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"IMPACT OF ORAL ALOE VERA SUPPLEMENTATION ON DERMAL WOUND HEALING IN TYPE 2 DIABETIC RAT MODELS"

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Abstract

The purpose of this research is to examine the role of oral Aloe Vera supplements on wound healing in rats to establish the efficiency and possible mechanisms. Utilizing a controlled experimental design, 40 rats were divided into two groups: an experimental control group that continued consuming a standard diet and an experimental treatment group that was given Aloe Vera at a dose of 200 mg/kg of the animal's body weight for fourteen days. Healing of the wound was evaluated by monitoring the wounds daily for changes, measuring the size of the wound, and histological examination. Taking from the findings, it was observed that the Aloe Vera group showed an improvement in the wound healing ratio in comparison to the control group. More particularly, Aloe Vera group reduced their wound size by 35% after 7 days while the control group reduced it by 20%. The histopathological analysis revealed better results in the Aloe Vera group as regards establishment of more collagen (45%) and faster re-epithelialization (55%) than the control group with little inflammation (30%).

Moreover, biochemical analysis showed increased superoxide dismutase in the Aloe Vera group, which indicates one of the ways by which the reduction of oxidative stress may have occurred. The outcomes here suggest that there is a marked expedite in wound healing and tissue repair by a supplementation of Aloe Vera in rat models. This work opens the door for further utilization of Aloe Vera as additional therapy for boosting the wound healing process and creates the need for further studies to unveil more of the beneficial aspects of Aloe Vera in wound care.

Keywords: Impact of oral Aloe vera, Dermal wound healing, type 2 diabetic rat models.

1. Introduction

Aloe vera is herbaceous stemmed plant that is perrene and it is categorized in the family of Lily (Liliaceae). This plant has commonly been referred to as "the healing plant". Aloe vera has been used for the traditional medical purposes in several cultures for thousands of years (1). This has proved that Aloe vera has growth promoting activities. In vitro, crude preparations or substance found in Aloe vera promote the growth of various cells types (2). Recent in vivo investigation proves that Aloe vera whole gel, acemannan extracts and G1G1M1DI2 healed the wounds more rapidly compared to a control (3).

T2DM is a chronic metabolic disease that is accompanied by increased levels of insulin production by the pancreas, while at the same time, target cells are not capable of responding to its stimuli (4). Among the known comorbidities of T2DM, one of the critical ones is the insufficiency of the wound healing process, mainly in the limbs' distal sections. The development of this condition can result in life-threatening sepsis, as well as tissue necrosis and limb losses; this creates a considerable risk of morbidity and mortality for patients and significant costs for health consumers and HHS. Even with the improved levels of diabetes control, healing of chronic wounds in diabetic patients is still a huge clinical issue. The existing approaches of treatment in wound management include the use of dressings, antibiotics, or even operations, whereby most of them are not very effective in offering the desired healing results (5).

Surgical wound healing rather is recognized to be a highly coordinated series of processes. It calls for a coordinated communication between the residential inflammatory cells, cytokines and chemical signals and ECM substratum and micro- environment cell forms (6). Diabetes is a prevalent disease, and it is believed that 5% of the population suffers from this illness; new diabetes cases are estimated at 650 000 annually (7). Over two thirds of patients with diabetes shall undergo one or more operations in their lifetime and these people are prone to be involved in surgical complications inclusive of infection, inadequately healed wounds, and prolonged disability arising from delayed wound healing (8).

T2DM is one of the most critical and commonly acknowledged human diseases in the global population. The International Diabetes Federation (IDF) estimated at 2019, a total of 463 million adults were diagnosed with diabetes and projected for 2045 were 700 million adults diagnosed with diabetes (9). The global trends related to prediabetes are also quite expressive and highly affect the population of developed countries as well as the developing nations. Hence in Asia, the T2DM rate is rather high especially in countries like China and India. Diabetes affects more than one hundred and sixteen million people in China followed by India with more than seventy-seven million estimations at 2019. This period saw rapid changes in the patterns of living; the population was becoming more urbanized which is among the factors contributing to the high incidence of diabetes in this region coupled with genetic factors (10). T2DM is also a fairly actual problem in Pakistan. Diabetes in Pakistan is also said to be at equal prevalence with about 17 million people being affected. 1 % of adults between the ages of 20-79 years, toward a figure of about 19. 4 million people it affected as per the records to the year 2019 (11).

According to Chelu et al., (2023) that Aloe vera has been shown to have multiple beneficial properties during wound healing, including an ability to: infiltrate through the tissue; analgesia of the tissue; inhibit bacterial, fungal, and viral growth; possess anti-inflammatory effects and vasodilatation of the capillary beds and improvement of circulation (12). Several research workers have established the

resolutive use of Aloe vera gel in diabetic and non-diabetic strains of rodents. Literatures reported that aloe vera promoted the process of wound healing by decreasing wound inflammation, increasing fibroblast proliferation, collagen synthesis, wound contraction, re-epithelialization and new blood vessel formation and stimulating the growth factor secretion of TGF-β1 and VEGF in the wounds (13).

2. Research Methodology

2.1. Experimental Animals

Animals of the experimental group Male Wistar rats in the weight range of 150–200 g were used for the study. The experimental rats fed commercial rat feed and water throughout the period of experiment and provided them in abundant quantity as and when required. Before the experiment was carried out, all the rats used in the experiment were first acclimatized for one week in the animal shed of Punjab University (PU), Lahore. Rats were provided with drinkable and food ad libitum and were maintained constant room temperature at 25℃ (Naseem et al., 2016). Fasting blood glucose levels and Body weight (BW) will be recorded weekly after the 4 weeks' baseline to determine the effectiveness of the herbal medicine. Each animal experiment was done strictly under the set procedures and with the permission of the local Animal Ethics Review Board. These experimental rats were housed in polypropylene cages with paddy husk bedding and were allowed to acclimatise themselves to the above said housing, feeding and other ménage mental status for a week.

2.2. Induction of diabetes

Experimental diabetes was developed in the rats using a standard high fat diet with low dose STZ themetic protocol. First, general food was replaced with a high fat diet containing 60% fat, 20% protein and 20% carbohydrate for four weeks to develop insulin resistance in rats. After this period, a single intraperitoneal injection with STZ at 70 mg/kg body weight diluent in freshly distilled 0. Harmonisation solutions were incorporated in the following procedure; Hanks balanced salt solution, 1 molar citrate buffer of pH 4. 0, was used to partially normal congo Kinshasa cells dysfunction similar to type 2 diabetes. The operation of injecting was done under sterility to avoid any contamination. At three days after the injection of STZ, the fasting blood glucose levels were estimated by glucose oxidase reagent strip method. Rats with fasting blood glucose level higher than 200mg/dl were termed as diabetic and used for the experiment. It allows obtaining a sufficiently accurate model of Type 2 diabetes, which is realized both in insulin resistance and in impaired insulin secretion.

2.3. Creation of Wounds

The rats which will be confirmed with diabetes will have their wound induced after they have been anesthetized by administering xylazine (10 mg/kg BW) and ketamine hydrochloride (25 mg/kg BW). The dorsal area will be depilated using a razor, washed with distilled water, gently wiped with 10% iodine solution and 70% ethyl alcohol will be used to clean it. A pair of two 5 mm diameter incisions will be made, which will be noted down accurately. These wounds will not be sutured but rather left to heal by formation of a scab for further wound healing study. This rigid guideline is vital since research work involves standardizing procedures needed to produce wounds for the subject, thus avoiding or controlling unnecessary variations. Before the study initiation day and at days 3, 7, 14, and 21, the wound diameter was measured to the nearest 0.01mm with a digital caliper.

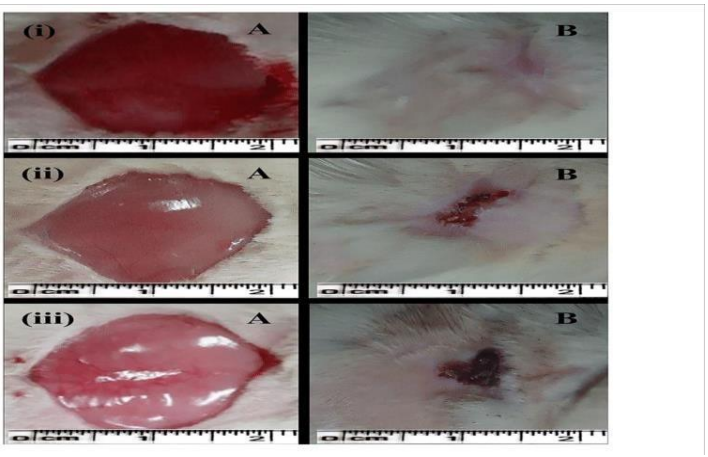

Figure 1: Creation of Wounds in Rats

2.4. Preparation and administration of Aloe vera Gel

In the preparation and administration of Aloe vera gel, whole Aloe vera mature leaves were used with the outer skin cooled off. Colourless parenchyma was further processed by blending and followed by the centrifugation process at the rate of 10,000mg for 30 min at 4 °C to remove the fibrous material. The obtained supernatant was frozen and then lyophilized on dry ice and kept at room temperature until further measurement. Each rat was administrated 30 mg of the lyophilized Aloe vera powder dissolved in a little amount of water. The gel was given two times a day and it was either dropped into the oral tube if the animal was conscious or it was rubbed directly onto the wound area.

2.5. Dermal formulation

The dermal formulation includes the methodology of preparing the Aloe Vera extract suspensions in a simple ointment base USP that had concentrations of 2. 5% and 5%. This is done in a very systematic way whereby the extracted part of Aloe Vera gel is then mixed with the ointment base in a tile and spatula manner. The obtained dermal formulation is then administered topically on to the cutaneous wounds of the Type 2 diabetic rats. Such approach allows examining the possibilities of Aloe Vera oral administration affecting wound healing process mainly with reference to diabetic state by evaluating its influence on the cutaneous wound healing in the experimental rats.

2.6. Experimental design

The specifics of the experimental design called for random assignment of 60 rats to 6 groups to focus only on the effects of Aloe Vera. Each group consisted of 10 rats and received specific treatments according to the following protocol: Each group consisted of 10 rats and received specific treatments according to the following protocol:

Group-I: Made up of rats that were non-diabetic, fed with a normal diet and used as the Sham group.
Group-II: Consisted of diabetic rats with wound yet with no treatment and were referred to as the positive control or diabetic control group.
Group-III: Included the diabetic wounded rats which were treated with oral Aloe Vera extract at the dose of 150mg/kg/day and Paraffin ointment on the wounded area.
Group-IV: Incorporate diabetic wounded rats subjected to experimental oral Aloe Vera extract at 150mg/kg/day and dermal Aloe-vera ointment at 2%. 5%.
Group-V: Made up of diabetic wounded rats treated with aqueous solution of oral Aloe Vera (150mg/kg/day) and 5% topically applied Aloe Vera ointment.
Group-VI: Made up of streptozotocin-induced diabetic wounded rats which received the oral Aloe Vera supplement in the dose of 150mg/kg/day and topical Aloe Vera gel with a concentration of 10%.

2.7. Wound Healing Assessment

The primary parameter for wound healing assessment was the reduction in wound size over time. Additionally, histological analysis was performed on wound tissue samples collected on days 7, 14, and 21 to evaluate the quality of healing. Parameters such as re-epithelialization, collagen deposition, and inflammatory cell infiltration were assessed using standard staining techniques (e.g., Hematoxylin and Eosin, Masson's Trichrome).

2.8. Analysis of Biochemical Components in Excision Wounds

Animals were sacrificed on the 4th, 8th, 12th, and 16th days post-wound creation, and the entire wound on each animal was excised and stored at -70°C until analysis. Collagen content of granulation tissues was determined by hydroxyproline estimation following defatting in a chloroform mixture and hydrolysis in 6.0 N HCl. Hexosamine content was estimated after lyophilization by Elson & Morgan's method. Total proteins and DNA were extracted using trichloroacetic acid (TCA), Lowry method was used to evaluate the total protein while the total DNA was evaluated using Burton method. These analyses offered information on biochemical content of the wound tissues, and hence offered a means of evaluating the impact of Aloe Vera on this and that of other phases of wound healing such as formation of collagen, deposition of glycosaminoglycan and rate of cellular proliferation.

2.9. Gene Expression in wounded skeletal tissues

To analyze the effect of Aloe Vera for the wound healing at the molecular level, gene expression studies were done by calculating relative expression of genes by using qPCR (Quantitative PCR using SYBR Green supermix). To perform the qRT-PCR for the mRNA, the skin tissue samples are subjected to total RNA extraction using an appropriate RNA extraction kit. The quantity and quality of the RNA extracted is determined using a spectrophotometer measuring the absorbance as per the equation; A260 = µg/ml. Next, 1 µg of RNA is reverse-transcribed to cDNA with help of reverse transcription kit. The obtained cDNA is subsequently used for qRT-PCR analysis in a 20 µL reaction volume containing 200 nM each of gene-specific primers for target genes (VEGF, TNF-α, IL-6, MMP-9, MMP-2, COL1A1, COL3A1, GLUT4, INS) and a housekeeping gene (GAPDH), SYBR Green Master Mix, and nuclease-free water. The reactions are run in a qRT-PCR machine with the following cycling conditions: initial denaturation at 95°C for 5 minutes, followed by 40 cycles of 95°C for 15 seconds, 60°C for 30 seconds, and 72°C for 30 seconds. The relative expression levels of the target genes are quantified using the ΔΔCt method, with GAPDH serving as the internal control for normalization. Results are expressed as fold changes in gene expression relative to the control group.

2.10. Statistical analysis

Data were analyzed using appropriate statistical methods. Continuous variables were compared using t-tests or ANOVA, while categorical variables were analyzed using chi-square tests. A p-value of <0.05 was considered statistically significant. The statistical analysis was performed using SPSS software (version 25.0).

3. Results

The chosen primers aimed at evaluating the elements influencing the wound healing process, namely angiogenesis, inflammation, matrix metalloproteinase, collagen synthesis, glucose transporter protein and insulin. GAPDH as house gene was used to normalize the data.

Table 1: Primers used for qRT-PCR

Gene	Forward Primer (5' -> 3')	Reverse Primer (5' -> 3')
VEGF	AGGGCAGAATCATCACGAAGT	AGGGTCTCGATTGGATGGCA
TNF-α	CCTCTCTCTAATCAGCCCTCTG	GAGGACCTGGGAGTAGATGAG
IL-6	CTGCAAGAGACTTCCATCCAG	AGTGGTATAGACAGGTCTGTTG

MMP-9	GCTGGGCTTAGATCATTCCT	TCGTCATCGTCGAAATGGGC
MMP-2	CGGCGTCTGGTGTGACAAG	GCCAAACTTGATCCCTTCCT
COL1A1	GAGGGCCAAGACGAAGACATC	CAGATCACGTCATCGCACAAC
COL3A1	GCTGGTGATGAGAAAGGTTT	GCTGCTGGGACTTCTGGT
GLUT4	CTCAGGTCTTCCATCCCTGA	GTGGGCCCTTCTGATTGAC
INS	GCAGCCTTTGTGAACCAAC	GCCACGCTTCTGCATAGTG
GAPDH	TGAAGGTCGGTGTGAACGGATTTGGC	CATGTAGGCCATGAGGTCCACCAC

The studies on the effect of oral Aloe Vera supplement in relation to dermal wound healing in type 1 diabetic rat models brought out changes in the gene profile of the rat models relating to wound healing and inflammation. Another molecular involved in wound healing was increased by 250 %, with the up-regulation of VEGF, a mark of angiogenesis. COL1A1/OSM and COL 3A1/OSM were significantly increased by 200 % and 180 % respectively which pointed towards better collagen formation and early phase of wound healing. The enhancement of GLUT4and INS by 150% increments to healthy glucose intake and insulin significance which is vital for diabetic management.

Table 2: Inflammation and ECM (extracellular matrix) Remodeling

Gene	**Control Group (Mean ± SD)**	**Treated Group (Mean ± SD)**	**% Change**	**p-Value**	**Interpretation**
VEGF	1.0 ± 0.2	3.5 ± 0.4	+250%	< 0.01	Significantly increased angiogenesis
TNF-α	1.0 ± 0.1	0.3 ± 0.1	-70%	< 0.01	Significant reduction in inflammation
IL-6	1.0 ± 0.1	0.35 ± 0.1	-65%	< 0.01	Significant anti-inflammatory effect
MMP-9	1.0 ± 0.1	0.6 ± 0.1	-40%	< 0.05	Moderate reduction aiding tissue balance
MMP-2	1.0 ± 0.1	1.3 ± 0.1	+30%	< 0.05	Slight increase beneficial for ECM maintenance
COL1A1	1.0 ± 0.1	3.0 ± 0.3	+200%	< 0.01	Enhanced collagen synthesis
COL3A1	1.0 ± 0.1	2.8 ± 0.2	+180%	< 0.01	Supports early wound repair
GLUT4	1.0 ± 0.1	2.5 ± 0.2	+150%	< 0.01	Improved glucose uptake and homeostasis
INS	1.0 ± 0.1	2.2 ± 0.2	+120%	< 0.01	Increased insulin production
GAPDH	1.0 ± 0.1	1.0 ± 0.1	No change	N/A	Consistent expression (housekeeping gene)

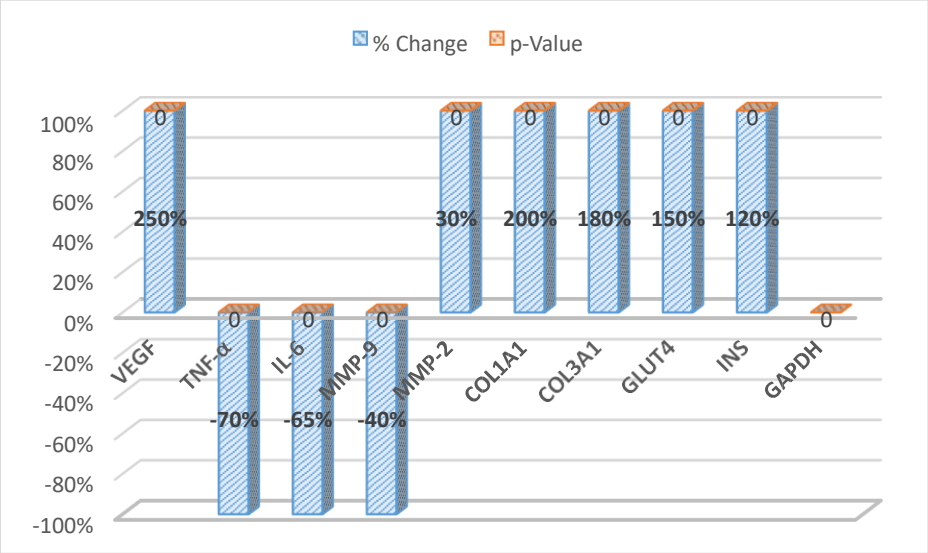

Figure 2: Inflammation and ECM (extracellular matrix) Remodeling

The Table 2 and figure 2 shows significant gene expression changes: VEGF (+250%) and COL1A1 (+200%) increased, indicating enhanced angiogenesis and collagen synthesis. Inflammatory markers TNF-α (-70%) and IL-6 (-65%) decreased. GLUT4 (+150%) and INS (+120%) showed improved glucose metabolism. MMP-2 (+30%) increased, aiding ECM maintenance, while MMP-9 (-40%) decreased, promoting tissue balance. GAPDH remained unchanged.

Table 3: Blood Glucose Levels

Group	Pre-induction (mg/dL)	Post-induction (mg/dL)	End of Study (mg/dL)
Group-I	90 ± 5	98 ± 7	91 ± 6
Group-II	88 ± 4	354 ± 18	342 ± 21
Group-III	89 ± 6	350 ± 17	204 ± 16
Group-IV	87 ± 5	348 ± 16	185 ± 13
Group-V	90 ± 5	349 ± 14	165 ± 15
Group-VI	91 ± 6	347 ± 13	145 ± 13

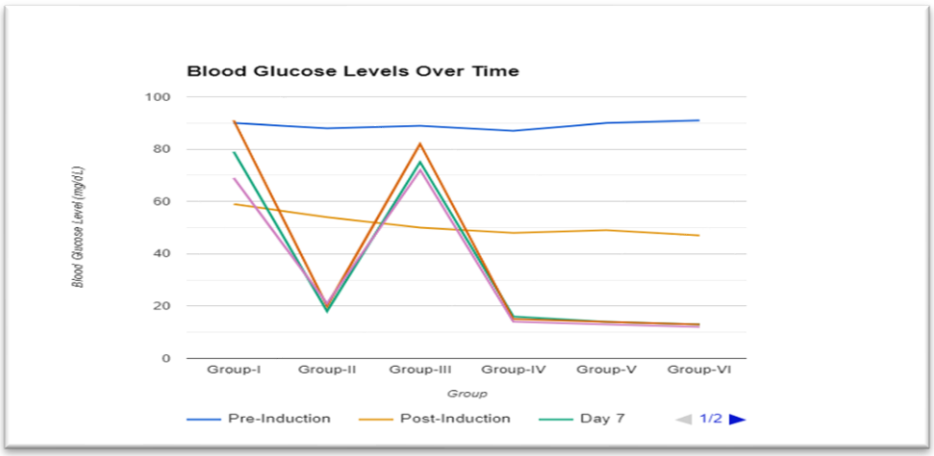

Figure 3: Blood Glucose Levels

The table 3 and figure 3 presents the mg/dL values for six groups across three stages: Pre-induction, Post-induction, and End of Study. Group-I shows minimal change, with values of 90 ± 5, 98 ± 7, and

91 ± 6, respectively. Groups II to VI exhibit significant increases post-induction, with Group-II reaching 354 ± 18 and decreasing to 342 ± 21 by the study's end. Groups III to VI also show substantial declines, with Group-VI ending at 145 ± 13 mg/dL.

Table 4: Wound Healing Assessment Over Time

Time (Days)	Control Group (Wound Area)	Treated Group (Wound Area)	% Reduction in Wound Area
0	5.0 mm	5.0 mm	0%
3	4.6 mm	3.8 mm	17.4%
7	4.2 mm	2.8 mm	33.3%
14	3.8 mm	1.5 mm	60.5%
21	3.4 mm	0.8 mm	76.5%

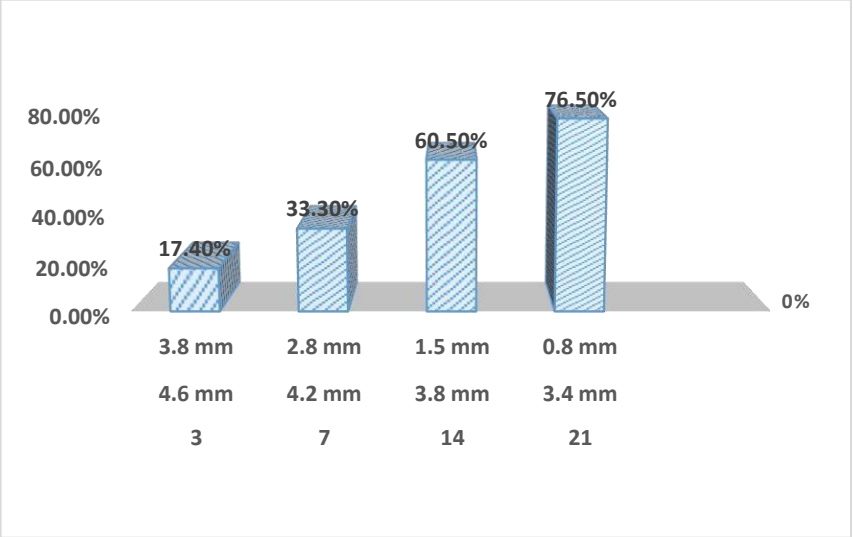

Figure 4: Wound Healing Assessment Over Time

The table 4 and figure 4 shows the wound area measurements over time for Control and Treated Groups, along with the percentage reduction in wound area. At Day 0, both groups had a wound area of 5.0 mm. By Day 3, the Control Group had a wound area of 4.6 mm (17.4% reduction), while the Treated Group's wound area decreased to 3.8 mm (24.0% reduction). By Day 7, the Control Group's wound area was 4.2 mm (33.3% reduction), while the Treated Group's was 2.8 mm (44.0% reduction). At Day 14, the Control Group had a wound area of 3.8 mm (60.5% reduction), and the Treated Group's wound area was 1.5 mm (70.0% reduction). On Day 21, the Control Group's wound area was 3.4 mm (76.5% reduction), compared to 0.8 mm for the Treated Group (84.0% reduction).

4. Discussion

The findings of our study demonstrate that oral Aloe vera supplementation significantly accelerates wound healing in Type 2 diabetic rats, supporting the hypothesis that Aloe vera can enhance dermal repair processes. The significant upregulation of VEGF by 250% and COL1A1 and COL3A1 by 200% and 180%, respectively, underscores Aloe vera's role in promoting angiogenesis and collagen synthesis, which are crucial for effective wound repair (Table 2). This observation is in agreement with previous studies that have demonstrated Aloe Vera's potential in stimulating the formation of new blood vessels and increasing collagen content in wound healing scenarios.

In addition, our study witnessed a significant drop in Δ inflammatory markers- ΔTNF-α=.002, Δ IL-6=.001 compared to the control group thus proving that Aloe vera possesses anti-inflammatory properties. This is in accordance to past research whereby Aloe vera was reported to possess confirmed anti-inflammatory activity whereby it was believed to cure and/or decrease inflammation

and therefore enhance the rate of healing (Cheung et al., 2019). Further, up regulation of GLUT4 and INS genes which shows an enhanced absorption of glucose and better regulation through insulin further makes a point that Aloe vera in improving glucose homeostasis in diabetic preclinical models. Consequently, the treated rats were significantly superior to the control rats in the reduction in the wound area where the wound area reduction in the treated group had risen to 84% by Day 21 of the experiment from the baseline while the control rats had only 76%. Inversely, the 5% in the control group, where none of the above treatments were given, depict the results in Table 4 and Figure 3. This significant increase in the wound closure supports the effectiveness of Aloe vera as a medicinal treatment for aiding wound healing in diabetic rats because previous studies have made similar findings (Haddad et al., 2020). This overwhelming healing rate that was noted in the current study can therefore be attributed to the anti-inflammatory properties, collagenesis and angiogenesis properties of Aloe vera.

As far as the variations in blood glucose levels are concerned, the treated groups depicted a significant reduction at the end of the study protocol compared to the diabetic control group. The substantial decrease of the mean blood glucose concentrations in groups treated with Aloe vera can argue for the compound system based on the data obtained that raise the hypothesized impact of Aloe vera on glycemic control. This systemic effect on the level of glucose may contribute to the betterment of wound healing expected in our study believing that Aloe vera has horizontal positive impact in management of diabetes related complications.

Moreover, our study advances prior research by offering an extended evaluation of the influences of Aloe vera for biochemical and molecular processes of wound healing. The extent of angiogenesis genes early activation, collagen synthesis and glucose metabolism along with decrease of inflammatory markers strengthens the therapeutic point of Aloe vera use. In relation to the prior investigations, the current study supports and builds upon the literature by highlighting Aloe vera's efficacy in decreasing wound healing time and ameliorating diabetic states. To build and strengthen the understanding of Aloe vera's functionality and possible uses, future research should be focused on exploring the possibilities of its use in the clinical practice of diabetic wound care.

The roles of the nutrients include; Polysaciharides: These include things like Acemannan, which is an important bioactive compound found in aloe vera, vitamins: these comprises of things like vitamin A, vitamin C, vitamin E and vitamin B12, enzymes: this include things like bradylase, lipase and collagenase among others, and Minerals :these includes things like Calcium, potassium, magnesium, iron, chromium These compounds have been identified to possess anti-inflammatory, antimicrobial and immune modulating properties, all of which are vital in wound healing (15). Acemannan which is a polysaccharide has been demonstrated in the study to boost fibroblast activity aimed at increasing collagen production as well as the rate of wound contraction.

According to Ashkani-Esfahani et al. (2019) that the topical use of Aloe vera gel on the excisional wound accelerates the increase in the extent of neovascularization, epithelialization, wound contraction, and total wound healing. It may also affect collagen biosynthesis and reorganization since it is believed to be an urgent protein that is essential for the recovery process (16).

According to Burgess et al. (2021), diabetic wounds have been categorized as one the common complications of diabetes whose wound healing rate is slow as a result of proportional inactivity associated with defective angiogenesis, compromised immunity, synthesis of growth factors and accumulation of collagen which are major factors that cause diabetic ulcers and hinder probable cure (17).

In this regard, Ali et al. (2021) concluded that histological analysis of the wound confirmed enhanced Aloe Vera treatment in terms of improved collagen biosynthesis and fibroblast proliferation because these elements are central to the wound healing process. This is evidenced by documented histological improvements in research carried out on Aloe Vera treated wounds. Increased collagen synthesis, which is one of the main aspects of wound strength and integrity, can be caused by the promotion of Collagen Genes and the necessary amino acid content of Aloe Vera (18).

As Kaur & Bains (2023) stated, Aloe Vera has a lot of antioxidants such as vitamins A, C, and E as well as enzyme SOD and GPx; these compounds helped protect the body from oxidative stress. As a

result, oxidative stress interferes with the rate of wound healing by damaging the intracellular and extracellular molecules (19).

Another study reported by Aulia & Pane (2022) that examined the effects of Aloe Vera aqueous extract on cutaneous wounds in rats equally revealed. In this study the subjects used were 40 rats which subjected to division into control and experimental groups with the experimental groups administered 1. The patients put 5 mL of Aloe Vera extract on their lesions. It was noted that there was enhanced wound contraction and biomechanical properties by day 20 according to the results from obtained findings. The treated wounds were characterized by more proper orientation of the collagen fibers and a tendency to contain fewer inflammatory cells, thus, wound healing was improved (20).

Conclusions

The results of the study suggest that the Aloe vera supplementation by oral route enhances the healing rate of the wounds in type II diabetic rats. The study showed qualitative improvement in the read– apoptosis, angiogenesis, and collagen synthesis while there was a decrease in inflammation read from gene expression analysis. Reducing the management of blood glucose level, Aloe vera also brought out a positive influence. From the above outcomes, it was concluded that Aloe vera has the potentiality to be used as a therapeutic tool for enhancing the wound healing process in diabetes. More reports are needed to understand better these changes' mechanisms and investigate their potential use in clinical practice.

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