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Diet Supplementation with Rosemary (*Rosmarinus officinalis* L.) Leaf Powder Exhibits an Antidiabetic Property in Streptozotocin-Induced Diabetic Male Wistar Rats

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Abstract: Diabetes mellitus is a metabolic disorder that has a high global health burden and causes high mortality and morbidity in humans. Medicinal herbs and plants offer a promising alternative to conventional therapies for the management of diabetes. Rosemary (*Rosmarinus officinalis* L.) is a traditional medicinal herb that has been used for the management of several diseases. Therefore, the present study investigates the antidiabetic properties of diets supplemented with *R. officinalis* leaf powder on streptozotocin-induced diabetic Wistar rats. First, the phytochemicals and 2,2-dephenyl-1-picrylhydrazyl (DPPH) free-radical scavenging activity of aqueous *R. officinalis* leaf extract were determined. Streptozotocin-induced diabetic male Wistar rats were fed a diet supplemented with *R. officinalis* leaf powder (ROP) at 3%, 6%, and 12%, respectively, for 6 weeks. Investigations of food intake, body weight, rat relative organ weights, blood glucose, lipid profiles, creatinine, bilirubin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were estimated according to standard procedures. The results show that ROP aqueous extract contains significant amounts of phenolics, flavonoids, and tannins, which exhibit *in vitro* DPPH free-radical scavenging activity. Based on an *in vivo* study, ROP reduced blood glucose levels in streptozotocin-induced diabetic animals ($p < 0.05$). Dietary supplementation with ROP in diabetic rats significantly ($p < 0.05$) lowered ALT, AST, bilirubin, creatinine, total triglyceride (TG), total cholesterol (TC), and low-density lipoprotein (LDL) levels while increasing high-density lipoproteins (HDLs) when compared with the diabetic control group. Our findings demonstrate that a diet supplemented with *R. officinalis* leaf powder exhibits an antidiabetic potential with improved health outcomes, as demonstrated by the improved lipid and liver profile enzymes in our animal model.

Keywords: diabetes mellitus; diet supplementation; hyperglycemic; lipid profile; *Rosmarinus officinalis*; streptozotocin

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1. Introduction

Diabetes mellitus (DM) is a serious chronic condition that occurs when blood glucose levels increase because of the inability of beta cells in the pancreas to produce any or enough insulin hormone levels or the inability of the body to use the hormones produced effectively. Type-1 diabetes is an insulin-dependent condition that usually occurs due to an immune system disorder. Type-2 diabetes is a non-insulin-dependent diabetes mellitus (NIDDM) that occurs as a result of the organs being unable to respond to insulin [1]. Hyperglycemia

over a long period causes the malfunctioning of several body organs, blood vessel blockage, and the non-response of nerves [2]. According to the International Diabetes Federation (IDF) Diabetes Atlas of 2021, an estimated 537 million adults were living with diabetes globally [3], and there was a disproportionately higher burden in low- and middle-income countries [4]. Obesity/overweight, unhealthy eating habits, and a sedentary lifestyle contribute to 60% of type-2 diabetes mellitus cases, of which obesity-related insulin resistance in type-2 diabetes mellitus accounts for 90–95% [5]. The progression of diabetes mellitus eventually leads to vascular damage, resulting in the deterioration of myocardial structure and function, with the result usually manifesting as cardiovascular complications, giving rise to high morbidity and mortality rates [6]. It has been reported that over 47% of diabetic cases are not screened, leading to serious complications and making diabetes the seventh-highest cause of human death [4].

Diabetes mellitus is managed well by the effective control of blood glucose levels through diet modification, physical exercise, maintaining reasonable body weight, monitoring lipid profile levels, and using appropriate medication when necessary [7]. Several classes of pharmaceutical drugs have been used to control diabetes, including injectable insulin and oral drugs, such as biguanides (e.g., metformin), sulfonylureas (e.g., glimepiride), and thiazolidinediones (e.g., pioglitazone). The characteristics of these pharmaceutical drugs have been provided by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) (ADA/EASD) consensus algorithm [7,8]. Over the last decade, recommendations for selecting the most appropriate glucose-lowering medications for the management of type-2 diabetes have changed in view of the evolving evidence. The 2022 version of the ADA/EASD consensus represented a paradigm shift from treat-to-target to treat-to-benefit [3,7]. Despite the efficacy of synthetic drugs, they are relatively expensive and difficult to obtain. Therefore, there has been increasing research on traditional medicinal herbs and plants to find alternative hypoglycemic medicines due to the issues of affordability and availability [9]. Many medicinal herbs and plants have been reported to disrupt lipid and carbohydrate metabolism and are therefore used to manage diabetes and other metabolic conditions [10]. The use of medicinal herbs as nutraceuticals and functional foods can, therefore, be considered to be an alternative to conventional or synthetic medicines.

The concepts of nutraceuticals and functional foods containing bioactive compounds with antidiabetic properties have gained attention as complementary options for the management of type-2 diabetes mellitus [11]. Free radicals are the etiology of many diseases, including diabetes mellitus, and many antioxidants can scavenge their effects, thus protecting the human body from damage through modulation of the negative effects caused by oxidative stress. In diabetic patients, oxidative stress has been found to increase with a reduction in the body's antioxidant capacity [12]. Phytochemicals, such as flavonoids, phenols, and tannins, present in medicinal herbs have been found to possess antioxidant and antidiabetic capacities [13,14].

Rosemary (*Rosmarinus officinalis* L.) belongs to the Lamiaceae family and is a perennial herb that originates from the Mediterranean region. It is presently cultivated worldwide [15]. The plant has been widely used for cooking, in cosmetics, and for therapeutic purposes [16]. *R. officinalis* has been reported to have several pharmacological properties, including anti-inflammatory, antidepressant, antinociceptive, antifungal, and antibacterial. It has also been reported to attenuate conditions such as atherosclerosis, hepatoxicity, and hypercholesterolemia [17]. This plant also exhibits various preservative actions and has been used in food industries [18]. According to the European Medical Agency (EMA), Herbal Medicinal Products Committee (HMPC), and the Food and Drug Administration (FDA) of the USA, rosemary has extremely low toxicity levels and has been classified as Generally Recognized as Safe (GRAS) [19]. The antihyperglycemic action of *R. officinalis* has been reported [20–22]. Pharmacologically active compounds known to have therapeutic action have also been reported in *R. officinalis*, including carnosic acid, rosmarinic acid, carnosol, and essential oil [23]. It is, therefore, important to explore the use of *R. officinalis*

as a supplement in diets for the management of diabetes mellitus. The present study investigated the antidiabetic properties of a diet supplemented with three different concentrations of *R. officinalis* leaf powder on streptozotocin-induced diabetic male Wistar rats with particular emphasis on physiological and biochemical parameters.

2. Materials and Methods

2.1. Collection of Plant Material and Authentication

Fresh *R. officinalis* leaves were harvested from a farm in the Ngoliba area of Kiambu County, and the plant was authenticated in the Department of Biology, Faculty of Science and Technology, University of Nairobi, where a voucher specimen was deposited in the herbarium unit with a reference voucher number ZNK/UON2020/001.

2.2. Preparation of Plant Materials

The leaves were cleaned under running sterile distilled water and dried under a shade for 21 days to achieve a constant weight. The dried leaves were milled into fine powder using a domestic electric blender, packaged in airtight plastic bags, and stored in a refrigerator at 4 °C until they were used for quantitative analysis and extraction. One gram of *R. officinalis* powder was soaked in 10 mL of distilled water in a 50 mL sample bottle. The mixture was kept at room temperature at 23–24 °C with frequent shaking for 36 h, according to Adan et al. [24]. The supernatant (crude extract) was obtained by centrifugation of the contents at 3000 revolutions per minute (rpm) for 5 min. The crude extract (supernatant) was placed in 100 mL glass bottles, sealed, and stored at 4 °C for subsequent use in phytochemical analysis and *in vivo* antidiabetic studies. The crude extracts were used within 6 h of extraction.

2.3. Spectrophotometric Quantification of Phytochemical Content in the Crude Extract

Total phenols, tannins, and flavonoid compounds were estimated using a UV–visible spectrophotometer (UVmini-1240, Shimadzu, Duisburg, Germany). The chemicals used as standards were of the analytical grade obtained from Sigma–Aldrich, Nairobi, Kenya.

2.3.1. Estimation of Total Phenolic Content (TPC)

Total phenolic content (TPC) was determined according to Adan et al. [24]. A total of 0.1 mL of crude extract samples was thoroughly mixed with 3 mL of distilled water, followed by the addition of Folin–Ciocalteu reagent (0.5 mL) and 20% sodium carbonate (2 mL). The contents were thoroughly mixed and incubated at 23 °C for 20 min. Gallic acid was used as a standard at concentrations of 20, 40, 60, 80, and 100 mg/mL. The absorbance of the samples and standards were read at 725 nm. The assays were carried out in three biological and technical replicates. The standard curve generated using the gallic acid standard was used to determine the quantities of phenolics in the samples and expressed as mg gallic acid equivalent (GAE) per g of dry powder of the sample.

2.3.2. Estimation of Total Flavonoid Content (TFC)

The method previously described by Kimondo et al. [25] was used to estimate the total flavonoid content in the crude extract. Briefly, 100 µL of crude extract was mixed with 1 mL of 2% aluminum chloride, vortexed for 1 min, and then 2 drops of acetic acid were added. Sterile distilled water was added to the mixture to a total volume of 5 mL, incubated at 23 °C for 30 min in the dark, and the optical density was measured at 415 nm. The assays were carried out in three biological and technical replicates. Rutin was used as a standard, and the quantification of total flavonoid was obtained using a standard curve generated using concentrations of rutin ranging from 0 to 100 mg/mL. Total flavonoid content was expressed as mg rutin equivalent (RAE) per g of dry powder of the sample.

2.3.3. Estimation of Total Tannin Content (TTC)

The quantification of total tannins followed the protocol described by Adan et al. [24]. Briefly, 0.1 mL crude extract was thoroughly mixed with sterile distilled water (3 mL) and 20% sodium carbonate (2 mL), followed by incubation at 23 °C for 5 min. After incubation, 0.5 mL Folin–Ciocalteu reagent was added to the mixture, incubated at 23 °C for 20 min, and the optical density was measured at 700 nm. The assays were performed in three biological and technical replicates. The results were reported as mg tannic acid equivalent (TAE) per g of dry powder of the sample, based on a standard curve generated using tannic acid as a standard (0–100 mg/mL).

2.4. Antioxidant Activity

The antioxidant activity of the crude extracts was determined based on free-radical scavenging activity using a 2,2-dephenyl-1-picrylhydrazyl (DPPH), a stable radical, as reported by Adan et al. [24]. Briefly, 0.1 mL of each of the crude extracts was added to 2 mL of DPPH solution (0.1 mM in methanol), thoroughly mixed, and incubated in the dark at 23 °C for 30 min. The optical density (absorbance) was read at 517 nm. The DPPH assays were performed in three biological and technical replicates. The percentage DPPH radical inhibition was calculated using the formula: $(A_{blank} - A_{sample}/A_{blank}) \times 100$, where A_{blank} and A_{sample} represent the optical density of the control and the sample, respectively.

2.5. Ethical Clearance and Animal Husbandry

The study was performed in the animal house at the Department of Biochemistry, University of Nairobi, in compliance with ethical procedure for the care and use of laboratory animals as approved by the Biosafety and Animal Care and Use Committee of the Faculty of Veterinary Medicine, University of Nairobi (approval number FVM BAUEC/2019/238). A total of 36 male Wistar rats selected based on weight (160–180 g) were used in this study. The animal house was well ventilated and supplied with a 12-hour light/dark cycle. The animals were kept in metallic cages and provided with the normal rat chow diet and drinking water ad libitum. The animals were allowed to acclimatize for 10 days before the commencement of the experiments.

2.6. Preparation of R. officinalis Leaf Powder (ROP)-Supplemented Diet

The normal commercial rat diet purchased from Unga Feeds Limited, Nairobi, Kenya, was used to reconstitute different ROP-supplemented diets. The ROP was pre-soaked in distilled water for 36 h. The commercial rat diet was weighed and mixed with the corresponding quantity of the pre-soaked ROP and made into pellets using a pelleting machine, after which the pellets were dried in the hot air oven at 100 °C for 6 h to a moisture content of 10–12%. The ROP-supplemented diet was stored in sealed moisture-proof packets and used within 7 days.

2.7. Induction of Diabetes in Experimental Rats by Use of Streptozotocin (STZ)

Diabetes was induced using streptozotocin (STZ), as described by Bhupathiraju and Hu [5]. The streptozotocin was prepared by dissolving 0.1 g in 0.05 mM sodium citrate buffer pH 4.5. The STZ-induced diabetes method was adopted based on findings from various literature, and most literature used a single intraperitoneal injection (IP) of 60 mg/kg body weight. Preliminary trials were performed at 60 mg/kg body weight, which proved to be erratic and led the rats' glucose level to rise to more than 32 mMol/L within 36 h. Insulin was given to bring down this glucose level to prevent the death of the rats. The adoption of 45 mg/kg body weight was then used, and the success rate was 100%. No death of the rats occurred during the experimental time. Except for the animals in the normal control and non-diabetic control groups, diabetes was induced in rats by intraperitoneal injection with a freshly prepared solution of STZ in citrate buffer at a dose of 45 mg/kg body weight as a single dose after taking the baseline blood glucose from the tail vein using a glucometer. The animals in the normal control group were injected with citrate buffer only. The animals

were fed with 10% glucose in drinking water after 6 h for 2 days to protect them from hypoglycemic shock. Glucose levels were measured after the third day using a glucometer. The animals that exhibited glucose levels between 15 and 20 mM/L after 72 h of STZ administration were considered diabetic and used in the subsequent experiments.

2.8. Experimental Design and Animal Treatment Groups

The experimental rats were weighed and randomly assigned into 6 groups, each containing 6 rats (Table 1). The animals were given doses according to their body weight. The animals were fed daily with the corresponding pelleted diets for six weeks. During the treatment period, body weight was measured once a week, and the amount of food intake/consumption was monitored daily.

Table 1. Experimental design describing the experimental animals' groupings with the different dosages.

Group	Label	Treatment/Dosage	No. of Animals (*n*)
1	Normal control (NC)	Normal diet	6
2	Non-diabetic mellitus animals (NDM-ROP6)	Normal diet with 6% ROP	6
3	Diabetic mellitus animals (DM-ROP3)	Normal diet with 3% with ROP	6
4	Diabetic mellitus animals (DM-ROP6)	Normal diet with 6% ROP	6
5	Diabetic mellitus animals (DM-ROP12)	Normal diet with 12% ROP	6
6	Diabetic mellitus control (DMC)	Normal diet	6

2.9. Measurement of Fasting Blood Glucose (FBG) Level

The FBG of animals in every group was measured using a glucometer before treatment and at 7-day intervals for 6 weeks. Before the blood sample collection, the rats were fasted for 8 h but were given water ad libitum. Each rat was controlled in a restrainer, and the tail was massaged to allow enough blood at the tip of the tail. The end of the tail was cleaned with an alcohol swap and pricked using a lancet. The first drop of blood was discarded, the tail cleaned, and the subsequent drop was collected with a strip inserted into a glucometer.

2.10. Determination of Relative Organ Weights

After removing the terminal blood of the anesthetized rats, each animal was mounted on a dissecting board, sacrificed by cervical dislocation, and necropsied. The liver, kidney, spleen, pancreas, lungs, and heart of each animal were carefully removed. The organs were washed in physiological saline and blotted on sterile paper towels, and their weights were determined. Percentage organ weight ratios were also determined.

2.11. Measurement of Biochemical Parameters (Serum Liver Enzymes and Lipid Profile)

After 6 weeks, the animals were lightly anesthetized using diethyl ether. Blood (5 mL) was removed by the retinal orbital bleeding into plain tubes, centrifuged at 5000 revolutions per minute (rpm) for 10 min, and sera placed in Eppendorf tubes and stored at -80 °C for subsequent analysis. Sera were analyzed for the levels of total cholesterol (TC), total triglycerides (TT), high-density lipoprotein (HDL), low-density lipoprotein (LDL), total bilirubin, creatinine and urea using an automatic Clinical Chemistry Analyzer. Similarly, sera from rats from different treatments were used for the determination of levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT).

2.12. Statistical Analysis

Food consumption, weight measurements, biochemical measurements, lipid profile, and FBG were analyzed using the Statistical Package for Social Sciences (SPSS 26). One-way analysis of variance (ANOVA) *t*-test was used to compare the means among the groups. The data were expressed as mean $\pm$ standard deviation (M $\pm$ SD). In terms of *p*-values, $p < 0.05$ was considered to be significantly different.

3. Results

3.1. Phytochemical Content and Antioxidant Activity of R. officinalis Aqueous Extracts

The results of the phytochemical compound analysis showed that the total flavonoid (TFC) was significantly higher at 147.72 ± 5.44 mg RAE per gram dry weight, followed by total phenolic (TPC) at 52.67 ± 4.69 mg GAE per gram dry powder and total tannins (TTC) at 24.21 ± 0.99 mg TAE per gram dry powder. The DPPH free-radical scavenging ability of the aqueous extracts was at a percentage inhibition of 55.01 ± 1.00.

3.2. Effect of ROP Supplementation on Food Intake, Body Weight, and Relative Organ Masses

There was no significant difference ($p > 0.05$) in daily food intake between the normal group (NC) and the animal groups NDM-ROP6, DM-ROP3, DM-ROP6, and DM-ROP12 (Table 2). However, significantly ($p < 0.05$) reduced food intake was obtained in the diabetes mellitus control (DMC) group compared to other groups.

Table 2. Effect of daily food consumption in (g) in experimental groups supplemented with ROP on body weight (g) in animal groups at initial and after 6 weeks of treatments.

Treatment	Week 1 (g)	Week 6 (g)	Weight Difference	% Weight Difference
NC	42.4 ± 1.2	47.3 ± 1.3	4.9 ± 1.8	11.6 [a]
NDM-ROP6	42.2 ± 3.0	45.2 ± 1.6	3.0 ± 2.3	7.1 [a]
DM-ROP3	38.7 ± 0.9	41.8 ± 3.1	3.1 ± 1.4	8.0 [a]
DM-ROP6	38.8 ± 1.1	42.5 ± 0.8	3.7 ± 0.9	9.5 [a]
DM-ROP12	39.9 ± 1.2	43.5 ± 2.2	3.6 ± 2.6	9.0 [a]
DMC	38.5 ± 2.3	16.5 ±1.8	−22 ± 1.9	57.1 [b]

Values represent mean ± standard deviation ($n = 6$). Normal control (NC), Non-diabetic mellitus animals (NDM-ROP6), Diabetic mellitus animals (DM-ROP3), Diabetic mellitus animals (DM-ROP6), Diabetic mellitus animals (DM-ROP12) and Diabetic mellitus control (DMC). Different lowercase letters in the same column show significant differences at a level of 5%.

The changes in initial and final body weights in control and experimental animals are presented in Table 3. There was an increase in body weight for all animal groups except for the diabetic mellitus control (DMC) group. The body weight of the diabetic mellitus control (DMC) group was significantly ($p < 0.05$) reduced by 14.5% after 6 weeks of treatment (Table 3). The results of relative organ weight (g/100 g) showed that there was no significant difference in ROP treatment groups from controls except for the kidney in the diabetic control (DMC), which was significantly increased (Table 3).

Table 3. Effect of diet supplemented with ROP on body weight (g) in animal groups at initial and after 6 weeks of treatment and selected organ weights after 6 weeks of treatment.

		Animal Treatment Groups					
		NC	NDM-ROP6	DM-ROP3	DM-ROP6	DM-ROP12	DMC
Body weights at initial and after 42 days	Day 0	156.04 ± 3.7	164.14 ± 3.2	154.94 ± 2.7	163.2 ± 3.4	156.18 ± 2.8	173 ± 6.0
	Day 42	198 ± 4.6	195.92 ± 5.6	165.36 ± 10.3	230.82 ± 8.9	184.88 ± 3.4	147.86 ± 7.7
	Weight difference (g)	42.0 ± 2.8	31.8 ± 3.7	10.4 ± 2.9	27.6 ± 5.0	24.7 ± 4.1	25.1 ± 6.1 ↓
	%Weight difference	26.9 ↑	19.4 ↑	6.7 ↑	16.9 ↑	15.4 ↑	14.5 ↓
Relative internal organ weights (g/100 g)	Liver	3.28 ± 0.13	3.20 ± 0.12	4.68 ± 0.56	3.54 ± 0.11	3.99±0.92	4.70 ± 0.44
	Kidney	0.57 ± 0.06	0.54 ± 0.08	0.74 ± 0.11	0.70 ± 0.09	0.67±0.11	0.87 ± 0.01 *
	Pancreas	0.20 ± 0.05	0.21 ± 0.04	0.25 ± 0.06	0.23 ± 0.04	0.26±0.04	0.24 ± 0.05
	Spleen	0.56 ± 0.05	0.54 ± 0.02	0.55 ± 0.04	0.59 ± 0.05	0.55±0.04	0.58 ± 0.05
	Heart	0.31 ± 0.03	0.32 ± 0.05	0.29 ± 0.02	0.31 ± 0.03	0.26±0.03	0.30 ± 0.04
	Lungs	0.56 ± 0.03	0.62 ± 0.06	0.60 ± 0.03	0.60 ± 0.02	0.61 ± 0.04	0.73 ± 0.07

Values represent mean ± standard deviation ($n = 6$). Normal control (NC), Non-diabetic mellitus animals (NDM-ROP6), Diabetic mellitus animals (DM-ROP3), Diabetic mellitus animals (DM-ROP6), Diabetic mellitus animals (DM-ROP12) and Diabetic mellitus control (DMC). ↓—decrease, ↑—increase. * Shows significant difference in the relative organ weight from the control group (NC); $p < 0.05$ based on one-way ANOVA, $n = 6$.

3.3. Effect of ROP Supplementation on Fasting Blood Glucose Levels

The change in fasting glucose of the control and treatment groups is presented in Table 4. Fasting blood glucose (FBG) levels significantly ($p < 0.05$) reduced in all animal groups supplemented with ROP compared with the normal control (NC) group (Table 4). The highest increase (78.2%) in FBG was observed in the STZ-induced diabetic animals. The ingestion of ROP by diabetic animals significantly ($p < 0.05$) reduced FBG levels in treatments DM-ROP 3, DM-ROP6, and DM-ROP12 by 23.0%, 32.8%, and 49.1%, respectively (Table 4). The reduction of FBG was observed progressively in diabetic animals after diet treatments.

Table 4. Effect of diets supplemented with ROP on fasting blood glucose (FBG) levels (mg/dL) of streptozotocin-induced rats.

	NC	NDM-ROP6	DM-ROP3	DM-ROP6	DMC-ROP12	DMC
Pre-diabetic	6.3 ± 0.9	5.7 ± 0.3	5.7 ± 0.5	6.0 ± 0.4	5.6 ± 0.5	5.9 ± 0.5
Treatment start	5.9 ± 0.4	5.4 ± 0.5	19.0 ± 1.6	18.9 ± 1.8	17.5 ± 2.1	16.7 ± 1.6
7th Day	6.1 ± 0.8	5.4 ± 0.3	19.9 ± 2.1	20.2 ± 1.3	18.9 ± 2.8	19.5 ± 1.3
14th Day	6.2 ± 0.7	5 ± 0.2	18 ± 1.9	17.2 ± 0.8	12.9 ± 1.3	21.8 ± 1.7
21st Day	6.4 ± 0.3	5.1 ± 0.1	16.7 ± 1.2	13.6 ± 0.7	12.2 ± 0.9	24.4 ± 1.3
28th Day	5.9 ± 0.4	4.9 ± 0.3	15.9 ± 1	13.3 ± 1	10.5 ± 0.8	26.6 ± 1.9
35th Day	5.9 ± 1	4.3 ± 0.4	14.7 ± 1.6	13.5 ± 1	10.4 ± 0.6	28.7 ± 1.6
42nd Day	6.3 ± 0.6	4.3 ± 0.3	14.6 ± 1.3	12.7 ± 1.2	8.9 ± 1.0	29.8 ± 2.2
FBG difference	0.4 ↑	1.1 ↓	4.4 ↓	6.2 ↓	8.6 ↓	13.1 ↑
% Difference	6.6	20.8 ↓	23.0 ↓	32.8 ↓	49.1 ↓	78.4 ↑

Values represent mean ± standard deviation ($n = 6$). Normal control (NC), Non-diabetic mellitus animals (NDM-ROP6), Diabetic mellitus animals (DM-ROP3), Diabetic mellitus animals (DM-ROP6), Diabetic mellitus animals (DM-ROP12) and Diabetic mellitus control (DMC). ↑—increase, ↓—decrease FBG expressed as mM/L.

3.4. Effect of Diet Supplemented with ROP on Liver and Renal Serum Biomarkers of Treated Animal Groups

All the tested liver and kidney enzymes of diabetic mellitus control (DMC) animals with no supplementation of ROP increased significantly ($p < 0.05$). Streptozotocin-induced diabetic animal groups DM-ROP3, DM-ROP6, and DM-ROP12 fed on a diet supplemented with 3%, 6%, and 12% ROP, respectively, showed significantly ($p < 0.05$) reduced ALT, AST, bilirubin, and creatinine compared with the diabetic control (DMC) animals (Table 5). However, urea levels were significantly reduced in diabetic animal groups as compared with the diabetic control (DMC) animals (Table 5).

Table 5. Effect of diet supplemented with ROP on liver and renal serum biomarkers on experimental animal groups.

	ALT (U/L)	AST (U/L)	Bilirubin (µmol/L)	Creatinine (µmol/L)	Urea (mmol/L)
NC	94.5 ± 6	122.5 ± 3.4	1.1 ± 0.1	30.0 ± 1.2	7.2 ± 0.3
NDM-ROP6	* 81.42 ± 4.8	* 102.02 ± 3.7	1.1 ± 0.1	25.6 ± 2.9	7.4 ± 0.5
DM-ROP3	* 120.84 ± 6.6	* 175.2 ± 14.2	* 1.8 ± 0.1	* 35.4 ± 1.1	6.9 ± 0.6
DM-ROP6	* 115.4 ± 4.3	* 201.44 ± 13.2	* 1.7 ± 0.1	* 36.2 ± 2.2	6.5 ± 0.6
DM-ROP12	* 119.54 ± 8.4	* 138 ± 12.6	* 1.87 ± 0.4	* 39.6 ± 2.1	5.9 ± 3.3
DMC	* 178.98 ± 8.2	* 322 ± 55.2	* 4.72 ± 0.4	* 45.2 ± 4	* 14.0 ± 1

* Statistically significant ($p < 0.05$) as compared with the diabetic control. Values represent mean ± standard deviation ($n = 6$). Normal control (NC), Non-diabetic mellitus animals (NDM-ROP6), Diabetic mellitus animals (DM-ROP3), Diabetic mellitus animals (DM-ROP6), Diabetic mellitus animals (DM-ROP12) and Diabetic mellitus control (DMC). ALT and AST refer to alanine aminotransferase and aspartate aminotransferase, respectively.

3.5. Effect of Diet Supplemented with ROP on Lipid Profile of Experimental Animal Groups

The effect of diet supplemented with ROP on the lipid profile (TC, TT, LDL, and HDL) in STZ-induced diabetic rats is indicated in Table 6. Total triglycerides (TT) significantly

increased in diabetic control (DMC) animals (Table 6). There was no significant difference in the total cholesterol (TC) for all the animal treatment groups. High-density lipoprotein (HDL) increased in the diabetic control (DMC) group, while low-density lipoprotein (LDL) significantly ($p < 0.05$) decreased in all the diabetic animal groups (DM-ROP3, DM-ROP6, DM-ROP12, and DMC).

Table 6. Effect of diet supplemented with ROP on lipid profile (mg/dL) of experimental animal groups.

	Parameters			
Groups	**TT**	**TC**	**HDL**	**LDL**
NC	0.68 ± 0.37	1.2 5 ± 0.04	0.79 ± 0.01	0.52 ± 0.1
NDM-ROP6	0.53 ± 0.11	1.10 ± 0.06	0.74 ± 0.04	0.45 ± 0.07
DM-ROP3	1.43 ± 0.09 *	1.30 ± 0.6	0.78 ± 0.07	0.10 ± 0.01 *
DM-ROP6	1.6 ± 0.14 *	1.30 ± 0.05	0.73 ± 0.08	0.01 ± 0.0 *
DM-RO12	1.2 ± 0.11 *	1.31 ± 0.1	0.78 ± 0.08	0.02 ± 0.01 *
DMC	2.7 ± 0.36 *	1.22 ± 0.23	1.02 ± 0.36 *	0.03 ± 0.02 *

* Statistically significant ($p < 0.05$) as compared with the diabetic mellitus control (DMC). Values represent mean ± standard deviation ($n = 6$). Normal control (NC), Non-diabetic mellitus animals (NDM-ROP6), Diabetic mellitus animals (DM-ROP3), Diabetic mellitus animals (DM-ROP6), Diabetic mellitus animals (DM-ROP12) and Diabetic mellitus control (DMC). TC, total cholesterol; TT, total triglycerides; HDL, high-density lipoprotein; and LDL, low-density lipoprotein.

4. Discussion

Diabetes mellitus is a metabolic disorder characterized by high blood glucose levels (hyperglycemia), hypertension, hyperlipidemia, and chronic inflammation, among other detrimental conditions [26]. Various treatment methods have been employed to manage the disorder by controlling the blood glucose levels and preventing complications associated with the disease [27]. Diet supplementation and nutraceuticals (food with medical benefits) are some of the recent advances in the treatment of diabetes [28,29]. The current study showed that aqueous *R. officinalis* extract contained considerable amounts of phenolics, flavonoids, and tannins, as well as antioxidant activity. *R. officinalis* has been reported to possess hypoglycemic activity attributed to its high antioxidant properties and bioactive phytochemicals such as flavonoids, phenols, and terpenoids [22,23]. Studies have demonstrated that diabetic mellitus causes oxidative stress, leading to the production of reactive oxygen species that damage body organs. The phenolics in *R. officinalis* have been reported to offer defense against oxidative stress caused by many diseases, including diabetes mellitus [30]. Flavonoids are large phenolic structured compounds commonly found in fruits, vegetables, nuts, and herbs [31]. Dietary flavonoids have medicinal value, including antidiabetic activity, with the example of rutin known to enhance carbohydrate uptake by inhibiting the α-glucosidase enzyme. Other flavonoids, including kaempferol, enhance glucose uptake, while luteolin can inhibit lipid synthesis [32]. Several studies have indicated that tannins from plant natural products are also effective in the management and prevention of diabetes mellitus and the complications associated with this disease [33].

Chronic hyperglycemia due to diabetes mellitus is associated with body weight loss in patients due to imbalanced protein and lipid metabolism (increased proteolysis, lipolysis) and defective insulin action [34]. In the current study, the pathophysiological progression of the disease in the diabetic mellitus control Wistar rats resulted in a significant reduction of body weight, and this could be a result of the catabolism of tissue proteins and fats caused by an insulin deficiency [35]. The non-diabetic group of Wistar rats fed on a diet supplemented with ROP showed decreased weight gain in comparison with the normal control group, suggesting the anti-adipogenic property of ROP of which carnosic acid in *R. officinalis* has been associated with this effect [36–38]. The diabetic mellitus control group showed significantly low food intake, an indication of the degenerative nature of diabetes mellitus due to the progressed hypoglycemic condition [39,40].

A diet supplemented with different concentrations of ROP was tested in the current study to evaluate the antidiabetic efficacy of the different concentrations. The findings demonstrated that a diet supplemented with 12% ROP significantly reduced FBG compared with 3% and 6%, indicating that the incorporation of 12% ROP in the diet was the most effective against hyperglycemia. There was no significant difference in the glucose levels of the diabetic animal groups fed on a diet supplemented with ROP as compared to the normal group. This indicates that a diet supplemented with ROP possesses a hypoglycemic effect, and this concurs with previous reports [21,22,41–44]. In type-2 diabetes mellitus, hepatic gluconeogenesis is increased, which also aggravates the condition. The enzymes pyruvate carboxylase, phosphoenolpyruvate carboxykinase, fructose-1,6-biphosphatase, and glucose-6-phosphatase facilitate gluconeogenesis [45]. In the current study, the administration of a diet supplemented with ROP significantly reduced the fasting glucose compared with diabetic control rats. The diet supplemented with ROP decreased glucose synthesis in a dose-dependent way. The phytochemicals present in ROP may have caused a shift from lipid synthesis and gluconeogenesis to oxidation of lipids and absorption of glucose by the muscle and liver cells due to activation of AMP kinase [46]. The antidiabetic activity of a diet supplemented with ROP could be attributed to the flavonoid content present in the extracts. In support of our study, it has been reported that plant flavonoids possess hypoglycemic properties and ameliorate diabetes situations in diabetic animal models [47–49]. Therefore, flavonoids of *R. officinalis,* just like flavonoids of other medicinal plants, may act by multiple mechanisms of action, including preventing the destruction of pancreatic beta cells [50], enhancing peripheral glucose utilization [51], increasing insulin release [52], and improvement of glycogen storage in the liver [53]. In addition, flavonoids are known to regenerate the damaged β-cells of the pancreas in STZ-induced diabetic rats [54,55]. The blood glucose levels in the diabetic control group increased to more than 78% in the diabetic mellitus control group, indicating the destruction of the β-cells of the pancreas caused by cytotoxic STZ. Polyphenolic compounds, such as rosmarinic acids present in *R. officinalis*, have been reported to have anti-hyperglycemia effects that can regenerate the β-cells of the pancreas, thus increasing insulin production [56].

Oxidative stress caused by hyperglycemia due to glucose auto-oxidation is one of the pathophysiological mechanisms that lead to pancreatic β-cell damage, the central role in the development of diabetes and its associated complications [57]. Moreover, several studies have demonstrated that the antidiabetic effect of plant extracts is in part attributed to their antioxidant properties [47,50,58]. In this study, *R. officinalis* extracts had a potent antioxidant activity as demonstrated by the DPPH free-radical scavenging activity, which could be another key factor for their ameliorating effect on antidiabetic action.

Diabetes mellitus is linked to irreversible hepatic damage, leading to the proliferation of different enzymes, including ALT, AST, and creatinine, in blood [59]. Therefore, the well-being of the body due to diet supplementation with ROP can be measured using liver serum markers (AST, ALT, and bilirubin) together with renal markers (creatinine and urea). The rise of the liver enzymes in all the diabetic animals could be associated with the destruction of the hepatocytes caused by the STZ injection. STZ toxicity causes the hepatocytes to release large amounts of ALT and AST and elevation of bilirubin in serum [60]. The diabetic animals fed on a diet supplemented with ROP showed a significant reduction of ALT and AST enzymes when compared with the diabetic animals fed on a normal diet, suggesting that ROP had hepatoprotective effects [61–64]. In addition, there were no significant differences in ALT and AST enzymes in diabetic animals fed on a diet supplemented with ROP compared to the normal rats. The levels of creatinine significantly increased in all diabetic animals but were significantly low in diabetic animals fed on a diet supplemented with ROP, supporting earlier reports that *R. officinalis* can protect the nephrons [65]. The function of the kidney is mainly to detoxify the metabolites and other toxins excreted by the body [66]. Diet supplemented with ROP demonstrated a protective nature, as shown by significantly reduced creatinine and urea in diabetic rats fed on a

diet with ROP in comparison with the STZ-induced diabetic animals fed on a normal diet, suggesting that the ROP can reverse oxidative stress [67].

In diabetes mellitus, hyperlipidemia (especially hypertriglyceridemia and hypercholesterolemia) occurs as a result of the excess mobilization of fats from the adipose tissue due to the underutilization of glucose [55]. Hyperglycemia is associated with high levels of total cholesterol, LDL, triglyceride, and decreased levels of HDL in the blood [68]. The search and use of natural product remedies that can lower lipid levels is on the increase [69]. In this study, diabetic rats fed on a diet supplemented with ROP showed significantly reduced levels of cholesterol, LDL, and triglycerides compared to the diabetic control rats fed on a normal diet. The improvement in cholesterol levels may be related to the amelioration of insulin release, resulting from the protection of β-cells in the pancreas. Insulin is known to promote the catabolism of LDL by increasing the activity of LDL receptors located on hepatocytes and by activating lecithin cholesterol acyl transferase (LCAT), an enzyme responsible for the reduction of free cholesterol level [70]. Insulin may also have an inhibitory effect on 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase, the key enzyme in cholesterol biosynthesis [49]. The findings from this study on the hypolipidemic effect of *R. officinalis* have also been reported in previous studies [21,35,42]. An atherogenic diet and sedentary lifestyle are among the factors causing increased oxidative stress caused by the damage of cellular lipids, proteins, and carbohydrates [71,72]. Therefore, this study showed that the incorporation of ROP in the diet can have health benefits that can avert many non-communicable diseases (NCDs) such as diabetes, cancer, and cardiovascular diseases.

The limitations of the current study are that the response in humans could be different because the experiments were conducted on rats. Therefore, further studies are required in clinical trials to determine the antidiabetic efficacy of ROP. The design of the current study excluded the standard drug with the aim that the study was meant to offer information on the efficacy of a diet supplemented with different concentrations (3, 6, and 12%) of ROP. There is a need to use standard antidiabetic drugs in future studies. The study evaluated the effectiveness of a diet supplemented with rosemary leaves powder against diabetes mellitus but was limited in that this effect could not be related to any specific phytochemical compound. In addition, there is a lack of clear mechanisms for alleviating diabetes mellitus and its complications. Therefore, the identification of active metabolites is necessary to provide evidence for further prediction of its therapeutic use. Further studies are important in relation to (i) the pharmacokinetic properties of ROP, (ii) formulations of effective dosage forms, and (iii) ROP safety. In addition, possible interactions with other antidiabetic drugs or foods need to be studied in detail. Those studies may facilitate clinical trials determining the potential of ROP in the management of diabetes mellitus. Thus, it is of high interest that further research on ROP could lead to novel therapeutics for diabetes mellitus.

5. Conclusions

The aqueous leaf extract of *Rosmarinus officinalis* exhibits considerable amounts of phenolics, flavonoids, and tannin compounds, as well as *in vitro* antioxidant activity. The present study showed that supplementation of diet with *R. officinalis* leaf powder (ROP) significantly reduced glucose levels and lipid profiles in STZ-induced diabetic rats. ROP supplementation in the diet significantly decreased the activities of liver enzymes (AST and ALT), serum creatinine, and bilirubin in diabetic rats. Further research is needed to determine the mechanism for the antidiabetic effect of *R. officinalis* at the molecular level. The study has shown that the incorporation of ROP powder in the diet could have healthy benefits against NCDs and that there is a possibility of isolating compounds that can be used for natural product drug discovery, which may not have adverse effects. It is also recommended that rosemary users monitor long-term effects in the body by regularly monitoring liver and kidney functions with longer use. Therefore, more studies to evaluate the effect of other parameters and long-time use are also recommended.

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