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Research Article

Rida Herbal Bitters Improve Cardiovascular Function in High-fat Diet/Streptozotocin-induced Diabetic Rats

Folasade Omobolanle Ajao[1]*, Damilola Ayodeji Balogun[1], Marcus Olaoy Iyedupe[1], Ayobami Olagunju[1], Esther Oparinde[1], Luqman Adeniji[1], Victor Abulude[1] and Funmilayo Elizabeth Olaleye[2]

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

[2]Department of Human Nutrition and Dietetics, College of Medicine, University College Hospital, Ibadan, Oyo State, Nigeria

More Information

***Address for correspondence:**
Folasade Omobolanle Ajao, Physiology Department, Faculty of Basic Medical Science, College of Health Science, Ladoke Akintola University of Technology, P.M.B. 4000, Ogbomoso, Oyo State, Nigeria,
Email: foajao@lautech.edu.ng

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Abstract

Background: Effective medication to manage diabetes mellitus-related organ complications with minimal adverse drug toxicity is still in pursuit by scientists worldwide. This study investigated the cardio-protective of Rida herbal bitter (RHB) in a high-fat diet/streptozotocin (STZ)-induced diabetic rats.

Methods: Thirty-two matured male Wistar rats (250 ± 20g) were used. The animals were fed with high-fat diet (HFD) for 6 weeks before diabetes induction. A single dose of (35 mg/kgb.wt) freshly prepared STZ was injected intraperitoneally to induce diabetes. The animals were allocated into four groups, 8rats/group. Group I: control; Group II: HFD/STZ-induced diabetic rats; Groups III & IV: HFD/STZ-induced diabetic rats treated with 0.3 ml RHB & 200 mg/kgb.wt metformin respectively. At the end of the experiment, the animals were sacrificed, blood was sample collected via cardiac puncture and the heart was excised and homogenized. The blood samples and cardiac homogenates tissue were centrifuged to retrieve clear supernatant plasma for biochemical assay.

Results: Diabetic rats exhibited significant ($p < 0.05$) elevated blood glucose, insulin, glycated hemoglobin (HbA1c), cardiac biomarkers, lipid profile, malondialdehyde (MDA), pro-inflammatory cytokines, food, and water intake levels with a reduction in body weight, cardiac antioxidant activity, and total protein. RHB administration significantly ($p < 0.05$) diminished the blood glucose, insulin, HbA1c, cardiac biomarkers, MDA, pro-inflammatory cytokines, lipid profile, food, and water intake, and improved the body weight cardiac antioxidant activity, and total protein.

Conclusion: Rida herbal bitter possesses a cardio-protective effect from this study and could be a better alternative medication for managing diabetes and its related cardiovascular complications.

Introduction

Diabetes Mellitus (DM) is well recognized as one of high prevalent metabolic diseases and continues to be a significant contributor to global mortality and morbidity [1]. According to the International Diabetes Federation (IDF) report, the global estimated number of adults (20 years - 79 years) living with diabetes in 2021 was 537 million and the number is projected to escalate to 783 million by 2045 [2].

DM is a metabolic disorder characterized by chronic persistent hyperglycemia resulting from alteration of carbohydrates, proteins, and lipids metabolism due to deficiency of pancreatic β-cells to produce sufficient insulin and/or impaired responsiveness of target cells to insulin or both [3]. The typical symptoms associated with diabetes include polyuria, polydipsia, and polyphagia [4]. Chronic persistence hyperglycemia in DM induces several long-term micro and macro-vascular complications including diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, and heart and blood vessels [5].

Cardiovascular Disease (CVD) complications account for approximately 80% of all causes of morbidity and mortality in diabetic patients [6]. Cardiovascular complications in diabetic patients include heart failure, peripheral arterial disease, and coronary heart disease [7].

The available synthetic diabetes drugs have been reported with many adverse effects and there has been a growing focus on exploring traditional and alternative medicines, as well as food-derived products that are abundant in phyto-constituents for DM treatment owing to the presence of bioactive compounds including alkaloids, flavonoids, glycosides, gums, carbohydrates, triterpenes, and various short peptides found in plants and plant-derived products [8].

Rida Herbal Bitter (RHB) is a medicinal herb from Nigeria prepared by an aqueous mixture of *Curculigo pilosa, Citrullus colocynthis, Hunteria umbellata, Uvaria chamae, and Senna alata*. It's traditionally proven to alleviate many ailments and demonstrated anti-diabetic, anti-hyperlipidemic, antioxidant, anti-inflammatory, immune-modulatory, and analgesic potentials [9]. These pharmacological activities of Rida herbal bitter on diabetes and its protective effect on hyperglycemia-induced organ injury in DM lack scientific experimental investigation. The cardio-protective efficacy of Rida herbal bitter on hyperglycemia-induced cardiovascular complications in high-fat diet/streptozotocin-induced diabetic rats was experimentally investigated in the present study.

Materials and methods

Drugs and chemicals

Streptozotocin, Phosphate buffer, glucose, ketamine, and xylazine. All chemicals used were of analytical grade.

Experimental animal

Thirty-two adult male rats of weight (250 ± 20 g) were purchased from the Physiology Department Animal House, Ladoke Akinola University of Technology, Ogbomosho, Oyo state, Nigeria. The animals were kept in a clean polypropylene cage for a week to acclimatize with access to standard feed and water ad libitum under a pathogen-free hygienic environment (25 °C ± 2 °C), relative humidity (45% ± 5%) and 12:12 hours light/dark cycles. All experimental procedures were conducted according to the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals and Ladoke Akintola Faculty of Basic Medical Sciences Ethical approval no: ERCFBMSLAUTECH:021/01/2024 was given.

Diabetes induction

The rats were fed with a High-Fat Diet (HFD) for six weeks before diabetes Induction. After fed the HFD, rats were subjected to overnight fasting (12 hours) before diabetes induction, and freshly prepared streptozotocin (35 mg/kgb. wt) was injected intraperitoneally to induce diabetes in the rats. The rats were orally gavaged with 2% glucose solution to prevent drug-induced hypoglycemic mortality. The fasting blood glucose levels of the rats were checked after 72 hours of streptozotocin injection to authentic diabetes Induction using an active Accu-Chek glucometer and tail-pricked vein blood of the rats. Rats with fasting blood glucose levels of ≥ 200 mg/dL were selected as diabetic rats for the experiment.

Experimental grouping

Thirty-two rats were aligned into four groups, 8rats/group as follows:

Group I: Non-diabetic rats (control).

Group II: HFD/STZ-induced diabetic rats (untreated)

Group III: HFD/STZ-induced diabetic rats + 0.3 ml Rida herbal bitter.

Group IV: HFD/ STZ-induced diabetic rats + 200 mg/kgb. wt metformin.

The experimental treatment phase lasted for 21 days. The control and diabetic rats were given distilled water. The rats' body weight, food intake, and water intake were taken daily, and blood glucose weekly. The dose of Rida herbal bitters administered was determined from the normal recommended intake for an adult.

Biochemical assay

The rats were fasted overnight after the last dose was administered. The rats were anesthetized with ketamine (40 mg/kgb.wt) and xylazine (20 mg/kgb.wt) as the combined anesthetic drugs are better and can give a desirable anesthetic effect than a single drug. Thereafter, the animals were sacrificed by cervical dislocation and blood samples were collected from the apex beat of the hearts. The hearts were excised after the blood collection, rinsed in normal saline, and homogenized with cold phosphate-buffered. The blood samples were centrifuged at 3,500 rpm for 15 minutes at 4 °C and the heart tissues homogenate was centrifuged at 10000 rpm for 10 minutes at 4 °C. The clear supernatant plasma retrieved from the centrifuged was used for biochemical parameters determination.

The glucose oxidase/peroxidase (GOD-POD) method was used to measure the fasting blood glucose levels using a digital Accu-Chek glucometer and test strips via pricked tail vein blood.

Glycated Hemoglobin (HbA1c) was estimated using a rat hemoglobin HbA1c assay kit following the manufacturer's instructions.

Lactate Dehydrogenase (LDH) and Aspartate aminotransferase (AST) were determined using a spectrophotometer and assay method with an available commercial kit.

Enzyme link immunosorbent assay was used to determine the plasma insulin, Creatine Kinase-Myocardial Band (CK-MB) troponin I, Tumor Necrosis Factor-alpha (TNF-α), cardiac interleukin-1β (IL-1β), cardiac interleukin-6 (IL-6), Brain Natriuretic-Peptide (BNP) and transforming growth factor-β1(TGF-β1) levels using a rat ELISA kit specific for each assay follow the instructions of the manufacturer's. Cardiac total protein was determined using a commercial ELIZA assay kit.

The cardiac Malondialdehyde (MDA), Catalase (CAT), and Superoxide Dismutase (SOD) activities were estimated using an ELISA assay kit in accordance with the manufacturer's guidelines.

Cardiac Total Cholesterol (TC), Triglyceride (TG), and High-Density-Lipoprotein-cholesterol (HDL-C) were estimated by enzymatic colorimetric method with commercial assay kits according to the manufacturer's protocol. Cardiac Low-Density Lipoprotein-cholesterol (LDL-C) was calculated based on Friedewald, et al. formula [10], LDL-C=TC-(HDL-C+TG/5) and cardiovascular risk indices (CRI) was calculated as TG/HDL-c ratio.

The Atherogenic Coefficient and Castelli's Risk Index-1 were determined based on the following formula:

Atherogenic Coefficient (AC) = (TC - HDL)/HDL.

Castelli's Risk index-1 (CRI-1) = TC/HDL.

Statistical analysis

All the data were represented as the standard mean of error (mean ± SEM). Data were analyzed with a statistical package for social sciences (SPSS version, 20.0) using One-way analysis of variance (ANOVA) followed by Bonferoni's test to determine the significant difference between groups. A P-value less than 0.05 is considered statistically significant.

Results

Effect of Rida herbal bitter on relative heart weight, body weight, water intake, and food intake in HFD/Streptozotocin-induced diabetic rats

Relative heart and body weights of HFD/STZ-induced diabetic rats reduced significantly ($p < 0.05$) compared with non-diabetic rats (control). Administered Rida herbal bitter improved the relative heart and body weights in comparison with untreated HFD/STZ-induced diabetic rats. Food intake and water intake increased significantly ($p < 0.05$) in HFD/STZ-induced diabetic rats compared with control rats. Rida herbal bitter supplementation slightly reduced the food intake and moderately lowered the water intake in comparison with untreated HFD/STZ-induced diabetic rats (Table 1).

Effect of Rida herbal bitter on insulin, fasting blood glucose and glycated hemoglobin and levels in HFD/Streptozotocin-induced diabetic rats

Plasma insulin, fasting blood glucose (FBG), and glycated hemoglobin (HbA1c) levels in HFD/STZ-induced diabetic rats were higher ($p < 0.05$) significantly compared with non-diabetic rats. Administered Rida herbal bitter to the HFD/STZ-induced diabetic rats diminished the plasma insulin, FBG, and HbA1c levels significantly in comparison with untreated HFD/STZ-induced diabetic rats (Figure 1A-C).

Effect of Rida herbal bitter on cardiac biomarkers function and total protein levels in HFD/Streptozotocin-induced diabetic rats

Cardiac function biomarkers CK-MB, troponin I, Lactate Dehydrogenase (LDH), and Aspartate aminotransferase (AST) levels significantly ($p < 0.05$) elevated in HFD/STZ-induced diabetic rats in comparison with non-diabetic rats. Administration of Rida herbal bitter significantly ($p < 0.05$) reduced the CK-MB, troponin I, LDH, and AST compared with untreated HFD/diabetic-induced rats (Figure 2A-D).

The heart total protein of HFD/STZ-induced diabetic rats lowered ($p < 0.05$) significantly compared with non-diabetic rats (control). Administered Rida herbal bitter increased the heart's total protein significantly in comparison with untreated diabetic rats (Figure 2E).

Effect of Rida herbal bitter on cardiac lipids profile, cardiac risk indices, atherogenic coefficient, and Castelli's risk index-1 in HFD/Streptozotocin-induced diabetic rats

The level of cardiac TC, TG, LDL-c, cardiovascular risk indices, atherogenic coefficient, and Castelli's risk index-1 significantly ($p < 0.05$) higher with lower cardiac HDL-c level in HFD/STZ-induced diabetic rats compared with control rats (non-diabetic). Treatment with Rida herbal bitter increased cardiac HDL-c significantly and decreased the cardiac TC, TG, LDL-c, cardiovascular risk indices, atherogenic coefficient, and Castelli's risk index-1 significantly in comparison with untreated HFD/STZ-induced diabetic rats (Table 2).

Effect of Rida herbal bitter on cardiac antioxidant levels in HFD/Streptozotocin-induced diabetic rats

Cardiac oxidative stress marker, malondialdehyde (MDA) level significantly ($p < 0.05$) elevated and activity of cardiac antioxidants Superoxide Dismutase (SOD) and Catalase (CAT) reduced ($p < 0.05$) significantly in HFD/STZ-induced diabetic rats compared with control. Rida herbal bitter administrations significantly elevated the activity of cardiac SOD and CAT and lessen the MDA level in comparison with untreated HFD/STZ-induced diabetic rats (Table 3).

Effect of Rida herbal bitter on cardiac pro-inflammatory cytokines, transforming growth factor and brain-natriuretic peptide in HFD/Streptozotocin-induced diabetic rats

In HFD/STZ-induced diabetic rats, cardiac pro-inflammatory cytokines tumor necrosis factor-alpha (TNF-α),

Table 1: Effects of Rida herbal bitter on (a) body weight (b) food intake (c) water intake (d) relative heart weight in HFD/streptozotocin (STZ)-induced diabetic rats.

Experimental groups	Body weight (g)	Food intake (g/day/rat)	Water intake (ml/day/rat)	Relative heart weight (g)
Control (non-diabetic rats)	262.20 ± 4.07	23.52 ± 1.14	76.90 ± 3.96	0.01 ± 0.00
HFD/ STZ-induced diabetic rats (untreated)	168.20 ± 8.42*	24.86 ± 0.89*	95.14 ± 2.91*	0.00 ± 0.00*
HFD/ STZ-induced diabetic rats + 0.3 ml Rida herbal bitter	235.50 ± 18.01#	24.39 ± 1.10#	75.31 ± 4.09#	0.01 ± 0.00#
HFD/ STZ-induced diabetic rats + 200 mg/kgb.wt metformin	263. 33 ± 6.96#	24.68 ± 2.39#	75.44 ± 5.26#	0.01 ± 0.00#

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

Table 2: Effects of Rida herbal bitter on lipid profile in HFD/streptozotocin (STZ)-induced diabetic rats.

Parameters	Control (non-diabetic rats)	HFD/ STZ-induced diabetic rats (untreated)	HFD/ STZ-induced diabetic rats + 0.3 ml Rida herbal bitter	HFD/ STZ-induced diabetic rats + 200 mg/kgb.wt metformin
TC (mg/dL)	140.87 ± 9.73	230.75 ± 16.93*	93.92 ± 23.87#	73.58 ± 30.86#
TG (mg/dL)	110.78 ± 7.78	248.10 ± 11.23*	105.67 ± 9.35#	104.09 ± 19.81#
LDL- C (mg/dL)	56.69 ± 5.94	146.44 ± 17.77*	52.85 ± 5.26#	51.45 ± 4.55#
HDL-C (mg/dL)	58.03 ± 1.21	34.68 ± 1.82*	44.73 ± 11.37#	36.22 ± 16.32#
Cardiovascular risk indices	1.92 ± 0.15	7.19 ± 0.30*	1.91 ± 0.21#	1.84 ± 0.42#
Atherogenic coefficient	1.42 ± 0.13	5.76 ± 0.69*	1.10 ± 0.06#	1.12 ± 0.20#
Castelli's risk index-1	2.42 ± 0.13	6.76 ± 0.69*	2.10 ± 0.06#	2.12 ± 0.20#

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

Table 3: Effect of Rida Herbal Bitter on Cardiac Antioxidant, Pro-inflammatory Cytokines, Transforming Growth Factor and Brain-Natriuretic Peptide in HFD/Streptozotocin-Induced Diabetic Rats.

Parameters	Control (non-diabetic rats)	HFD/ STZ-induced diabetic rats (untreated)	HFD/ STZ-induced diabetic rats + 0.3 ml Rida herbal bitter	HFD/ STZ-induced diabetic rats + 200 mg/ kgb.wt metformin
MDA (µM)	0.73 ± 0.03	1.85 ± 0.05*	0.89 ± 0.02#	0.87 ± 0.02#
SOD (u/ml)	1.36 ± 0.02	0.60 ± 0.07*	1.48 ± 0.04#	1.44 ± 0.05#
CAT (u/mg protein)	24.55 ± 1.29	16.98 ± 0.53*	25.92 ± 1.07#	23.87 ± 1.45#
TNF-α (pg/ml)	16.80 ± 0.89	22.82 ± 1.78*	15.56 ± 1.63#	16.68 ± 0.89#
IL-1β (pg/ml)	6.75 ± 0.93	16.05 ± 2.13*	7.15 ± 0.38#	6.82 ± 1.58#
IL-6 (pg/ml)	49.57 ± 4.38	65.90 ± 5.07*	49.21 ± 1.13#	47.47 ± 2.27#
TGF-B1 (ng/ml)	0.29 ± 0.02	5.51 ± 0.30*	0.25 ± 0.02#	0.22 ± 0.00#
BNP (Pg/ml)	58.78 ± 2.96	80.77 ± 8.96*	59.09 ± 3.57#	58.14 ± 3.57#

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

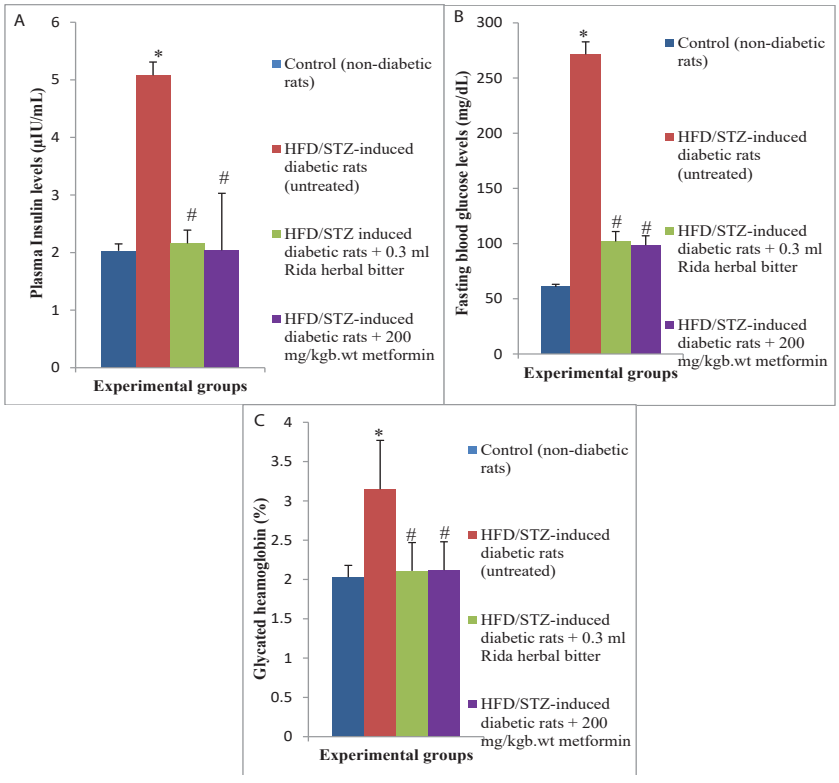

Figure 1: Effects of Rida herbal bitter on (A) Plasma insulin (B) Fasting blood glucose (C) Glycated hemoglobin in HFD/STZ-induced diabetic rats. Values are expressed as mean ± SEM (n = 8). *significant at $p < 0.05$ compared with control; #significant at p < 0.05 compared with untreated diabetic group.

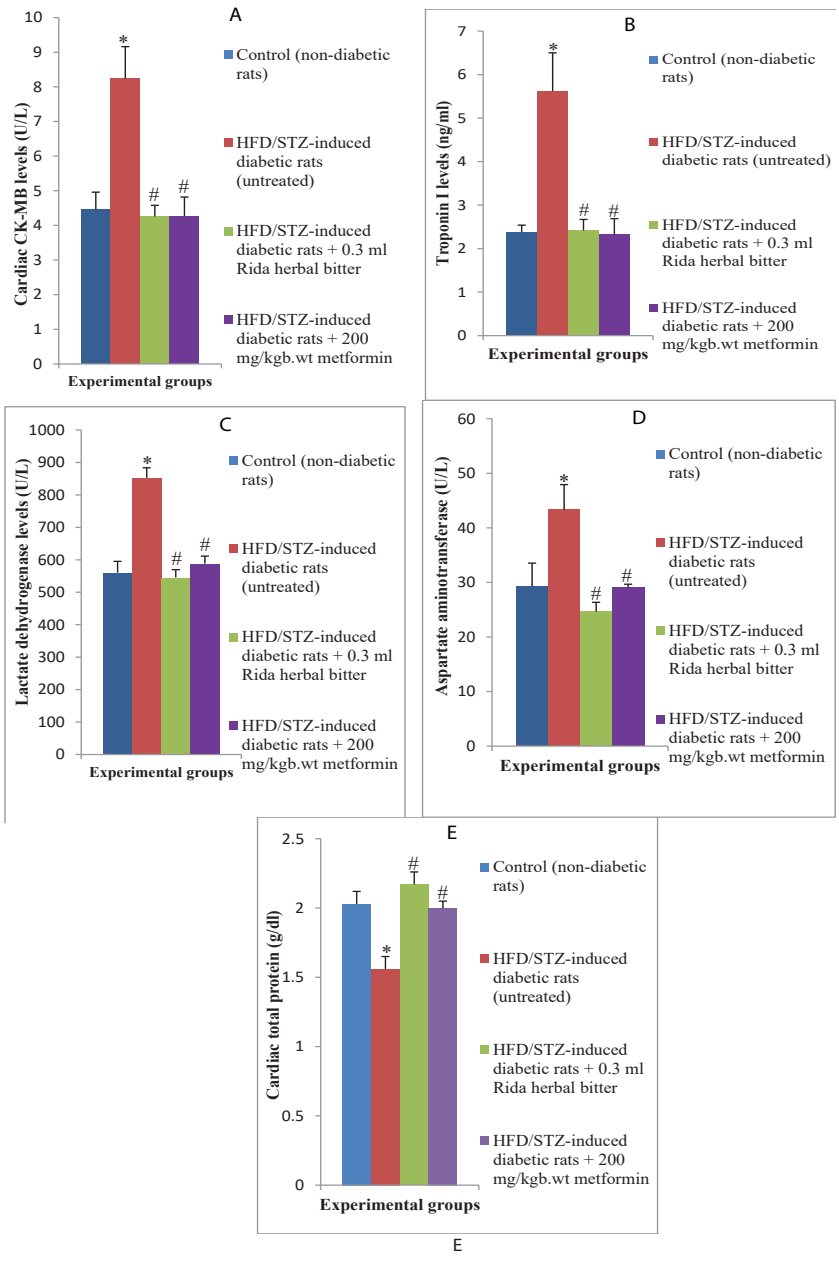

Figure 2: Effects of Rida herbal bitter on cardiac biomarkers (A) CK-MB (B) Troponin I (C) Lactate dehydrogenase (D) Aspartate aminotransferase (E) Cardiac total protein in HFD/streptozotocin (STZ)-induced diabetic rats. Values are expressed as mean ± SEM (n = 8). *significant at $p < 0.05$ compared with control; #significant at $p < 0.05$ compared with untreated diabetic group.

interleukin-1β (IL-1β), interleukin-6 (IL-6), transforming growth factor-β1 (TGF-β1) and brain natriuretic-peptide (BNP) levels increased ($p < 0.05$) significantly compared with non-diabetic rats. Administration of Rida herbal bitter significantly reduced the level of TNF-α, IL-1β, IL-6, TGF-β1, and BNP in comparison with untreated HFD/STZ-induced diabetic rats (Table 3).

Discussion

The extensive utilization of natural medicinal plants has increased modern medicine's advancement. Currently, there is a growing emphasis on harnessing the potential of medicinal plants to create innovative therapies for many ailments. This renewed interest is driven by their cost-effectiveness, minimal side effects, and abundant accessibility [11]. Medicinal plants are crucial in managing diabetes mellitus, a severe metabolic disorder [12]. Furthermore, both traditional practices and scientific researchers have reported numerous herbal medicines in managing diabetes and Cardiovascular Diseases (CVDs) [13]. This experimental research investigated the cardio-protective of Rida herbal bitter in streptozotocin-induced diabetic rats fed with a high-fat diet.

Persistent uncontrolled hyperglycemia has been widely known with common diagnosis features such as increased urination (polyuria), excessive hunger (polyphagia), excessive thirst (polydipsia), extreme fatigue, and loss of body weight [14]. In this experiment, there's a manifestation of weight

loss, polyphagia, polydipsia, and a decrease in heart-relative weight of all diabetic rats. These findings align with previous studies that have documented body weight reduction in cases of uncontrolled hyperglycemia [15]. This decrease in body weight can be linked to changes in energy metabolism and the excessive breakdown of structural proteins resulting from insulin deficiency during hyperglycemic conditions [16]. Oral gavage of Rida herbal bitter moderated the water and food intake and improved the body weight as well as heart weight, suggesting the ability of this herbal to normalize insulin secretion for metabolic activities. This supported the findings of Wang, et al. [17], on amelioration of body weight, water, and food intake by Piperinein diabetic rats.

Hyperglycemia is a prominent clinical diagnosis of diabetes status in poorly controlled diabetic individuals [18]. Insulin, a crucial hormone, plays a central role in the regulation of blood glucose levels [19,20]. Also, HbA1c serves as a sensitive indicator for the early detection of diabetes in individuals at high risk and assessing the effectiveness of diabetes treatment [21,22]. In a state of hyperglycemia, where glucose homeostasis is disrupted, both HbA1c and insulin levels in the body become abnormal [23]. Similar to high insulin and HbA1c levels previously reported in a hyperglycaemic state [24], the current study observed hyperglycemia and hyperinsulinemia accompanied by high levels of HbA1c in diabetic rats. Hyperglycemia-hyperinsulinemia is a typical confirmation of type-2 diabetes and a state of insulin resistance establishment in rats fed with HFD. The elevated level of blood insulin is a compensatory mechanism response to high blood glucose [25]. The Rida herbal bitter administration remarkably ameliorates elevated blood glucose, insulin, and HbA1c levels. The anti-hyperglycemic effect of this herb might be linked with the stimulation of target tissues to respond to insulin for glucose uptake and inhibition of hepatic gluconeogenesis, corroborating with the blood glucose-lowering properties of medicinal plants reported [26].

Diabetes mellitus is commonly associated with hyperlipidemia, insulin resistance, and inflammation, which cause oxidative in the mitochondria and are known to play a major role in the pathogenesis of many diabetic-related cardiac dysfunction complications [27]. Hyperlipidemia exacerbates cellular damage and cardiac dysfunction in individuals with diabetes. It fosters the accumulation of triglycerides and cholesterol within the heart muscle, thereby impacting adverse cardiac complications such as coronary artery disease [28]. In the current study, diabetic rats exhibited cardiac dyslipidemia noticeably by a high level of Total Cholesterol (TC), Triglycerides (TG), and Low-Density Lipoprotein-cholesterol (LDL-C), Cardiovascular Risk Indices (CRI) as well as a predictor of atherosclerosis predictor; Atherogenic Coefficient (AC) and Castelli's Risk Index-1 (CRI-1) with a concomitant decrease in High-Density Lipoprotein-cholesterol (HDL-C) in cardiac tissue. Treatment of diabetic rats with Rida herbal bitter attenuates cardiac dyslipidemia notably by a reduction in TC, TG, LDL-C, cardiovascular risk indices, atherogenic coefficient, and Castelli's risk index-1 with an enhanced level of HDL-C, cardio-protective cholesterol. These findings indicate the cardio-protective, anti-atherogenic, and lipid-lowering efficacy of Rida herbal bitter, parallel with Al-Rasheed, et al. [29] report on the cardio-protective of simvastatin in diabetic cardiomyopathy rats.

The progression of cardiac dysfunction complications in diabetes is influenced by hyperglycemia-hyperlipidemia-induced oxidative stress that specifically leads to the production of Reactive Oxygen Species (ROS) from mitochondria [30]. Accumulation of ROS results in DNA damage, cardiac cell apoptosis, reduced myocardial contractility, and the development of cardiac fibrosis. In addition, excessive ROS leads to the weakening of the antioxidant defense system function and further exacerbates cellular damage [31]. This study observed elevated oxidative stress maker Malondialdehyde (MDA) overwhelming cardiac antioxidant enzyme Superoxide Dismutase (SOD) and Catalase (CAT) in diabetic rats, which accord to the findings of Rosa, et al. [32]. However, cardiac antioxidant enzymes SOD and CAT activity were restored with diminished MDA levels after treatment of diabetic rats with Rida herbal bitter, which proves its potent antioxidant properties with free radical scavenging. These properties might result from bioactive compounds present in this herb and are consistent with Li, et al. [33] finding on the alleviation of high glucose-induced cardiac oxidative stress and apoptosis in microvascular endothelial cells through AMPK/ Sirt1 activation.

In the diabetic heart, hyperglycemia-induced oxidative stress has been documented for the etiology of cardiac inflammation, apoptosis, and fibrosis. These inflammatory responses are marked by substantial increases in cardiac pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) [34]. Also, transforming growth factor-β1 (TGF-β1) the primary cytokine plays a pivotal role in mediating the development of fibrosis in various tissues due to tissue damage and inflammatory processes [35]. The diabetic rats showed over-expression of cardiac pro-inflammatory TNF-α, IL-1β, IL-6, and TGF-β1, which are in line with the findings of Safhi, et al. [36]. The supplementation of Rida herbal bitter suppressed the over-expression of pro-inflammatory cytokines in cardiac diabetic rats, denoting the inhibitory effect of Rida herbal bitter on inflammatory cytokines, consistent with the findings of Sun, et al. [37]. These anti-inflammatory effects might be linked to the strong antioxidant properties possessed by this herb.

The release of myocardium enzymes due to myocardial damage or necrosis has been previously documented in diabetic hearts [38]. These biomarkers, CK-MB and Lactate

Dehydrogenase (LDH) are widely recognized as good indicators to determine the degree of cardiac injury [39]. The levels of LDH and CK-MB have been reported to be elevated in individuals with cardiomyopathy under diabetes conditions [40]. Furthermore, B-type Natriuretic Peptide (BNP) is a firmly established biomarker that serves both diagnostic and prognostic [41]. Elevated levels of brain-natriuretic peptides associated with left ventricular dysfunction. Increased production of these peptides has also been correlated with the presence of coronary artery disease [42]. Elevation of these cardiac injury biomarkers, CK-MB, troponin I (Tn I), LDH, Aspartate aminotransferase (AST), and BNP are noticeable in these diabetic rats, which implies hyperglycemia-induced cardiac oxidative stress and inflammation causes myocardial necrosis and this consistent with the findings of Awad, et al. [43]. Treatment with Rida herbal bitter ameliorates these cardiac injury biomarkers in diabetic rats and it revealed that this herb can protect the integrity of cardiomyocyte membrane and attenuate cardiac injury through its antioxidant efficacy on cardiac dyslipidemia, oxidative and inflammation induced by chronic hyperglycemia in diabetes mellitus and is in accord with previous findings of Sandamali, et al. [44].

Conclusion

This study scientifically proved the cardio-protective potential of Rida herbal bitter by ameliorating hyperglycemia-induced cardiac dyslipidemia, oxidative stress, and inflammation. This herb could be a novel therapy for diabetes mellitus with less or no adverse organ toxicity. Also, further study on the cytotoxicity of Rida herbal bitter should be investigated.

Declarations

Authors' contributions

FO and DA conceived the original idea, and designed and supervised the research. DA, MO OA, OE, AV, and AL performed the experiments with the support of FO. FO, DA, and MO collected the data. DA, MO, and FE analyzed the data and prepared the manuscript. FO reviewed the manuscript. All authors have read and approved the final manuscript.

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