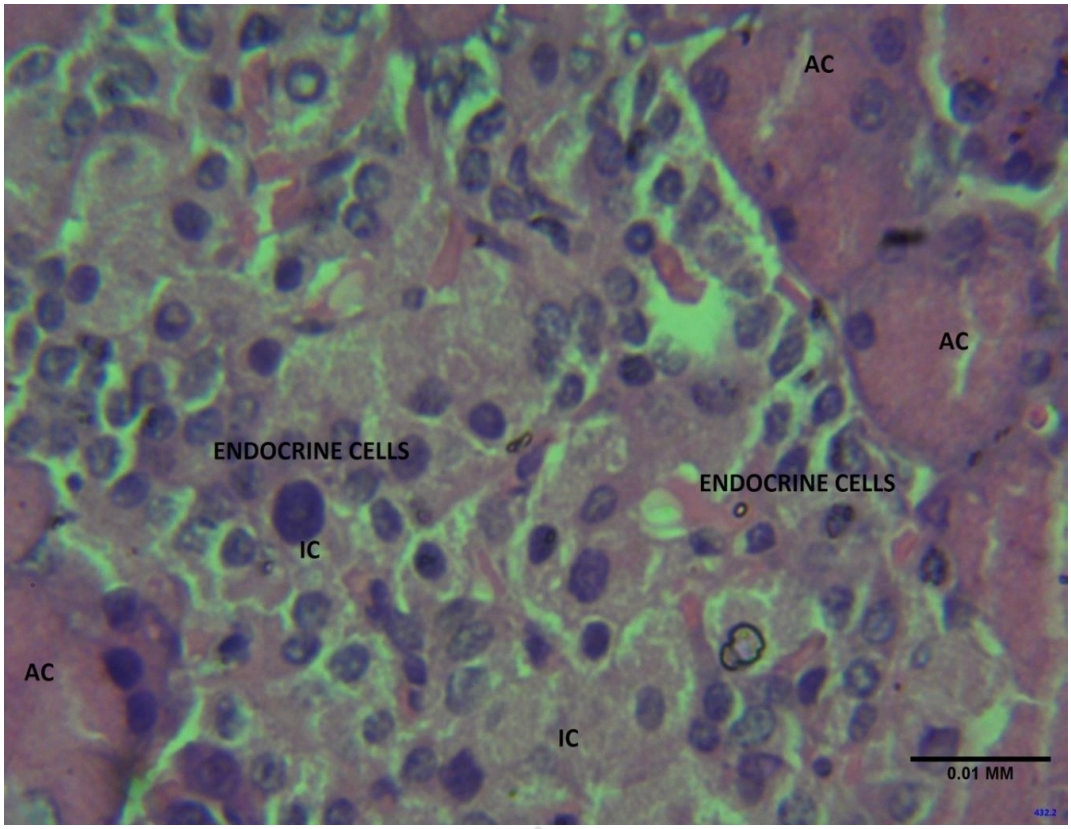
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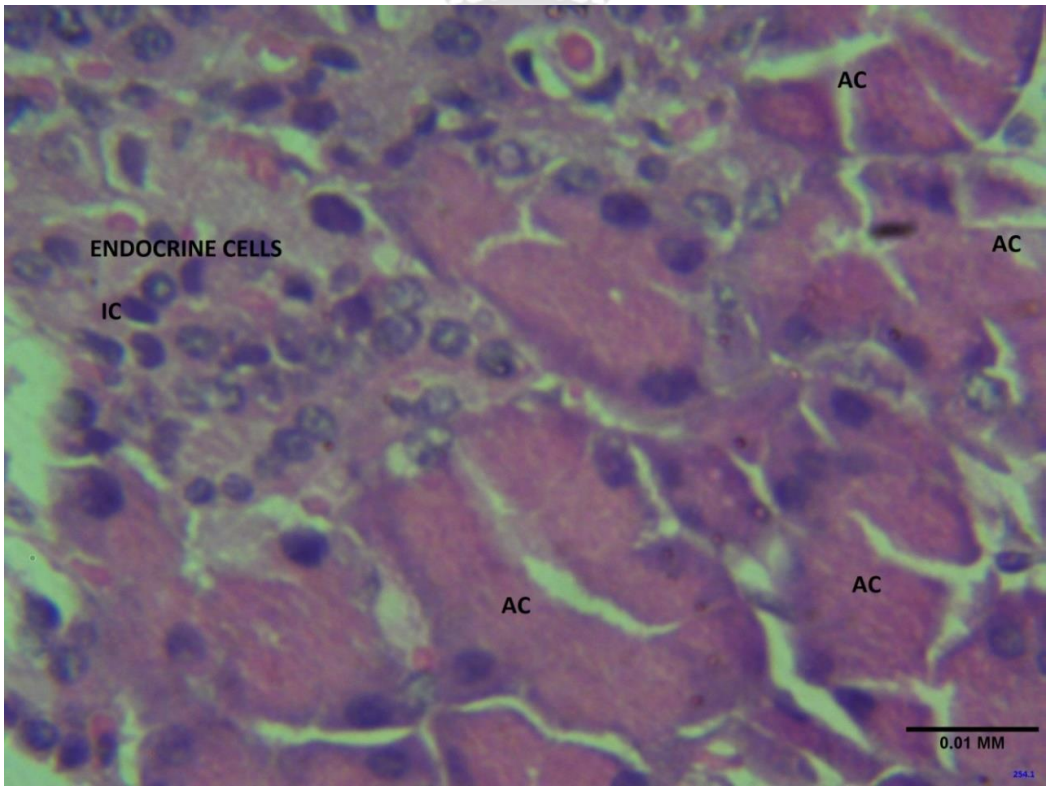
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Fig 4: Pancreatic tissues section histological examination (H & E stain 400x). (**a**) Control (non-diabetic): the section shows normal pancreatic tissue morphology, composed of the endocrine unit made up of the islet cells (IC), the exocrine unit made up of the acinar cells (AC) lined by regular epithelium and the pancreatic duct, all dispersed with a loose connective tissue and separated by the interstitium (INT). The pancreatic vessel and ducts appear unremarkable. (**b**) Diabetic control: pancreatic tissues morphological distortion in this section. The pancreatic vessel appears congestion (Star**)**with surveilling white blood cell (arrow head), features suggestive of vascular response to inflammation. (**c**) Diabetic rats + 0.3ml Rida herbal bitters (RHB): the pancreatic vessel and ducts appears unremarkable. Features consistent with normal pancreatic histo-morphology. (**d**) Diabetic rats + 200 mg/kgb.wt metformin (MET): the pancreatic vessel and ducts appears unremarkable**.** Features consistent with normal pancreatic histo-morphology.

DISCUSSION

Diabetes mellitus is a globally well-known disease with hyperglycemia hallmark which stimulate the progression of many diabetic-related complications that leads to morbidity and mortality [13]. The role of inflammatory and oxidative stress in the pathogenesis of diabetes and its complications via uncontrolled hyperglycemia has been previously reported [14]. In this study, the potential of Rida herbal bitters on oxidative stress, inflammatory and β- cells apoptotic markers in pancreas of high-fat diets and streptozotocin (STZ)-induced diabetic was investigated.

Clinical symptoms such as body weight loss, polyuria (frequent urination), polyphagia (increase food intake), and polydyspia (increase thirst) often occurred in patient with diabetes [15].In consonance with the findings of Guo et al [16], severe weight loss and high water intake experienced by diabetic rats typifies diabetes induction in this study, primarily as a consequence of muscle wasting due to high fat metabolism or tissue proteolysis as energy sources rather than glucose utilization for energy [17]. Administrations of Rida herbal bitters or metformin to the diabetic rats improve the body weight and attenuate elevated water consumptions and could possibly resulted from the action of Rida herbal bitter on glucose metabolism by stimulating glucose uptake in insulin target tissues and by inhibiting the gluconeogenic enzymes activities, thereby preventing muscle wasting.

Insulin secreted from pancreatic β-cells is known to induce suppression of hyperglycemia is affected in chronic diabetes mellitus [18].In our results, diabetic rats exhibited hyperglycemia

coupled with hyperinsulinemia, contrary with other previous findings [19-21], who reported hyperglycemia and decrease in insulin level in diabetic rats. Increase in insulin concentration level symbolizes a state of insulin resistance in the diabetic rats and insulin resistance is atypical feature of type-2 diabetes mellitus. Also, increased insulin release in diabetic rats resulted from compensatory response against high glucose in the blood. Rida herbal bitters administration as well as reference drug, boost glycemic control via normalizing blood glucose and insulin levels by stimulating peripheral tissue sensitivity to insulin action, enhance peripheral glucose uptake and inhibition of extra-hepatic gluconeogenesis, this finding is in line with the report of Shaymaa et al [22].

The progression of diabetes-related complications have been linked with imbalance in the cellular process between pro-oxidants and enzymatic antioxidants defense systems, which arises via the excessive reactive oxygen species (ROS) production by oxidative stress from hyperglycemia. Enzymatic antioxidants superoxide dismutase (SOD), catalase (CAT) and reduced glutathione (GSH) are the most essential antioxidants, performing crucial roles in removing ROS and preventing tissues and cells from pro-oxidants molecules toxicity [23]. In the current findings, oxidative stress marker malondialdehyde (MDA) was elevated with diminution in antioxidant defence enzymes SOD, CAT and GSH activities in pancreatic tissues of diabetic rats and is in accord with the findings of Pashapoor et al [24]. Activities of antioxidant enzymes SOD, CAT and GSH were effectively restored accompanied by lessen in oxidative stress marker MDA level in pancreas of diabetic rats after administration of Rida herbal bitters. This indicates Rida herbal bitters stabilize the cellular process between oxidants and antioxidants enzymes by prohibit releasing of ROS that can damage pancreatic tissues and cells, which support the findings of Wenbin et al [25], on antioxidant activities of ethanolic seed extract of *Annona reticulata* L. in pancreas of diabetic rats.

In addition, over-expression of inflammatory cytokines biomarkers aggravates diabetes mellitus development by exacerbates ROS production and other free radicals [26]. In several studies, up-regulation in the expression of pro-inflammatory cytokine tumor necrosis factor-alpha (TNF-α) accompanied by down-regulation of anti-inflammatory cytokine interleukin-10 (IL-10) have been reported in diabetes mellitus. However, down-regulation in the expression of pro-inflammatory cytokine TNF-α significantly abrogates beta-cells (β-cells) apoptotic level and ameliorates pancreatic function [27]. Over-expression of pro-inflammatory cytokine TNF-α and reduced expression of anti-inflammatory cytokines IL-10 along with elevated level of apoptotic biomarker caspase-3 and reduced anti-apoptotic

biomarker B-cell lymphoma-2 (Bcl-2) level were confirmed in pancreatic tissues of diabetic rats in the present study, concordance the findings of Adama et al [28]. These findings revealed that activation of oxidative stress can cause inflammatory responses and pancreatic tissue apoptosis. Natural products or bioactive compounds from medicinal plants display role to impede diabetes pathogenesis via inflammatory process inhibition [29–32]. Similarly, pro-inflammatory cytokine TNF-α expression and apoptotic marker caspase-3 were markedly down-regulated with up-regulation in anti-inflammatory cytokine IL-10 expression and anti-apoptotic biomarker Bcl-2 in pancreatic tissues of diabetic rats after supplement of Rida herbal bitters, corresponding with findings of Qihu et al [33]. These anti-inflammatory and anti-apoptotic potential of Rida herbal bitters possibly could be due to elimination of reactive oxygen species on pancreatic cells damage through its antioxidants property.

CONCLUSION

Rida herbal bitters suppress oxidative stress, inflammatory and pancreatic apoptosis induced by hyperglycemia and may be used as an alternative therapy to prevent the progression of diabetes and its related comorbidities complications.

ABBREVIATIONS

RHB: Rida herbal bitters; HDF: high fat-diet; STZ: streptozotocin

DECLARATIONS

Authors' Contributions

Ajao FO conceived the original idea, designed and supervised the research. Iyedupe MO, Oluwole RP, Jejeola MO, Lawal IA, Busari SA, Adeseye DA and Adegbola RO performed the experiments with the support of Ajao FO. Iyedupe MO, Oluwole RP and Jejeola MO, support Lawal IA, Busari SA, Adeseye DA and Adegbola RO in data collection. Iyedupe MO analyzed the data and wrote the manuscript. Ajao FO reviewed the manuscript. All authors' have read and approved the final manuscript.

Ethical Approval

All procedures were approved by the Animal Care committee of the Ladoke Akintola University of Technology and conducted according to the "Principles of Laboratory Animal Care" and specific national laws where applicable.

Consent for Publication

All authors agreed to publish the article.

Availability of Data and Materials

All data generated and analyzed during this study are included in this article.

Competing Interests

No competing interests.

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Image *Author -1*	***Author Name - Corresponding Author*: Ajao Folasade Omobolanle*** Department of Physiology, Faculty of Basic Medical Sciences, College of Health Sciences, Ladoke Akintola University of Technology, P.M.B 4000, Ogbomoso, Oyo State, Nigeria
Image *Author -2*	***Author Name*: Iyedupe Marcus Olaoye** Department of Physiology, Faculty of Basic Medical Sciences, College of Health Sciences, Ladoke Akintola University of Technology, P.M.B 4000, Ogbomoso, Oyo State, Nigeria
Image *Author -3*	***Author Name*: Oluwole Rebecca Promise** Department of Physiology, Faculty of Basic Medical Sciences, College of Health Sciences, Ladoke Akintola University of Technology, P.M.B 4000, Ogbomoso, Oyo State, Nigeria
Image *Author -4*	***Author Name*: Jejeola Martins Olumakinde** Department of Physiology, Faculty of Basic Medical Sciences, College of Health Sciences, Ladoke Akintola University of Technology, P.M.B 4000, Ogbomoso, Oyo State, Nigeria
Image *Author -5*	***Author Name*: Lawal Idris Adebayo** Department of Physiology, Faculty of Basic Medical Sciences, College of Health Sciences, Ladoke Akintola University of Technology, P.M.B 4000, Ogbomoso, Oyo State, Nigeria
Image *Author -6*	***Author Name*: Busari Sheriff Adedamola** Department of Physiology, Faculty of Basic Medical Sciences, College of Health Sciences, Ladoke Akintola University of Technology, P.M.B 4000, Ogbomoso, Oyo State, Nigeria

Image *Author -7*	***Author Name*: Adeseye Damilola Adedoyin** Department of Physiology, Faculty of Basic Medical Science, College of Health Sciences, Ladoke Akintola University of Technology, P.M.B 4000, Ogbomoso, Oyo State, Nigeria.
Image *Author -8*	***Author Name*: Adegbola Rapheal Oneosinina** Department of Physiology, Faculty of Basic Medical Sciences, College of Health Sciences, Ladoke Akintola University of Technology, P.M.B 4000, Ogbomoso, Oyo State, Nigeria