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Healing Effects of Saroglitazar Gel in Thermally Induced Burn in Rats

Aram Ismaeel Ibraheem,[1] Hawkar Qadir Baiz,[2] Zheen Aorahman Ahmed,[3] Hemn Hassan Othman,[4] and Tavga Ahmed Aziz[3,*]

[1] *Department of Pharmaceutics, College of Pharmacy, University of Sulaimani, Sulaimani, Kurdistan Region, Iraq.*
[2] *Department of Clinical Pharmacy, College of Pharmacy, University of Sulaimani, Sulaimani, Kurdistan Region, Iraq.*
[3] *Department of Pharmacology and Toxicology, College of Pharmacy, University of Sulaimani, Sulaimani, Kurdistan Region, Iraq.*
[4] *Department of Basic Sciences, College of Pharmacy, University of Sulaimani, Sulaimani, Kurdistan Region, Iraq.*

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ABSTRACT

Background: Burn is associated with several consequences, including an increased incidence of infection, extended duration of hospitalization, and an increased mortality rate. Both PPARα and PPARβ are shown to play crucial roles in the keratinocyte response to skin damage.
Objectives: To evaluate the healing effects of saroglitazar (SAR) in thermally induced burns.
Materials and methods: Twenty male adult Wistar rats were allocated into four groups: Negative control, positive control, SAR treated, and silver sulfadiazine (SV) treated groups. The burn was induced thermally in all groups except the negative control, and the treatments started after the induction and continued daily for 21 days. Burn areas were measured on days 0, 7, 14, and 21. On day 21, the animals were euthanized and the blood samples were used to measure the complete blood count, hs-CRP, tumor necrosis factor-α (TNF-α), VCAM-1, and interleukin-10 (IL-10). Burned areas were sent for histopathological analysis.
Results: The burned areas significantly decreased after 14 days of treatment with SAR, and more significant attenuations occurred after 21 days, along with decreased VCAM level and significant attenuation of hs-CRP and TNF-α and nonsignificant elevation of IL-10. The histopathological findings support the biochemical findings and show remarkable improvements in skin regeneration and lesion scoring.
Conclusion: SAR has shown a notable burn-healing effect comparable to that of SV which could be attributed to its anti-inflammatory effects. This finding suggests SAR a candidate to be tested in a clinical setting.
Keywords: Saroglitazar; Burn induction; Anti-inflammatory effects; Local peroxisome proliferator-activated receptors.

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INTRODUCTION

Burns are often classified as injuries caused by exposure to external factors, including but not limited to elevated temperatures, electricity, friction, radiation, chemicals, and the subsequent local and systemic consequences [1]. Burn is associated with several consequences, including an increased incidence of infection, extended duration of hospitalization, and an increased mortality rate [2]. The injuries induced by burns are considered very detrimental since they have a profound impact on both the physical and physiological functioning of affected individuals [3]. Furthermore, burns have the potential to elicit psychological complications as a result of scarring, prolonged periods of hospitalization, and anatomical deformities [4].

* Corresponding author: E-mail: tavga.aziz@univsul.edu.iq

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Every kind of burn triggers a physiological reaction aimed at healing the wound, which involves three interconnected stages: Inflammation, proliferation, and remodeling [4, 5]. Hemostasis promptly ensues after an injury, facilitated by the activation, adhesion, and aggregation of platelets at the specific location of the damage [6]. Inflammation, as a subsequent phase of the wound healing process, initiates the activation of the innate immune response and its associated cellular components, therefore safeguarding the damaged region from potential infections [7]. Neutrophils, monocytes, and macrophages constitute the key cells throughout the inflammatory phase [6]. As a consequence of tissue damage, local keratinocytes secrete interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), which are crucial cytokines involved in the inflammatory process. These cytokines facilitate the recruitment and activation of leukocytes in the affected area, playing a significant role in coordinating various mechanisms involved in wound healing. With these facts, keratinocytes, macrophages, platelets, and endothelial cells within the affected area release a range of mediators, including growth factors such as epidermal growth factor (EGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), and transforming growth factor-beta (TGF-β), as well as cytokines such as IL-1β, interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), TNF-α, and interferon-gamma (IFN-γ). Additionally, chemokines are also released. These mediators play a crucial role in regulating subsequent mechanisms involved in the process of skin wound healing [8].

The inflammatory mechanism plays a crucial role in facilitating the proper and synchronized process of wound healing [9]. However, when inflammation becomes dysregulated, it may result in consequences such as the development of pathological scarring [10]. The persistence of chronic non-healing wounds may be attributed significantly to the presence of excessive inflammation [11]. Understanding the mechanisms behind the inflammatory response has the potential to facilitate the development of novel therapeutic interventions for wound repair and the mitigation of healing problems such as hypertrophic scars, keloids, chronic inflammation, skin infections, and non-healing lesions [9].

Immunomodulatory biomaterials, including bioactive substances such as anti-inflammatory medicines or growth factors, have emerged as potential strategies to enhance the wound healing process by facilitating the development of a pro-regenerative milieu [12].

Peroxisome proliferator-activated receptors (PPARs), a class of nuclear receptors, have shown involvement in the process of immunomodulation. PPARs function as transcription factors, which are activated by lipid-soluble ligands [13]. The expression of PPARs has been seen in the human epidermis. Specifically, it has been shown that PPARα is elevated during the inflammatory phase of wound healing [14]. PPARs play a crucial role in a wide range of biological processes in the epidermis, including the regulation of keratinocyte proliferation and differentiation, the maturation and restoration of the epidermal barrier, the modulation of sebocyte activity, and the differentiation of melanocytes. Furthermore, the comprehensive anti-inflammatory properties of these entities have been well characterized [15]. Both PPARα and PPARβ play crucial roles in the keratinocyte response to skin damage, according to a study of mouse models in which the activity of these two receptors was altered. Wound bed neutrophil and monocyte/macrophage recruitment are decreased in PPARα-null mice, and there is a transient delay in healing that occurs during the inflammatory phase [16]. PPARs may be interesting targets for the treatment of various epidermal disorders, including those characterized by inflammation. As such, the current study aims to determine the healing effect of saroglitazar, a dual PPAR-α and PPAR-γ agonist, in thermally induced burn wounds in rats.

MATERIALS AND METHODS

Animals

This is an experimental animal study. Twenty male adult Wistar rats, weighing 250–350 g, were gained from the animal house of the College of Pharmacy, University of Sulaimani, and were kept in plastic cages that were well-ventilated. The temperature in the room was maintained at 25 ± 2°C, and the humidity was kept at 55 ± 5%. The room had a 12-hour light-dark cycle. Free access to standard rodent food and tap water was provided. The animals had a one-week acclimation period prior to the study. The Guidelines for Animal Experimentation were followed during the experimental procedures and were granted approval by the Research and Ethics Committee of the University of Sulaimani, College of Pharmacy (Certificate number PH103-23 on 12th June 2023). The research was conducted in compliance with the 1998 recommendations of the Canadian Council on Animal Care (CCAC). The animals were arbitrarily allocated into four distinct groups each of 5 as follows:

1. Group 1 (G1): Negative control group (NC): Used as a control for the biochemical tests.
2. Group 2 (G2): Positive control group (PC): Induction of burn injury was done in this group, and received no treatment.
3. Group 3 (G3): Saroglitazar (SAR) treated group: Received 1 ml of saroglitazar gel (0.1%) topically from the start of burn induction.
4. Group 4 (G4): Silver-sulfadiazine group (SV): Received silver-sulfadiazine cream (Silvderma 1% cream, ALDO-UNIÓN, Spain)

The duration of the study was two months (from 1st of September to 1st of November 2023). All the treatments were received topically from the start of burn induction (at the same day) in the morning till 21 days, then euthanized on day 21 post-burn injury induction.

Induction of burn injury

The rats were anesthetized by administering ketamine (50 mg/kg) and xylazine (5 mg/kg) intraperitoneally to induce a burn wound. Following the removal of back hair using a blade and disinfection with 70% alcohol, a deep second-degree burn was intentionally induced using a heated metal bar measuring 2×2 cm. The bar was heated to a temperature of 105°C for a duration of 15 seconds. The burn area covered approximately 4 cm^2 and was caused by applying the heated bar for 5 seconds without exerting pressure. Subsequently, daily therapy with different materials started till the end of the experiment.

Preparation of saroglitazar 0.1% gel

The following chemicals were utilized in the preparation of the gel: SAR powder, carbopol 940, ethanol, propylene glycol, and triethanolamine.

A sufficient amount of carbopol 940 powder was dissolved in distilled water to form a 1% carbopol 940 hydrogel. The

hydrogel was then left for a few days to enable the polymer to swell. Subsequently, a solution of SAR was prepared using ethanol at a concentration of 0.1%. The medication solution and the hydrogel were mixed using a magnetic stirrer. To achieve a neutral pH, an adequate quantity of triethanolamine was added to the mixture. Additionally, propylene glycol (10%) was used to enhance drug permeability and act as a preservative for the gel [17].

Evaluation of the prepared hydrogel

Homogeneity

The prepared hydrogel gel was visually inspected to ensure homogeneity.

Grittiness

The prepared hydrogel was examined under a light microscope to evaluate the presence of particulate matter.

Measurement of pH

Using the MAAN Medical & Laboratory pH meter, the pH of the prepared gel was determined. The pH of the hydrogel was 6.83.

Gel viscosity measurement

The Fungil Lab Visco Basic Plus viscometer was used to determine the hydrogel's viscosity. The viscosity was measured at 25°C and found to be 3964 mpa.s using the R5 spindle at 100 rpm.

Gel spreadability

The method used to assess the gel's spreadability was as follows: 0.5 g gel was placed on a glass plate and spread in a circle of 2 cm diameter. A second glass plate was placed on top, The upper glass plate was given a 500 g weight to rest on for five minutes. It was observed that the diameter had increased as a result of the gels spreading.

The spread ability of the gel was calculated using the following formula:

% Spread by area = A2/A1× 100

where, A1= 2 cm, and A2 = Final area after spreading. The result of the spread ability of the hydrogel was 280%.

Biochemical parameters and assessment of burn area

On day 21, the animals were euthanized and blood samples were collected by cardiac puncture and the burned skins were sent for histopathological examinations. The blood samples were used for measuring complete blood count (CBC), hs-CRP, TNF-α, VCAM-1, and IL-10. ImageJ software (NIH, USA) was used to measure the burn area and expressed as cm^2. Burn contraction was calculated using the following equation:

Percentage of burn contraction = (Initial wound burn size – specific day wound size)/Initial wound burn size × 100.

Histopathological protocol

Generally speaking, the staining procedure was performed using Harris's hematoxylin and eosin method in histotechnique. Animals were euthanized in a humane rehearsal at the end of the experimental period, and the skin wound patches were isolated and processed for histological preparation. In the beginning, skin samples were placed into tissue cassettes and fixed in a 10% formaldehyde solution for at least 72 hours. Then, tissue sections were set for the processing scheme, starting with the dehydration step by passing through ascending concentrations of ethanol, followed by two-step cleaning with xylene. After that, processed tissues were fixed and embedded in melted paraffin blocks at (60-70 °C) using a tissue embedder. Following that, the fixed-tissue paraffin blocks were trimmed and sectioned to 5 µm using a semi-automated rotary microtome. Later on, sections will be mounted on glass slides and dried using a hot plate tissue dryer. Afterward, the glass slide with the fixed skin sections was deparaffinized from excess paraffin debris and then cleaned for the last time with xylene solution for 20 to 30 minutes and oven-dried for 10 minutes. At the end of the protocol, the sections were stained with Harris's hematoxylin and eosin solutions then cleaned as a final step in xylene and covered with glass or plastic coverslip using DPX.

Semi-quantitative histological evaluation of skin tissues

Tissue samples were analyzed under the light microscope (NOVEL XSZ-N107, China) by the means of image-snap analyzer software (AmScope Ver. 3.7) using a microscope digital camera (MU300, 2019). Morphometric semi-quantitative measures of skin wound sections from each animal were evaluated and measured in µm and statistically analyzed as mean percentage of the obtained values. Briefly, the area of granulation tissue distribution, proliferated collagen fibers, newly formed blood vessels (angiogenesis), inflammatory exudates, and epidermal re-epithelization thickness were estimated in µm via image analyzer software programmed, then semi-quantitatively measured in mean percentage. The mean percentage of calculated values were assessed as following lesion scores (score > 75% as mild lesion; score 50-75% as moderate lesion; score between < 50% or 10-50 as severe lesion). On the other hand, normal skin patches that are sent to histopathology assay, score < 10% as no lesion (Table 2).

Statistical Analysis

GraphPad Prism8 was used for the statistical analysis. Data are presented as the mean ± standard deviation (SD). A one-way ANOVA was used for the comparisons between different groups, followed by Tukey's test to compare each group with the positive control group. The level of significance was set up at a P-value < 0.05.

RESULTS

Effect of saroglitazar on burn area and burn contraction in thermally induced burns in rats

On the first day of burn induction, there was a significant increase in the burned area in both SAR and SV groups when compared to the PC group, (P-value = 0.01) and (P-value = 0.02) respectively. However, after 7 days of burn induction, there were no significant differences between the groups, (P-value > 0.05). After 14 days of treatment SAR group showed a significant attenuation of the burned area compared with the PC group (P-value = 0.04). No significant change was noted with the SV group (P-value > 0.05). Moreover, a significant reduction in the lesion and burn area after 21 days of induction was observed in both SAR and SV groups, (P-value = 0.004) and (P-value = 0.003) respectively, when compared to the PC group (Figure 1 A-D). Table 1 shows the effect of

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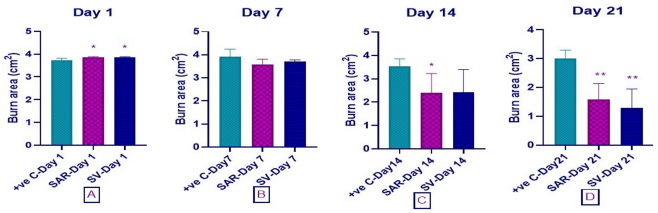

Figure 1. Effect of saroglitazar (SAR) on burn area in thermally induced burn in rats. Values presented as mean ± SD, * (P-value < 0.05), and ** (P-value < 0.01) were significantly different compared to the positive control (+ve C) group using one-way ANOVA. SV = Silver sulfadiazine, +C = Positive control.

Table 1. Effect of saroglitazar on burn contraction at different time intervals*.

Day	Burn Contraction %		
	Positive Control N = 5	Silver sulfadiazine N = 5	Saroglitazar N = 5
7	4.5[a]	2.9[b]	7.6[c]
14	12.6[a]	38[b]	27.23[c]
21	21.1[a]	72[b]	59[c]

* Values presented as percentages; N: Number of animals; different letters significantly different from the positive control group in each group (paired t-test, P-value < 0.05).

the treatment groups on the percentage of burn contraction. A significant increase in burn contraction percentage in the SAR group was observed on days 7 (7.6%), 14 (27.23%), and 21 (59%). The results were comparable to those produced by the SV group on days 7 (2.9%), 14 (38%), and 21 (72%). These results significantly (P-value < 0.05) differed from the PC group, days 7 (4.5%), 14 (12.6%), and 21 (21.1%).

Effect of saroglitazar on inflammatory markers, hematological ratios and markers in thermally induced burn in rats

There was a significant reduction in the level of hs-CRP in the NC group when compared to the PC group, (P-value = 0.03). Both SAR and SV resulted in more significant attenuation in comparison to the PC group (P-value = 0.012) and (P-value = 0.014) respectively (Figure 2 A). TNF-α was significantly declined in the NC group when compared to the PC group (P-value = 0.0007), and both SAR and SV groups also ameliorated the level of TNF-α significantly in comparison with the PC group, (P-value = 0.05) and (P-value = 0.028) respectively (Figure 2 B). Regarding VCAM-1 level, there was a significant increase in the PC group when compared to NC group (P-value = 0.026), and only the SV treated group significantly (P-value = 0.009) attenuated the level in comparison with the PC group (Figure 2 C). The anti-inflammatory marker IL-10 significantly declined in the PC group when compared to the NC group (P-value = 0.027), however, none of the treatment groups produced significant changes (Figure 2 D).

No significant changes were seen in the platelets to lymphocyte ratio in any of the treatment groups (P-value > 0.05), (Figure 3 A). Meanwhile, a significant decrease was seen in

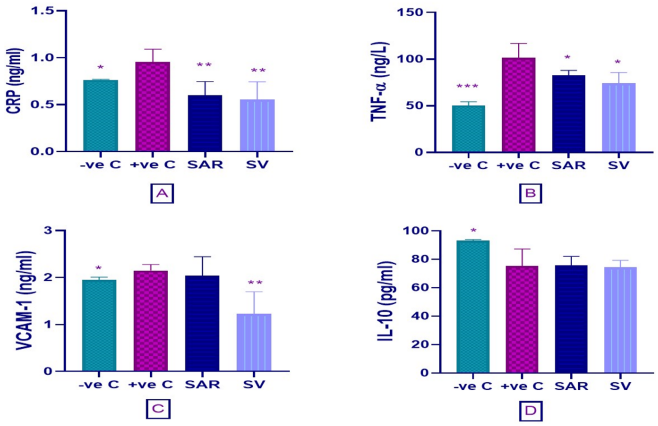

Figure 2. Effect of saroglitazar (SAR) on inflammatory markers, in thermally induced burn in rats. Values presented as mean ± SD, * (P-value < 0.05), ** (P-value < 0.01), *** (P-value < 0.001) were significantly different compared to the positive control (+ve C) group using one-way ANOVA. SV = Silver sulfadiazine.

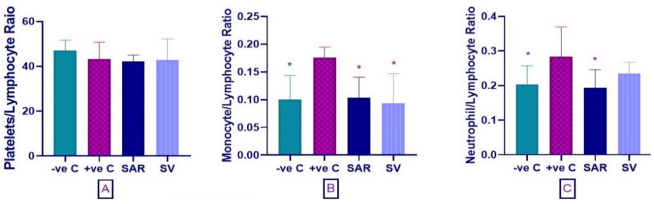

Figure 3. Effect of saroglitazar (SAR) on hematological ratios, in thermally induced burn in rats. Values presented as mean ± SD, * (P-value < 0.05), ** (P-value < 0.01), *** (P-value < 0.001) were significantly different compared to the positive control (+ve C) group using one-way ANOVA. SV = Silver sulfadiazine.

each of the treatment groups when compared to the PC group in the monocyte-to-lymphocyte ratios (P-value = 0.017), (P-value = 0.012) and (P-value = 0.02) respectively (Figure 3 B). However, only the NC and SAR groups were able to attenuate the neutrophil to lymphocyte ratio in comparison with the PC group (P-value = 0.048) and (P-value = 0.049) respectively (Figure 3 C).

Regarding the levels of WBC, RBC, platelets, Hg, and HCT%; no significant changes were observed in each of the treatment groups except for the NC group, which showed a significant increase in RBC level, (P-value = 0.005), and a decrease in HCT%, (P-value < 0.0002), in comparison with PC group (Figure. 4 A-E).

Histopathology

Generally speaking, all three experimental groups at the end of the experiment (day 21) demonstrated significant advancement in the healing processes, manifested by a considerable amount of subepidermal granulation tissue distribution together with a heavy and clear proliferation of dermal collagenous fibers mixed with many regenerative dermal follicles (Figure 5). Yet, according to the lesion scoring system as shown in Table 2, topical application of 0.1% SAR gel proved to exert a clear healing approach compared to the PC

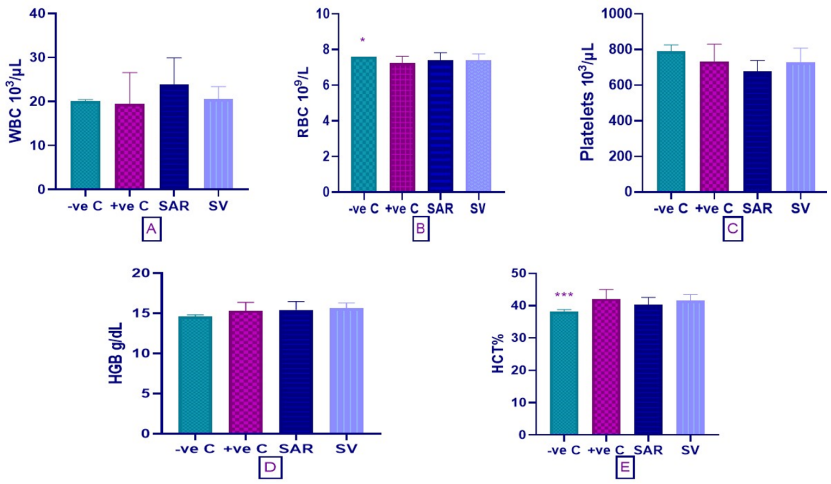

Figure 4. Effect of saroglitazar (SAR) on hematological markers, in thermally induced burn in rats. Values presented as mean ± SD, * (P-value < 0.05), ** (P-value < 0.01), *** (P-value < 0.001) were significantly different compared to the positive control (+ve C) group using one-way ANOVA. SV = Silver sulfadiazine.

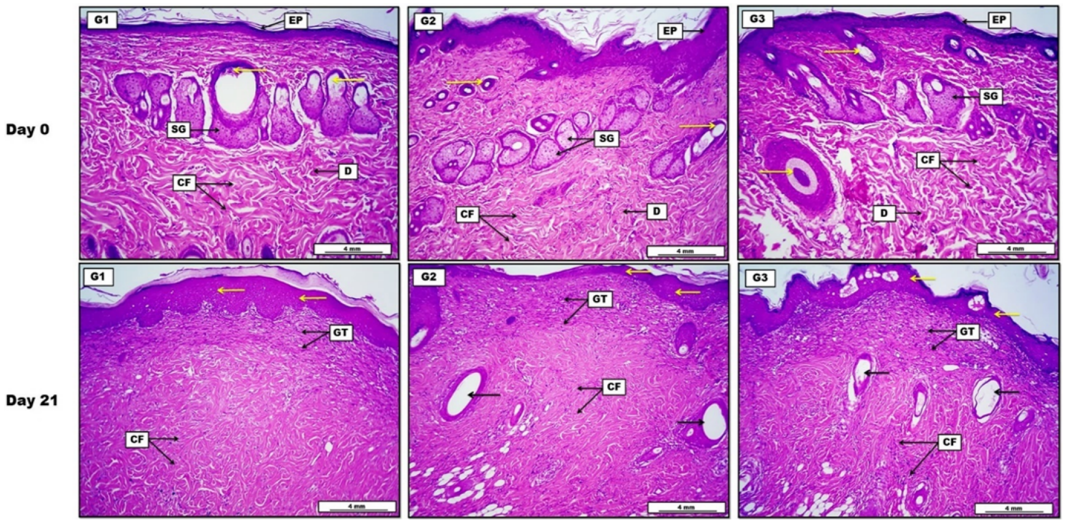

Figure 5. Photomicrograph of skin from groups; G1: PC group (5 rats): Burn wound with no treatment. G2: SAR treatment group (5 rats): Burn wound received treatment with 0.1% gel topically. G3: SV treatment group (5 rats): Burn wound received treatment with 1% SV cream to. picallyIn different time intervals; (Day 0 and 21). Day 0: Skin samples in all groups seem typical with no morphological changes in the epidermal squamous layers (EP). Ordinarily distributed hair follicles (yellow arrows) and sebaceous glands (SG) in the given section, together with distinctive dissemination of dermal (D) collagen fibers (CF). Day 21: Skin patches in all experimental groups demonstrate considerable deposition of granulation tissue together with collagenous proliferation, as follows, samples in G1 reveal clear epidermal regeneration with keratin deposition (yellow arrows), along with acidophilic collagenous proliferation (CF) in the dermal layers, moreover, subepidermal layer shows significant deposition of granulation tissue. G2 Skin samples on the 21st day of treatment display profound subepidermal distribution of granulation tissue (GT) interwoven with CF, with the presence of newly regenerated hair follicles (black arrows). Additionally, the sections pictured significant regeneration of epidermal epithelial tissue (yellow arrows). Finally, dermal samples in G3 determine significant redistribution of dermal hair follicles (black arrows) together with many SG, besides a clear re-epithelization of the epidermis with keratin deposition (yellow arrows). The section also reveals visible areas of collagenous distribution and subepidermal GT deposition interlaced with angiogenic tissue. H&E. Scale bars: 4 mm.

group. On the other hand, treatment with standard 1% SV cream demonstrated the same typical healing effect as the SAR group with no significant differences in their curative efficiency in the remediation of thermal wounds.

DISCUSSION

The vital involvement of both PPARα and PPARβ in the keratinocyte response to skin damage rendered SAR an interesting candidate to be evaluated for wound healing activity. To the best of our knowledge, this is the first time

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Table 2. Histological semi quantitative assay of skin wound with different treatment approach*.

Experimental Groups N=12	Granulation Tissue Formation* (Mean%)**	Area of Angiogenesis* (Mean%)**	Collagen Fibers Proliferation* (Mean%)**	Skin Epidermal regeneration* (Mean%)**	Lesion Scoring (0 -100%)	Lesion Grading
			Day 0			
(G1) PCG†	4.12 % ^{A}	4.72 % ^{A}	5.28 % ^{A}	4.61 % ^{A}	0-10 %	No lesion
(G2) SAR 0.1%	4.56 % ^{A}	5.32 % ^{A}	5.79 % ^{A}	3.45 % ^{A}	0-10 %	No lesion
(G3) SV 1%	2.31 % ^{A}	5.68 % ^{A}	4.63 % ^{A}	3.15 % ^{A}	0-10 %	No lesion
			Day 21			
(G1) PCG†	76.63 % ^{D}	77.49 % ^{D}	82.78 % ^{D}	81.43% ^{D}	75-100 %	Mild
(G2) SAR 0.1%	80.55 % ^{D}	74.28 % ^{D}	86.41 % ^{D}	76.29 % ^{D}	75-100 %	Mild
(G3) SV 1%	79.26 % ^{D}	73.81 % ^{D}	87.29 % ^{D}	82.36 % ^{D}	75-100 %	Mild

* Area of granulation tissue formation, angiogenesis, collagen fibers proliferation, inflammatory exudates, and skin epidermal regeneration were estimated in µm of the given section. **Each value represents the mean percentage of n = 12. Statistical comparison among groups: Mean values with different capital letters have significant differences at (P-value < 0.05). †: G1: Positive control group: Burn wound with no treatment. G2: Saroglitazar (SAR) treatment group: burn wound received topical treatment with 0.1% SAR gel. G3: Silver-sulfadiazine (SV) cream treatment group: Burn wound received topical treatment with 1% SV cream.

SAR is used as a topical formulation in the treatment of burns and the results are promising and shed light on its potential therapeutic effects. Regarding the burn area, the findings revealed dynamic changes in the burn area over 21 days, demonstrating the efficacy of SAR in attenuating burn-induced damage. SAR treatment significantly attenuated the burn area at days 14 and 21 post-burn, indicating its potential to promote wound healing and accelerate tissue repair in burn injuries. This observation aligns with previous studies demonstrating the role of PPAR agonists in regulating cellular processes crucial for wound healing [18, 19]. Activation of these PPAR receptors by SAR may have contributed to the observed beneficial effects on burn area, as it has been observed that macrophage PPARγ deficiency leads to impaired skin wound healing, with reduced collagen deposition, angiogenesis, and granulation formation [18].

Evidence suggests that both PPARα and PPARγ play an important role in inflammatory skin disorders and that PPAR agonists could be promising for treating these conditions [20]. Inflammation is a key factor in both the progression and healing of wounds. Simultaneously, the levels of inflammatory mediators generated by the infiltrating inflammatory cells rise after an injury and subsequently decline as the healing processes advance.

In the current study, SAR demonstrated a notable reduction in hs-CRP levels compared to the PC group, signifying its anti-inflammatory properties. Similarly, the attenuation of TNF-α levels in both SAR and SV groups indicates a potential suppression of pro-inflammatory pathways. SAR had no significant effect on VCAM-1, this suggests that activation of PPARα and PPARγ may regulate different pathways in the inflammatory cascade. In addition, IL-10, an anti-inflammatory marker, did not show significant changes with SAR treatment. This could suggest that SAR may primarily exert its effects by suppressing pro-inflammatory pathways rather than directly enhancing anti-inflammatory responses. Overall, this study confirms that SAR possesses anti-inflammatory properties. Numerous previous studies have also shown that PPAR agonists have anti-inflammatory properties, Paukkeri et al. [21] showed that dual PPAR $\alpha/gamma$ agonist muraglitazar has several anti-inflammatory effects in activated macrophages and carrageenan-induced inflammation in the mouse. Another study [19] Showed that PPAR-γ agonists reverse the pro-inflammatory effects of a diabetic wound environment. Koufany et al. [22] and Sener et al. [23] found that the thiazolidinediones rosiglitazone and pioglitazone decreased the levels of TNFα, IL-1β, and basic fibroblast growth factor in the synovial tissue. They also observed a reduction in the clinical symptoms of synovitis in rats with Freund's adjuvant-induced arthritis.

Hematological analyses revealed intriguing insights into the effects of SAR on various blood parameters. The decrease in the monocyte-to-lymphocyte ratio in the SAR group suggests a potential role of SAR in modulating immune cell dynamics. High monocyte and low lymphocyte counts are used as markers of inflammation and have been used as poor prognostic markers in several conditions including, lymphoma [24], peripheral artery occlusion [25], and as a predictor of diabetic kidney injury in diabetic subjects [26]. The ability of SAR to attenuate the neutrophil-to-lymphocyte ratio further supports the anti-inflammatory potential of SAR, because the neutrophil-to-lymphocyte ratio may be an emerging marker of the relationships between the immune system and diseases [27] and may serve as an early warning of pathological states or processes such as cancer, atherosclerosis, infection, inflammation, psychiatric disorders, and stress [28] Notably, the lack of significant changes in the platelets-to-lymphocyte ratio indicates a specific modulation of certain immune cell populations without affecting platelet dynamics. Furthermore, the histopathological findings in both groups treated with SAR and SV demonstrated a clear healing capacity.

The main limitation of the current study is the small sample size, which prevented the animals from being sacrificed on days 7 and 14 for better comparison in the biochemical parameters and histopathological examination. Additionally, measuring the lesion area using the skin halted the use of the burned skin to prepare tissue homogenate for measuring some specific markers in the tissue, such as the levels of antioxidant enzymes.

CONCLUSION

Local application of 0.1% SAR gel showed a remarkable lesion-healing capacity that manifested by attenuating lesion

area, inflammatory markers, and increasing burn contraction. The histopathological findings greatly support the biochemical results by producing a pronounced amelioration in lesion grading and scoring and enhancing skin regenerations, granulation formation, angiogenesis, and collagen production. This finding may suggest topical use of SVR in the clinical setting.

ETHICAL DECLARATIONS

Acknowledgments

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Ethics Approval and Consent to Participate

The study was approved by the Research and Ethics Committee of the University of Sulaimani, College of Pharmacy (Certificate number PH103-23 on 12th June 2023). The consent to participate is not applicable.

Consent for Publication

Not applicable (no individual personal data included).

Availability of Data and Material

The data of the current study are available from the corresponding author upon reasonable requested.

Competing Interests

The authors declare that there is no conflict of interest.

Funding

No funding.

Authors' Contributions

All of the listed authors significantly, directly, and intellectually contributed to the work and consented to its publication.

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