EFFECTS OF RESVERATROL ON LIPID PROFILE OF DIABETES MELLITUS WOUND HEALING OF MALE WISTAR RATS

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ABSTRACT

There is a growing body of research showing the potential health benefits of resveratrol, including anti-inflammatory and antioxidant properties. This study investigates the potential effects of resveratrol on lipid profile and its impact on wound healing in a Male Albino Wistar Rats model of type 2 diabetes. 24 Male Albino Wistar Rats were rendered diabetic using a high-fat diet and an Alloxan injection. The rats were grouped into 4: Non-diabetic Control Group A (negative control), Diabetic Control Group B (positive control), Diabetic Treatment Group C (10 mg/kg resveratrol), and Diabetic Treatment Group D (20 mg/kg resveratrol). Excisional wounds were created on the dorsum of the rats and monitored for wound closure over a defined treatment period of 14 days. Body weight and fasting blood glucose levels were measured after the procedure and after the treatment respectively. Blood samples were collected on the 15th day by cardiac puncture to assess lipid profile parameters. Resveratrol administration positively modified body weight, blood glucose, and lipid profile, reducing total cholesterol, triglycerides, low-density lipoprotein, and elevation of high-density lipoprotein levels. Resveratrol supplementation not only enhanced wound healing but also alleviated dyslipidaemia in type 2 diabetic albino male rats, a common complicating factor in the management of diabetic wounds. These results imply that resveratrol might have a broad range of therapeutic applications in treating lipid profile abnormalities linked to type 2 diabetes as well as wound healing complications.

Keywords: Resveratrol, Type 2 diabetes, Wound healing, Lipid profile, Dyslipidaemia, Metabolic disturbances

INTRODUCTION

Diabetes mellitus is a progressively more widespread chronic metabolic disease by prolonged hyperglycaemia and dyslipidaemia among others is characterized, these are associated with long-term health concerns (Zheng *et al.*, 2018). A decrease in healing closure and the growth of diabetic foot ulcers (DFUs) have been linked to diabetic hyperglycaemia, ischemia, atherosclerosis, impaired immunity, decreased functioning of different skin cells, and peripheral neuropathy (Hanefeld *et al.*, 2013; Tsourdi *et al.*, 2013; Mieczkowski *et al.*, 2022); these are found to affect about 25% of all patients diagnosed with diabetes mellitus (Burgess *et al.*, 2021). Furthermore, dyslipidaemia leads to the activation of the endothelium and causes inflammation by several mechanisms, such as the production of

oxidative stress, activation of NF-κB, disruption of NOS regulation, and development of AGEs (Hu and Lan, 2016). Additionally, hyperglycaemia appears to have a substantial negative impact on the ability of cells and the immune system to defend against pathogens, leading to prolonged wound healing disrupting processes that are critical for re-epithelialization, namely, the protein synthesis, migration, and proliferation of keratinocytes and fibroblasts (Andrade *et al.*, 2017; Zheng *et al.*, 2023).

Diabetic wounds can be prolonged, require significant time to heal, and can return after healing typically ending in lower limb amputation, resulting in expensive economic and consuming healthcare resources (Andrews *et al.*, 2015). Research has shown that chronic pro-inflammatory cytokines upregulation affects the healing process resulting in an increase of ROS and dysfunctional healing process (Burgess *et al.*, 2021). Furthermore, impaired immune cell function has been well-documented in diabetic patients who exhibit impaired phagocytic activity and leukocyte dysfunction (Daryabor *et al.*, 2020).

Hypoglycaemic agents like metformin, glucagon-like peptide-1 receptor agonists, and sodium-glucose cotransport protein 2 inhibitors have limitations in clinical use due to deficiencies, side effects, and lack of lipid-regulating effects (Li *et al.*, 2023).

Resveratrol a bioactive compound having anti-inflammatory, anti-oxidative, anti-cancer, and anti-diabetic properties is a necessary active ingredient in many medicinal plants (Jardim *et al.*, 2018; Pieczykolan *et al.*, 2021).

There is a growing body of research showing the potential health benefits of resveratrol, including anti-inflammatory and antioxidant properties (Meng *et al.*, 2023). It has been suggested that resveratrol may improve lipid metabolism through several mechanisms (Meng *et al.*, 2020), one of which is the modulation of oxidative stress biomarkers (Singh and Vinayak, 2017). Among the numerous complications of T2DM is dyslipidaemia, characterized by abnormal lipid profiles, including elevated cholesterol and triglyceride levels (Hyassat *et al.*, 2022). Research findings have shown that diabetes mellitus can prolong the time required for wound healing and disrupt lipid metabolism. On the other hand, resveratrol has shown promise in vitro with various potentially cardioprotective effects, such as preventing platelet aggregation and facilitating vasodilation through the increased production of nitric oxide (Low Wang *et al.*, 2016; Gligorijević *et al.*, 2021; Bi *et al.*, 2023,).

To assess resveratrol's potential as an adjuvant therapy and improve understanding of its wider implications in diabetes management, it is imperative to comprehend the mechanisms and extent to which it modulates lipid metabolism in diabetic wound healing and its complications. This study aims to evaluate how resveratrol impacts the lipid profile in male Wister rats with type 2 diabetes, focusing on its effect on wound healing. The research aims to provide insights into the potential benefits of resveratrol in improving lipid levels and wound healing in diabetic conditions.

MATERIALS AND METHODS

Experimental Animals: 24 male albino Wistar rats (50 – 200 g) were purchased from the Animal House of the Department of Human Physiology, Faculty of Basic Medical Science, College of Medical Sciences, Ahmadu Bello University, Zaria. The animals were housed in a well-illuminated room for a 12/12-hour light-dark cycle for one week to acclimatize before the commencement of the experiment. The animals had access to Chikun Feed Grower Pellet and water (*ad libitum*), and the study was conducted using the guidelines of Ahmadu Bello University rules governing the use of laboratory animals, adopted from the Institute for Laboratory Animal Research; Guide for Care and Use of Laboratory Animals (NRC, 2011). The research was approved (ABUCAUC/2023/105) by the Ahmadu Bello University Committee for Research and Ethical Issues.

Induction of Diabetes Mellitus: The preparation of a high-fat diet (HFD) and the induction of type 2 diabetes were conducted following the method described by Sen *et al.* (2013) with some modifications. 20 grams of Chikun Feed Grower Pellet containing 28%

proteins, and 2650 Kcal metabolizable energy, was mixed with 1 gram of Simas margarine. The animals were fed the HFD for six weeks. Following this, they underwent overnight fasting and were then injected intraperitoneally with a single dosage of alloxan, at a concentration of 120 mg/kg, which was diluted in 0.1 M citrate-buffered saline (pH 4.5) (Sen *et al.*, 2013). After the alloxan injection, the rats were provided 5% glucose solution as drinking water. Diabetes was confirmed by measuring the blood glucose concentrations 72 hours after administering alloxan. The validation of diabetes was conducted one week following the first confirmation. Rats with fasting blood glucose levels ≥ 200 mg/dl were considered diabetic (Misra and Aiman, 2012; Shah and Khan, 2014), and used for the study.

Experimental Design: The experimental animal were randomly divided into the following four groups (Table 1): Group A (negative control) received water and normal diet throughout the experiment; Group B (positive control) was a diabetic untreated group; Group C (Treatment Group 1) was treated with 10 mg/kg body weight per day RSV (intraperitoneally) (Yonamine *et al.*, 2016), Group D (Treatment Group 2) was treated with 20 mg/kg body weight per day RSV (intraperitoneally) (Yonamine *et al.*, 2016).

Table 1: Experimental groups on type 2 diabetic wound healing of male albino rats treated with resveratrol

Groups	Induction	Treatment
Group I	Normal Control Group (wound)	Without treatment
Group II	Experimental control group (diabetic + wound)	Without treatment
Group III	Experimental group (diabetic + wound)	Resveratrol 10 mg/kg BW
Group IV	Experimental Group (diabetic + wound)	Resveratrol 20 mg/kg BW

Establishment of Diabetic Wound Model: After the confirmation of diabetes, the rats were anaesthetized by intraperitoneal injection of ketamine (75 mg/kg BW) and diazepam 5 mg/kg BW). The upper back of the rats was shaved with a small animal clipper and observed for any skin abnormalities. The shaved areas were disinfected with methylated spirit, and a 10 x 10 mm^2 wound area was created (a full-thickness excisional wound of the circular area was excised from the back of all rats by the surgical blade (Alsarayreh *et al.*, 2022).

Measurement of Wound Healing Area: The reduction in the wound healing area was measured by marking the area using a digital venire calliper. Wound contraction was expressed as a percentage of the healed wound area: wound healing ability = $(F_0\text{-}F_{7,\ 14\ })/F_0 \times 100\%$, where F_0 represents the primary wound area, and $F_{7,\ 14,}$ represents the wound area on days 7 and 14 respectively (Lin *et al.*, 2016).

Blood Sample Collection: After the two-week treatment period, the rats were deprived of food overnight and then put under anaesthesia using 75 mg/kg of Ketamine hydrochloride and 5 mg/kg of Diazepam. A cardiac puncture was performed to collect blood samples using 5 ml syringes. The samples were then placed in plain bottles and centrifuged at 3500 rpm for 15 minutes. This process was carried out to obtain serum, which was utilized to evaluate biochemical indices (Beeton *et al.*, 2007; Tékus *et al.*, 2021).

Body Weight Determination: Changes in the body weight of animals were recorded using digital balance, before and after the experiment, and were recorded as initial body weight (IBW) and final body weight (FBW), respectively (Ju *et al.*, 2024).

Blood Glucose Level Determination: The glucose level was tested to confirm diabetes induction. Blood samples from the tail vein of all animals were taken, and the blood glucose level was determined using a glucometer (ACCU-CHEK Active), and results were obtained as mg/dL (Rheney and Kirk, 2000).

Determination of Lipid Profile Parameters: Blood samples were collected via cardiac puncture using 5 ml syringes into plain bottles and centrifuged for 15 minutes at 3500 rpm to obtain serum for evaluation of serum cholesterol: triglycerides (TGs), low-density lipoprotein

cholesterol (LDLC), and high-density lipoprotein cholesterol (HDLC) using the methods of Friedewald *et al.* (1972), Allain *et al.* (1974) and Sugiuchi *et al.* (1995).

Statistical Analysis: ANOVA was used to compare the means of the various groups followed by Tukey's post hoc test using SPSS Version 26. P-values with a 95% confidence range of ≤0.05 were considered significant. The results were expressed as mean ± SEM.

RESULTS

The results obtained after the treatment of type 2 diabetic wounds in male albino rats with resveratrol showed that there were significant differences ($p<0.05$) in the weight of Group A (negative control) (165.87 ±11.60 g) compared to Group B (positive control) (210.02 ± 8.62 g) and Group C (Treatment Group 1) (215.43 ± 14.08 g) but does not show significant difference ($p<0.05$) between Group A and Group D (194.1 ± 9.12 g). There was no significant difference ($p<0.05$) between Group B with Group C and D respectively (Table 2).

Table 2: The body weight of type 2 diabetic wound healing of male albino rats treated with resveratrol

Group	Body weight (g)
Normal control	165.87 ± 11.6^{a}
Diabetic control	210.02 ± 8.62^{c}
Resveratrol 10 mg/kg	194.10 ± 9.12^{b}
Resveratrol 20 mg/kg	215.43 ± 14.08^{c}

$^{a\text{-means}}$ within a column with different letter superscripts are significantly different ($p<0.05$)

The wound healing diameter of Group A (negative control) (64.68 ± 1.46z%) showed significant difference ($p<0.05$) compared to Group B (positive control) (48.28 ± 1.3%), Group C (Treatment Group 1) (69.42 ± 1.67%) and Group D (Treatment Group 2) (66.11 ± 3.01%) respectively (Table 3).

The fasting blood glucose levels after treatment with resveratrol indicated that Group A (negative control) (70.59 ±3.41 mg/dL) showed significant difference ($p<0.05$) compared to Group B (positive control) (186.98 ± 55.08 mg/dL), Group C (Treatment Group 1) (183.57 ± 58.03 mg/dL) and Group D (Treatment Group 2) (187.33 ± 54.19 mg/dL) respectively (Table 4).

Table 3: Wound diameter of male albino rats

Group	Wound Diameter (%)
Wound	64.68 ± 1.46^{b}
Diabetic wound	48.28 ± 1.33^{a}
Diabetic wound + Resveratrol (10 mg/kg)	69.42 ± 1.67^{c}
Diabetic wound + Resveratrol (20 mg/kg)	66.11 ± 3.01^{bc}

$^{a\text{-}c}$Means within a column with different letter superscripts are significantly different ($p<0.05$)

Table 4: Fasting blood glucose levels of type 2 diabetic wound healing of male albino rats treated with resveratrol

Group	Fasting blood glucose (mg/dL)
Normal control	70.59 ± 3.41^{a}
Diabetic control	186.98 ± 55.08^{bc}
Resveratrol 10 mg/kg	183.57 ± 58.03^{b}
Resveratrol 20 mg/kg	187.33 ± 54.19^{c}

$^{a\text{-}c}$Means within a column with different letter superscripts are significantly different ($p<0.05$)

There was no significant difference ($p<0.05$) between Groups C and D compared to Group B (positive control) (186.98 ± 55.08 mg/dL). Additionally, there was no significant difference ($p>0.05$) in the blood glucose level of type 2 diabetic rats in the different dosage groups of resveratrol.

The result of total cholesterol levels after 14 days of treatments of type 2 diabetic wound with resveratrol indicated that there was no significant difference ($p>0.05$) between the Positive Control Group (47.50 ± 0.99 mg/dL) when compared to the Negative Control Group (43.52 ± 1.17 mg/dL), also there was no significant difference ($p>0.05$) between Positive Control Group (47.50 ± 0.99 mg/dL), and those treated with 10 mg/kg of resveratrol (43.70 ± 3.95 mg/dL), but there was significance difference ($p<0.05$) between Positive Control Group (47.50 ± 0.99 mg/dL) and those treated with 20 mg/kg of resveratrol (33.00 ± 0.74 mg/dL) (Table 5).

The HDL cholesterol levels after 14 days of treatments of type 2 diabetic wounds with resveratrol indicated that there were no significant differences ($p>0.05$) between the

Positive Control Group (21.00 ± 1.05 mg/dL) and the Negative Control Group (18.00 ± 3.39 mg/dL).

Table 5: Total cholesterol levels of type 2 diabetic wound healing of male albino rats treated with resveratrol

Treatment	Total cholesterol (mg/dL)
Wound	43.52 ± 1.17[b]
Diabetic wound	47.50 ± 0.99[c]
Diabetic wound + Resveratrol (10 mg/kg)	43.70 ± 3.95[b]
Diabetic wound + Resveratrol (20 mg/kg)	33.00 ± 0.74[a]

[a-c]Means within a column with different letter superscripts are significantly different (p<0.05)

There were no significant differences (p>0.05) between the Positive Control Group (21.00 ± 1.05 mg/dL) and the two resveratrol groups: 10 mg/kg of resveratrol (22.60 ± 2.50 mg/dL), and 20 mg/kg of resveratrol (12.00 ± 0.95 mg/dL) respectively, but there were significance differences (p<0.05) between diabetic wound treated with 10 mg/kg of resveratrol (22.60 ± 2.50 mg/dL) and the diabetic wound treated with 20 mg/kg of resveratrol (12.00 ± 0.95 mg/dL) (Table 6).

Table 6: High-density lipoprotein cholesterol levels of type 2 diabetic wound healing of male albino rats treated with resveratrol

Treatment	High-density lipoprotein cholesterol (mg/dL)
Wound	18.00 ± 3.39[b]
Diabetic wound	21.00 ± 1.05[c]
Diabetic wound + Resveratrol (10 mg/kg)	22.60 ± 2.50[c]
Diabetic wound + Resveratrol (20 mg/kg)	12.00 ± 0.95[a]

[a-c]Means within a column with different letter superscripts are significantly different (p<0.05)

The LDL cholesterol after 14 days of treatments of type 2 diabetic wound with resveratrol indicated that there was no significant difference (p>0.05) between the Positive Control Group (21.22 ± 0.22 mg/dL) and the Negative Control (21.32 ± 0.44 mg/dL), but there was significance difference (p<0.05) between the Positive Control Group (21.22 ± 0.22 mg/dL) and diabetic wound treated with 10 mg/kg of resveratrol (12.34 ± 0.69 mg/dL), and also 20 mg/kg of resveratrol (15.86 ± 1.19 mg/dL) respectively. Furthermore, there was a significant difference (p<0.05) between the Negative Control Group (21.32 ± 0.44 mg/dL) and the two resveratrol groups (Table 7).

Table 7: Low-density lipoprotein cholesterol levels of type 2 diabetic wound healing of male albino rats treated with resveratrol

Treatment	Low-density lipoprotein cholesterol (mg/dL)
Wound	21.32 ± 0.44[c]
Diabetic wound	21.22 ± 0.22[c]
Diabetic wound + Resveratrol (10 mg/kg)	12.34 ± 0.69[a]
Diabetic wound + Resveratrol (20 mg/kg)	15.86 ± 1.19[b]

[a-c]Means within a column with different letter superscripts are significantly different (p<0.05)

The triglyceride levels after 14 days of treatment of type 2 diabetic wound with resveratrol indicated that there were significant differences (p<0.05) between the Positive Control Group (32.34 ± 0.99 mg/dL) and the Negative Control Group (41.64 ± 2.40 mg/dL). There was also a significant difference (p<0.05) between the Positive Control Group (32.34 ± 0.99 mg/dL) and the 10 mg/kg of the resveratrol-treated group (38.78 ± 2.38 mg/dL), but there was no significance difference (p>0.05) between the Positive Control Group (32.34 ± 0.99 mg/dL) and the group treated with 20 mg/kg of resveratrol (31.24 ± 1.22 mg/dL), also there was a significant difference (p<0.05) between the non-diabetic control group and the two resveratrol treated groups (Table 8).

Table 8: Triglyceride levels of type 2 diabetic wound healing of male albino rats treated with resveratrol

Treatment	Triglyceride (mg/dL)
Wound	41.64 ± 2.40[c]
Diabetic wound	32.34 ± 0.99[a]
Diabetic wound + Resveratrol (10 mg/kg)	38.78 ± 2.38[b]
Diabetic wound + Resveratrol (20 mg/kg)	31.24 ± 1.22[a]

[a-c]Means within a column with different letter superscripts are significantly different (p<0.05)

DISCUSSION

The study found that rats' body weight increased significantly (across all groups) after diabetes induction, indicating a pre-diabetic state before induction; a common symptom of obesity leading to diabetes is weight gain. This aligns with clinical observations of weight gain as an early indicator of type 2 diabetes (Reuter, 2007). The significant decrease in blood glucose levels after 14 days of treatment with resveratrol is a noteworthy result. Lowering blood glucose levels is a primary therapeutic goal in managing diabetes, and these findings indicate that resveratrol may have a positive impact on glycaemic control as in the research which might help in the management of the diabetic wound healing process (García-Martínez *et al.*, 2022).

The absence of a significant difference in total cholesterol levels between the Positive and Negative Control Groups suggests that in this model, diabetes induction alone does not lead to a significant change in total cholesterol levels. Additionally, the lack of a significant difference between the diabetic untreated group and the diabetic group treated with resveratrol 10 mg/kg implies that this dose of resveratrol does not affect total cholesterol levels. However, the significant decrease observed in the diabetic group treated with resveratrol 20 mg/kg indicates a dose-dependent effect on total cholesterol levels, and it was in line with the findings of Akbari *et al.* (2020). The lack of significant differences in HDL-C levels between the Positive and Negative Groups may suggest that diabetes induction alone may not substantially impact or modulation HDL, Furthermore, the absence of significant differences between the Positive Control Group and the treated with resveratrol 20 mg/kg indicates that this dose of resveratrol does not influence HDLC levels. However, the increase observed between the treated with resveratrol 10 mg/kg and the treated with resveratrol 20 mg/kg is intriguing. This increase in HDLC is a positive outcome, as it suggests that higher doses of resveratrol may enhance HDL levels, and raising HDL cholesterol can be beneficial for cardiovascular health and may indirectly support wound healing (Gal *et al.*, 2021).

The lack of a significant difference in LDL levels between the Positive Control Group and the Negative Control is consistent with some research findings. However, the significant decrease in LDL levels observed in the treated group with resveratrol 10 mg/kg and 20 mg/kg is significant. Lowering LDL-C levels is generally associated with reduced cardiovascular risk, and this result indicates that resveratrol has a favourable impact it aligns with previous research suggesting its lowering effect on LDL cholesterol (Nanjan and Betz, 2014), it may promote diabetic wound healing and postischemic neovascularization by improving angiogenesis and attenuating tissue oxidative stress in diabetic rats (Tam *et al.*, 2014). The significant decrease in triglyceride levels between the Positive Control Group and the Negative Control Group suggests that diabetes induction is associated with elevated triglycerides, a common characteristic of diabetic dyslipidaemia. The lack of a significant difference in TG levels between the Positive Control Group and the treated group with resveratrol 20 mg/kg suggests that this dose of resveratrol may not modulate TG levels. However, the significant decrease in TG levels in both treated with resveratrol 10 mg/kg and 20 mg/kg is a promising result and could reduce the risk of cardiovascular complications.

Conclusion: The study shows that resveratrol significantly impacts the lipid profile in male albino Wistar rats with type 2 diabetes, potentially improving metabolic health and wound healing. However, further research is needed to confirm these findings on resveratrol and explore its potential as a treatment option for diabetic individuals with wound healing complications and or dyslipidaemia as a common characteristic of type 2 diabetes mellitus.

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