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EFFECTS OF RESVERATROL ON HISTOLOGY OF WOUND (MAST CELLS, FIBROBLASTS. COLLAGEN AND KERATINOCYTES) IN TYPE II DIABETIC WOUND HEALING OF MALE WISTAR RATS

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ABSTRACT

Background: Resveratrol contains anti-inflammatory, antidiabetic, antioxidant, anti-apoptotic, and cytoprotective properties.

Aim: This study examines how resveratrol affects mast cells, keratinocytes, collagen, and fibrinocytes in Male Albino Wistar Rats during wound healing.

Methods: 20 Adult Albino Male Wistars were used. High-fat diets and Alloxan injections made rats diabetic. The rats were divided into four groups: Negative Control, Positive Control, Diabetic Treatment Group 1 (10mg/kg resveratrol), and Diabetic Treatment Group 2 (20mg/kg). For 14 days, excisional wounds were produced and monitored for closure. Biochemical indicators, histology, and macroscopic approaches were used to study. Biochemical, histological, and macroscopic evidence showed wound healing.

Results: There was not statistical difference in Fasting Blood Glucose between the Diabetic Control Group with the treatment groups. There was statistical difference between Diabetic Control Group (210.02 ± 8.62) comparedtothegrouptreatedwithResveratrol20 mg/kg (215.43 ±14.08) in the weight of the experimental animals. There was a significant acceleration in wound closure rate, higher fibroblasts, collagen and keratinocytes presence in the diabetic untreated group from the photomicrographs of skin wounds while the photomicrographs of skin wounds from the diabetic wounded group treated with resveratrol (10mg) and (20 mg) showing abundance collagen fiber in the dermis and moderate keratinocyte, the evidence collagen formation in skin and marked granulation with more connective tissue markers.

Conclusion: Resveratrol supplement effectively reduced the fasting blood glucose and increased the rate of wound healing as evident in the histological assessment of the treated groups with resveratrol.

Keywords: Type 2 Diabetes, wound healing, resveratrol, mast cells, keratinocytes, fibroblasts.

1.0 INTRODUCTION

Diabetic Mellitus wound healing complication results from compounding complications. Hyperglycemia, dyslipidemia, altered immune function are associated with alterations in cellular morphology, decreased proliferation and abnormal differentiation of keratinocytes (1,

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2). According to an estimation, the lifetime incidence of chronic non-healing wounds, such as diabetic foot ulcers (DFUs), among patients with DM ranges from one in three to one in five. These ulcers have a concerning recurrence rate of forty percent within one year and sixty-five percent within five years, and there are currently no dependable methods to forecast their occurrence. (3, 4).

Notwithstanding the recent advancements in diabetes mellitus, pathophysiology, the disease's prevalence continues to intensify unabatedly, leading to incapacitating and life-threatening ramifications for the human economic and health on a long term forecast. (5). The management of diabetes mellitus (DM) remains complex and intricate. The use of new anti-diabetic drugs and their mechanisms of action, together with their benefits and adverse effects, have led to the need for the discovery of alternative therapeutic agents (6).

Resveratrol, a naturally-occurring polyphenolic molecule, predominantly found in grapes and peanuts, has been extensively documented in scientific literature for its advantageous properties in the prevention and management of several diseases (7). Studies have shown that resveratrol can reduce blood sugar, improve insulin resistance, regulate abnormalities in lipid metabolism and lower the secretion of and expression of inflammatory factors (8).Ithasbeenfoundtoexertseveralpharmacological actions,mainlyanti-inflammatory, antioxidant, anti-apoptotic and, in general, cyto-protective effects(9).

Given the complexity and intricacy with the pathophysiology of diabetes mellitus, the prevalence and complication of diabetic wounds, it is believed that plant-based chemicals with demonstrated multiple pharmacological effects may be the solution in finding a cost-effective, effective, and safer treatment for the disease and its related consequences. (10). While several studies have evaluated the antidiabetic effects of resveratrol this study will aim to evaluate the effects of Resveratrol on histology of wound (mast cells, fibroblast, collagen and keratinocytes) in Type II Diabetic wound healing of male Wistar rats.

2.0 MATERIALS AND METHODS

2.1 Materials

Digital glucometer (2Accu-Chek Advantage, Roche Diagnostic), glucose strip, gloves, weighing balance (GF2000), dissecting kits, Assay kits, centrifuge, plain bottles, Petridis, cannula, beakers, petri-dishes,cottonwool,plasticcages,sawdust,animalfeed,normalsaline,syringe,andneedle, Alloxan monohydrate (Sigma Chemicals Co., USA), Polysorbate 80, mega resveratrol (Sigma Chemicals Co., USA), citrate buffer, normal saline, ketamine, diazepam, distilled water, high fat diet, and Vitamin E. All chemicals in the experiment were analytical grade.

2.1.1 Experimental Animals

20 Male Adult Albino Wistar Rats (150g-200g) were purchased from the Animal House of 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

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cycle for one week to acclimatize prior to the commencement of the experiment. The animals had access to commercial pellet feed and water (ad libitum) before the commencement of the experiment, and the study was conducted in accordance with the guidelines of Ahmadu Bello Universityrulesgoverningtheuseoflaboratory animalsasacceptedinternationallyby (National Institute of Health Guide for Care and Use of Laboratory Animals)

2.1.2 Ethical Approval

Ethical approval on guidelines for care and use of laboratory animals in scientific research was sought from Ahmadu Bello University Committee on Animal Use and Care (ABUCAUC) and ABUCAUC/2023/105 was assigned.

2.2 Methodology

2.2.1 Induction of Diabetes Mellitus

The modified Sen et al. (11) technique was used to prepare and induce type II diabetes with a high-fat diet (HFD). NDF (18% Fats, 28% Proteins, 54% Carbohydrates) was blended with Simas margarine (99.9% Fats). HFD was made by combining 20 grams NDF with 1-gram Simas margarine. After six weeks on the HFD, the animals were fasted overnight and injected intraperitoneally (IP) with 120 mg/kg Alloxan diluted in 0.1 M citrate-buffered saline (pH 4.5). (11). After Alloxan injection, the rats were provided 5% glucose solution as drinking water immediately. Diabetes was confirmed after Alloxan administration 72 hours via blood glucose concentrations while the validation of diabetes were done one week after initial confirmation; rats with fasting blood glucose levels ≥ 200 mg/dl were considered diabetic(12).

2.2.2 Wound incision model

After the confirmation of diabetes in the rats, the upper back of rats were shaved with small animal clippers and observed for any skin abnormalities. The shaved areas were disinfected with methylated spirit; then, rats were anaesthetized by intraperitoneal injection of ketamine (75 mg/kg bw)anddiazepam5mg/kgbw).10mmx10mm woundareawascreated(afull-thicknessexcisional wound of circular area was excised from the back of all rats by surgical blade (13).

2.2.3 Wound healing measurement

There duction in the wound healing area was measured by marking the area using a digital venire caliper. Wound contraction was expressed as a percentage of the healed wound area: wound healing ability = (F0-F7, 14)/F0 × 100%, where F0 represents the primary wound area, and F7, 14,represents the wound area on days 7 and 14respectively (14, 15).

2.2.4 Experiment design

The experimental animal were divided randomly into the following four groups. Group1received water and normal diet throughout the experiment; Group2 was diabetic untreated group; Group 3 was a diabetic group treated with 10mg/kg body weight per day RSV (i.p.) (16); Group 4 was a diabetic group treated with 20mg/kg body weight per day RSV (i.p.) (16).

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Table 1: Experimental Design Groupings

Grouping	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 b.w
Group IV	Experimental Group (diabetic + wound)	Resveratrol 20 mg/kg b.w

2.2.4 Sample Collection

After two weeks of treatment, the rats were starved overnight and anesthetized with 75mg/Kg Ketamine hydrochloride and 5mg/Kg Diazepam. Serum for biochemical indices was obtained via cardiac puncture with 5ml syringes into plain bottles and centrifuged for 15 min at 3500 rpm. Wound samples were also obtained using a skin-biopsy punch and divided into two for histological examination and serum analysis. The homogenates of one part of the tissue were spun for 10 min at 3000 xg and the resulting supernatant will be utilized for analyzing various biochemical parameters.

2.2.5 Determination of Body Weight

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, respectively (17).

2.2.6 Blood Glucose Level Determination

The glucose level were tested to confirm diabetes induction. Blood samples from the tail vein of all animals were taken, and the blood glucose level were determined using a glucometer (ACCU- CHEK Active®), and results obtained as mg/dL (18).

RESULTS

The Weight of Wistar Rats of Type II Diabetic Wound Healing Treated With Resveratrol

The results (Table 2) showed the weight of each group before, during, and after the treatment of type II diabetic wound in Male Albino Wistar Rats with resveratrol. The result obtained showed that there was nosignificant($p<0.05$)differenceintheweightofthenormalcontrolgroup(144.8kg,168kgand 184.8 kg before, during, and at the end of the experiment respectively) compared to the diabetic untreated group(194.8 kg,211.8 kg, and 224 kg respectively).After treating type II diabetic wound rats with resveratrol 10 mg,

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results obtained were 178 kg, 209.8 kg, and 194.6 kg, and upon treating with 20 mg, results recorded were 190.2 kg, 238.8 kg and 217 kg respectively. Both resveratrol dosages showed no significant ($p<0.05$) difference compared to the diabetic untreated group, and there was no significant ($p<0.05$) difference between the two groups.

Fasting Blood Level of Type II Diabetic Wound Healing in Wistar Rats Treated with Resveratrol

The results (Table 3) showed that blood glucose level before and after treatment of the normal control group (71.2 mg/dl and 76.1 mg/dl respectively) in type II diabetic wound healing shows no significance ($p<0.05$) difference compared to the diabetic untreated group (was 246.5 mg/dl and 237.5 mg/dl respectively).Also,10 mg resveratrol administration in type II diabetic wound healing shows no significant ($p<0.05$) difference (250.26 mg/dl and 232.48 mg/dl) in glucose level of Wistar rats compared with the diabetic untreated group. 20mg of resveratrol administration also showed no significant ($p<0.05$) difference (248.26mg/dland234.5mg/dl) compared with the type II diabetic untreated group. Additionally, there was no statistical ($p<0.05$) in blood glucose level of type II diabetic rats in the different dosage group of resveratrol.

Groups	Mean ± SEM
Normal Control	165.87±11.6b,d
Diabetic Control	210.02 ± 8.62a
Resveratrol 10 mg/kg b.w	194.1±9.12
Resveratrol 20 mg/kg b.w	215.43 ±14.08a

Table 2: Fasting Blood Levels of Type II Diabetic wound healing in Wistar Rats treated with resveratrol for 14 days

Groups	Mean±SEM
Normal Control	70.59±3.41b,c,d
Diabetic Control	186.98 ±55.08a
Resveratrol 10 mg/kg b.w	183.57 ±58.03a
Resveratrol 20 mg/kg b.w	187.33 ±54.19a

*Fasting Blood Level of Type II Diabetic Wound Healing in Wistar Rats Treated With Resveratrol. a=significant difference ($P<0.05$) when compared to the normal control group. b= significant difference ($P<0.05$) when compared to the diabetic control group. c=significant difference ($P<0.05$) when compared to the group treated with Resveratrol 10 mg/kg. d=significant difference ($P<0.05$) when compared to the group treated with Resveratrol 20 mg/kg.

Table 3: Bodyweight of in Wistar Rats Treated with resveratrol for 14 days

*a=significant difference ($P<0.05$) when compared to the normal control group. b = significant difference ($P<0.05$) when compared to the diabetic control group. d= significant difference ($P<0.05$) when compared to the group treated with Resveratrol 20 mg/kg. There was statistical difference between Diabetic Control Group (210.02 ± 8.62)

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comparedtothegrouptreatedwithResveratrol20 mg/kg (215.43 ±14.08).

Histological results of Diabetic Wound Healing in Wistar Rats Treated with Resveratrol

Group 1: Normal Control Group

The result in plate 1: 1A was a photo micrographs of skin wounds from the normal control group showing normal epithelial growth with moderate fibroblast hyperplasia and slight leukocyte hyperplasia fourteen days post wound period (H & E × 200). The result in plate 1B was a photomicrographs of skin wounds from the normal control group showing abundance collagen fiber in the dermis and keratinocyte with some blood vessels (Mason's Trichrome stain, × 400).

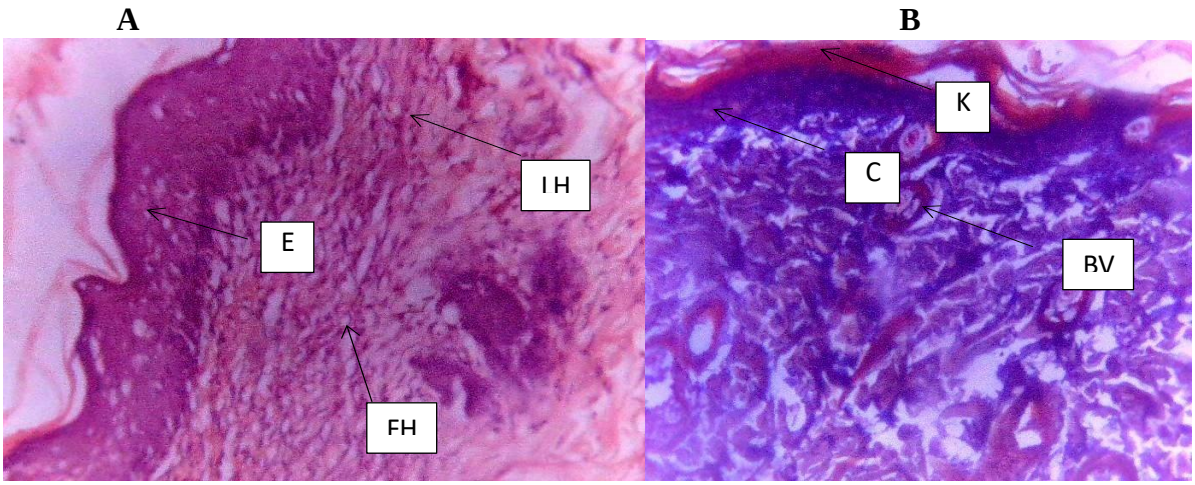

Plate 1. A Photomicrographs of skin wounds from the normal control rats

E, LH and FH means epithelial layer, leukocyte hyperplasia, and fibroblast hyperplasia respectively.1B shows abundance keratinocyte (K), moderate collagen (C), and some blood vessels (BV).

Group 2: Type II Diabetic Wound Untreated Group

The result in plate 2A is a photomicrographs of skin wounds from the diabetic control group showing moderate epithelial atrophy with moderate fibroblast hyperplasia fourteen days post wound period (H & E × 200). The result in plate 2B is a photomicrographs of skin wounds from the diabetic control group showing sparse collagen fiber in the dermis and sparser keratinocyte (Masson's Trichrome stain, × 400).

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A B

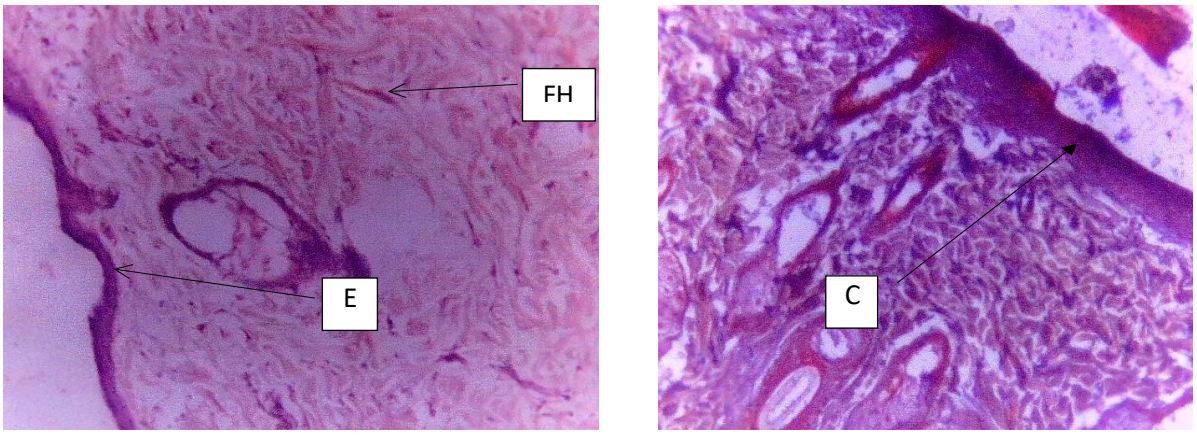

Plate 2. A Photomicrographs of skin wounds from the diabetic control group rats showing epithelial layer (E) and fibroblast hyperplasia (FH). 2B shows poor keratinocyte and collagen (C) presence.

Group 3: Type II Diabetic Wound Group Treated with Resveratrol (10mg) group

The result in plate 3A is a photo micro graphs of skin wounds from the diabetic wounded group treated with resveratrol (10mg) showing continuous epithelial regeneration with moderate glandularhyperplasiaandsomebloodvesselsfourteendaysposttreatmentperiod(H&E×200). The result in plate 3 B is a photo micrographs of skin wounds from the diabetic wounded group treated with resveratrol (10mg) showing abundance collagen fiber in the dermis and moderate keratinocyte (Masson's Trichrome stain, × 400).

A B

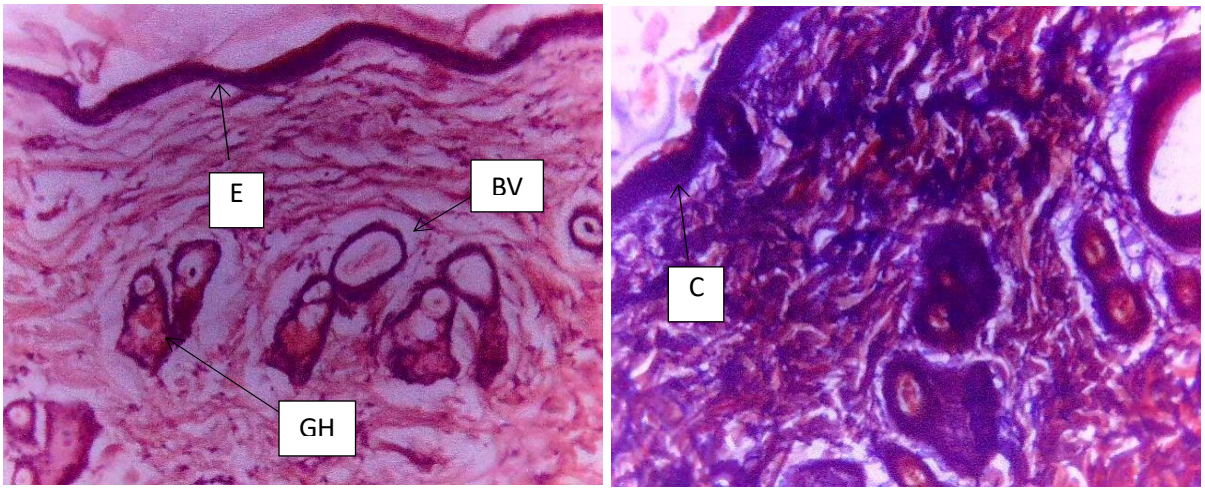

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Plate 3. A Photomicrographs of skin wounds from the type II diabetic wounded group treated with resveratrol (10mg). Epithelial layer (E) regenerated and continuous, glandular hyperplasia (GH) and blood vessels were visible (BV). 3B shows moderate keratinocyte and abundant collagen presence (C).

Group 4: Type II Diabetic Wound Group Treated with Resveratrol (20mg)

The result in plate 4A was a photo micrographs of skin wounds from the type II diabetic wounded group treated with resveratrol (20mg) showing slight epithelial regeneration with minor atrophy, moderate glandular hyperplasia and fibroblast hyperplasia fourteen days post treatment period (H & E × 200). The result in figure 4B was a photomicrographs of skin wounds from the diabetic wounded group treated with resveratrol (20mg) showing moderate collagen fiber in the dermis and abundance keratinocyte (Masson's Trichrome stain, × 400).

A B

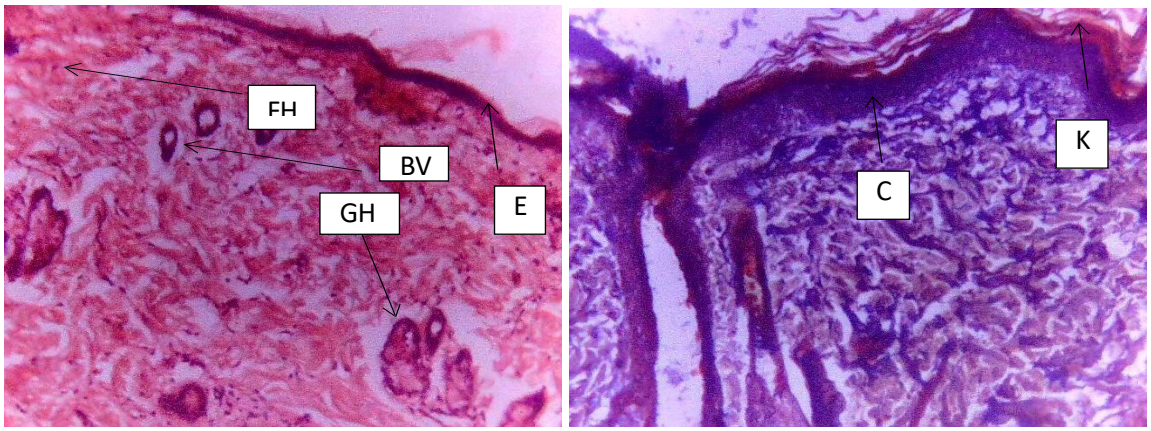

Plate4.APhoto micrographs of skin wounds from the diabetic wounded group treated with resveratrol (20mg), showing moderately continuous epithelial layer (E), follicular hyperplasia (FH), blood vessels (BV), and glandular hyperplasia (GH). 4B shows abundant keratinocyte (K) and abundant collagen presence (C).

DISCUSSIONS

Body Weight and Blood Glucose Level

From the results in the above, it was noticed that the body weight from all groups increased from the initial values after treatment in diabetic Groups 3 and 4 and in both Group2 and Group1. With this it can be inferred that the treatment had no effect on the body weight of the Wistar rats. Also, the blood glucose level in the groups that received treatment with 10 mg/kg (Group 3)

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and 20 mg/kg (Group 4) of resveratrol saw no significant change in blood glucose levels from diabetic levels to normal levels.

Previous studies have shown RSV supplementation improved glycemic control in rats with diabetes induced through a combination of fructose and High fat Diet (HFD) feeding and a single dose of Alloxan. This model serves as an alternative, non-genetic rat model for type II diabetes (19)Most of the earlier researchers have reported the hypoglycemic effect of resveratrol; their studies demonstrated that resveratrol lowered plasma glucose in both normal and diabetic rats in a dose dependent manner (7, 20, 21).Resveratrol stimulated insulin release in normal and diabetic rats with the capability of secreting insulin from the. This however was not the case of this study as RSV had no significant effect on blood glucose level or body weight as shown in some studies (22, 23) where it had no effect on body weight and where it had no effect on blood glucose levels (24).

Wound Histology

From the first set of photomicrographs of the non-diabetic control group (Plate 1), the presence of leukocyte and fibroblast hyperplasia, show progression in the inflammatory stage of wound healing. The presence of keratinocytes, collagen and blood vessels is evidence in advancement of Proliferation stage after two weeks. This is all in accordance with normal wound healing and is expected to progress into the remodeling stage as described by Gonzalez et al (25).

The second set of photomicrographs in from the Diabetic untreated control group (Plate 2), showed sparse fibroblast hyperplasia, all together absence of leukocytes and leukocyte hyperplasia showing impairment of Inflammatory stage. Sparse keratinocytes and collagen deposits and absence of blood vessels shows impairment of Proliferation stage. This shows a failure of proper progression in wound healing process and shows hallmark symptoms of chronic diabetic ulcers as described by Burgresset al (26).

The next set of photomicrographs in (Plate 3 and 4) from group 3 (Diabetic group treated with 10 mg/kg of RSV) showed improvement since there is greater collagen presence and some presence of blood vessels with moderate glandular hyperplasia and keratinocyte showing continuous epithelial regeneration fourteen days post treatment period. The final set of photomicrographs Group 4 (Diabetic group treated with 20 mg/kg of RSV) showed greater improvement in terms of epithelial regeneration, moderate glandular hyperplasia, fibroblast hyperplasia and showing moderate collagen fiber in the dermis and abundance in keratinocytes, follicular cell regeneration and blood vessels at fourteen days post treatment period. Hence showing improved wound healing for group 4 over group 3, with progression close to that of group 1 (Normal wound healing).

This difference may be due to the hypoglycemic effect of RSV Raskovic et al (19), since hyperglycemia is a major cause of impaired wound healing in Chronic wounds such as Diabetic Ulcers (4, 26). As earlier studies have shown resveratrol lowered blood

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glucose in both normal and diabetic rats in a dose dependent manner (27).

CONCLUSION

Theresveratroltreatmentwasobservedtoeffectivelyimprovethewoundhealingprocessofthe Diabetic Adult Male Albino Wistar Rats.

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Authors' contributions

Conceptualization: Jimoh, A., Methodology: Daniel, M., Experimentation, Daniel, M., Jumoh, A., Formal analysis and investigation: Yusuf, N.O., Daniel, M., Idris, A.,Writing - original draft preparation: Idris, A., Daniel, M., Writing - review and editing: Jumoh, A., Idris, A., Yusuf, N.O., Funding acquisition: Daniel, M., Resources: Jumoh, A., Dawud, F.A., Supervision: Jumoh, A., Dawud, F.A.

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