

Comparative evaluation of wound healing with different treatments in rats: Cytokine modulation, histological remodeling, and scar outcomes

Nino Kuridze¹, Sophio Giorgadze², Luiza Gabunia¹, Ketevan Ghambashidze³, Nodar Sulashvili⁴, Tamar Didbaridze⁵, Nino Gvajaia^{6*}, Vasil Kupradze⁶, Levan Ratiani⁷

1. Department of Clinical Pharmacology, Tbilisi State Medical University, Georgia
2. Department of Histology, Cytology, and Embryology, Tbilisi State Medical University, Georgia
3. Department of Pathophysiology, Tbilisi State Medical University, Georgia
4. Scientific Research-Skills Center, Tbilisi State Medical University, Georgia
5. Department of Microbiology, Tbilisi State Medical University, Georgia
6. Department of Medicine, Tbilisi State Medical University, Georgia
7. Department of Anesthesiology, The First University Clinic of Tbilisi State Medical University, Georgia

ABSTRACT

Background: Skin injury repair depends on a tightly regulated sequence of inflammation, proliferation, and matrix remodeling, where mediators such as IL-1 and IL-6 contribute to immune activation and extracellular matrix formation. Variability in cytokine control influences scar maturation, prompting exploration of treatment strategies capable of shortening the inflammatory phase and enhancing structural regeneration.

Methods: This study compared four wound-care approaches in rats with surgically induced full-thickness lesions: a polysilicon-siloxane formulation (PS), a silicone-based gel (Sil), a betamethasone preparation (BMt), and a heparin-containing agent (Hep). Topical formulations were applied two to three times daily, while BMt was delivered weekly by subcutaneous injection. Serum IL-1 and IL-6 concentrations were quantified by ELISA, scar evolution was documented using the Vancouver Scar Scale, and tissue organization was examined through histological staining protocols, including trichrome-based collagen visualization and elastic fiber assessment.

Results: Early cytokine elevation was evident across groups, with IL-1 returning to near-baseline most rapidly in PS- and Sil-treated animals by day 21, and one week later in BMt-treated rats. Hep and untreated controls maintained higher values for longer. IL-6 peaked later than IL-1, normalizing by day 28 in the PS, Sil, and BMt groups alone. Microscopy demonstrated faster vascular normalization and earlier collagen and elastic-fiber restoration with PS, followed by Sil and BMt, while Hep improved matrix architecture only during later stages.

Conclusions: Overall, PS produced the most favorable and accelerated recovery pattern, Sil and BMt provided moderate benefit, and Hep displayed slower reparative capacity.

Keywords: collagen, fibroblast, interleukin-1 (IL-1), interleukin-6 (IL-6), skin wound healing

Received: 9 December 2025; Accepted: 16 February 2026; Published: 9 March 2026.

INTRODUCTION

Skin forms the first line of defense between the body and the external environment, shielding deeper tissues from physical, chemical, and microbial threats while maintaining hydration, thermoregulation, and electrolyte stability [1-3].

Disruption of this barrier through trauma, burns, lacerations, or surgical injury initiates a cascade of biological events aimed at restoring tissue continuity [4]. Efficient repair is essential not only for preventing infection and fluid loss, but also for limiting long-term functional and

cosmetic impairment, making the biology of wound closure a topic of considerable clinical relevance [5].

Cutaneous healing unfolds through sequential yet overlapping phases. Initially, coagulation prevents further bleeding and seals the wound surface. This is followed by inflammatory activation, during which innate immune cells migrate into the damaged area. Subsequent proliferative activity promotes fibroblast expansion, extracellular matrix accumulation, angiogenesis, and re-epithelialization, while the final remodeling stage reshapes collagen architecture and gradually increases tensile strength [6-10].

* Corresponding author: Nino Gvajaia, Department of Medicine, Tbilisi State Medical University, Georgia. E-mail: ninogvajaia1@gmail.com

Cytokine signaling plays a decisive role in regulating these events. Interleukin-1 is a key initiator of early inflammatory responses, whereas interleukin-6 influences both acute-phase protein synthesis and later matrix formation. Fibroblasts, collagen fibers, and elastic components are central to achieving structurally resilient tissue; however, if cytokine activity or matrix deposition becomes dysregulated, healing may stall or progress toward hypertrophic or keloidal scarring [11-13].

Supportive clinical management plays a decisive role in the outcome of tissue repair. Core therapeutic principles involve removing nonviable tissue, reducing microbial burden, preserving adequate hydration at the wound surface, and selecting dressings that encourage granulation and re-epithelialization [14-16]. In more extensive or slow-healing injuries, clinicians may employ supplementary modalities such as vacuum-assisted closure systems, hyperbaric oxygen exposure, or engineered biological scaffolds designed to promote vascularization and matrix replacement [17-23].

Given the impact of inflammation on the quality and speed of tissue restoration, this work compares polysilicon-siloxane, silicone-based, betamethasone, and heparin-containing treatments to determine how each influences cytokine trends and tissue organization in experimental full-thickness wounds.

METHODS

Approval for animal use was granted by the Tbilisi State Medical University Animal Welfare and Ethics Committee (Protocol No. N59.30.11.22; issued 10 June 2024). Adult male laboratory rats, with an age range of 6–8 weeks (weighing 200-250 g), were used for the study. Animals were obtained from the Aleksandre Natishvili Institute of Morphology, Tbilisi, Georgia.

All experimental rats were under one-week stabilization (acclimatization) period to ensure physiological baseline stability before procedures began. They were maintained in a temperature-controlled environment at $23\pm 2^{\circ}\text{C}$, 12-hour light/12-hour dark cycle and had unrestricted access to standard laboratory chow and water.

To induce full-thickness wounds, rats were anesthetized with Nembutal (50 mg/kg). The fur over the dorsal region was clipped, the skin surface disinfected with 70% ethanol, and circular excisional lesions were created aseptically. A continuous suture line, approx. 5 cm in length and spaced at 1 cm intervals, was then applied along the wound area.

Post-Wound Induction animals were housed individually in standard polycarbonate cages to prevent wound interference by cage mates and ensure aseptic recovery, minimize social stress that could confound healing data, while maintaining the same environmental temperature and light cycle used during the stabilization period.

Wound treatment

Sixty rats were randomly allocated into six experimental groups. Each group consisted of 10 animals, as follows: Group 1 - healthy, uninjured baseline control; Group 2 - wounded but untreated controls; Group 3 - PS-treated animals; Group 4 - Sil-treated animals; Group 5 - BMt-treated animals; Group 6 - Hep-treated animals.

Topical formulations were administered directly to the wound bed two to three times daily for four weeks. The PS preparation contained polysilicon-siloxane with vitamin C ester; the Sil gel consisted of silicone combined with hypochlorous acid and sodium hypochlorite; and the Hep agent contained onion extract, heparin, and allantoin. Betamethasone (BMt) was delivered separately via weekly subcutaneous injection into the lesion area at a dose of 0.2 mL.

Systemic inflammation assessment

Systemic inflammatory markers (IL-1 and IL-6) were quantified by ELISA using the Kit (REF: E-EL-H0088; Elabscience®, USA). The results were recorded on a Human HS ELISA Reader (Germany). The analytical measuring range for IL-1 α was 1.25 to 250.0 pg/mL. Serum IL-6 levels were determined using the test Kit (Immunofluorescence Assay) REF: IF1088; Getein Biotech, Inc., China; European Representative: Lotus NL B.V., Netherlands. The quantification was performed using a Getein 1100 Immunofluorescence Quantitative Analyzer. The analytical measuring range for IL-6 was 1.5 pg/mL to 4000.0 pg/mL.

The blood was collected between 9:00 AM and 11:00 AM from the lateral tail vein of the rats into sterile tubes. To ensure optimal vasodilation, animals were placed in a warming chamber at 38°C for 10 minutes prior to the procedure. Following stabilization in a standard plastic restrainer, the tail was disinfected with 70% ethanol. Venipuncture was performed using a 25-gauge needle inserted into the lateral tail vein at a 20° angle. Blood samples (approximately 1.0 mL) were collected without anticoagulant, allowed to clot at room temperature, and centrifuged at 3,000 rpm for 15 minutes at 4°C to obtain serum for cytokine ELISA analysis. Blood collection occurred on days 7, 14, 21, and 28 to track changes in cytokine expression throughout healing.

Scar assessment

Scar morphology was evaluated using the Vancouver Scar Scale, which assesses four parameters: vascularization (0–3), pigmentation (0–2), pliability (0–5), and elevation (0–3 mm). Individual parameter values were summed to produce a total score ranging from 0 (normal skin) to 13 (most severe scarring). This scale is widely used clinically and in research to monitor scar development over time [24-26].

Tissue processing and staining overview

Wound-site samples were collected at designated time points to examine vascular maturation, extracellular matrix deposition, fibroblast presence, and elastic fiber architecture. Multiple histological approaches were utilized, such as Masson's trichrome, Van Gieson, Weigert's elastic stain, and routine hematoxylin–eosin.

Hematoxylin–eosin (H&E) staining

Samples were fixed in 10% neutral buffered formalin for 24–48 hours at room temperature to preserve tissue architecture. Following fixation, tissues were processed using standard histological procedures, including graded alcohol dehydration, xylene clearing, and paraffin embedding. Paraffin blocks were sectioned at a thickness of 4–5 μm using a rotary microtome. Sections were mounted onto glass slides and dried prior to staining.

Paraffin sections were deparaffinized in xylene and rehydrated through a descending series of ethanol concentrations to distilled water. Sections were stained with hematoxylin to visualize cell nuclei, followed by thorough rinsing under running tap water. Differentiation and bluing were performed as required to enhance nuclear contrast. Subsequently, sections were counterstained with eosin to delineate cytoplasmic components and extracellular matrix structures. After staining, slides were dehydrated through ascending ethanol concentrations, cleared in xylene, and mounted with a permanent mounting medium.

Masson's trichrome for collagen visualization

Paraffin-embedded slides were sequentially deparaffinized in xylene and rehydrated through descending alcohol concentrations. Bouin's solution was used for mordant fixation (1 hour at 56°C or overnight at room temperature). After thorough rinsing, nuclei were stained with Weigert's hematoxylin, followed by cytoplasmic staining using Biebrich scarlet–acid fuchsin. Differentiation was carried out in phosphomolybdic–phosphotungstic acid, after which collagen fibers were selectively colored using aniline blue. Final steps included an acetic acid rinse, dehydration, clearing in xylene, and coverslip mounting in a permanent medium.

Van Gieson staining for collagen and muscle fibers

Paraffin-embedded tissues were deparaffinized, passed through a descending alcohol series, and subsequently placed into Van Gieson solution for five minutes to differentiate collagen from muscle fibers. Following staining, slides were dehydrated in 95–100% ethanol, cleared with xylene, and mounted for microscopic evaluation.

Weigert's resorcin–fuchsin for elastic fibers

Sections were prepared by standard deparaffinization and hydration, then immersed in Weigert's resorcin–fuchsin reagent for 10–30 minutes. After rinsing, selec-

tive differentiation was achieved in 70% ethanol containing ferric chloride until elastic fiber networks became distinct. Hematoxylin was used as a nuclear counterstain. Prepared slides were dehydrated, xylene-cleared, and mounted in a permanent medium.

Statistical Analysis

All quantitative data were analyzed using two-way repeated-measures ANOVA to assess the effects of treatment, time, and their interaction on pro-inflammatory cytokine levels (IL-1 and IL-6). When significant main or interaction effects were identified, Tukey's multiple comparisons test was applied as a post-hoc analysis to compare experimental groups at individual time points.

Data are expressed as mean $\pm$ standard deviation (SD). Statistical significance was defined as $p < 0.05$. All analyses were conducted using standard statistical software packages appropriate for biomedical research [27].

RESULTS

The healing response was evaluated through inflammatory cytokines, microscopic tissue characteristics, and Vancouver Scar Scale (VSS) scores over 7, 14, 21 and 28 days. Treatment outcomes for PS, Sil, BMt and Hep preparations were compared against untreated controls.

On day 7, serum IL-1 concentrations showed a marked increase across all groups compared to pre-injury levels (Day 0). In the untreated control group, IL-1 levels peaked at 73% above the baseline (Day 0). In contrast, the PS and Sil groups demonstrated significantly higher peaks (100% and 106%). The BMt and Sil groups also demonstrated high levels of IL-1 (85% and 74%) above the baseline (Day 0).

By day 14, values declined in PS, Sil and BMt groups, but they were still high above the baseline by 47%, 49% and 73%, respectively. In contrast, Control and Hep data were even slightly increased. Differences in all groups were statistically significant.

By day 21, IL-1 levels in all groups were above the baseline values, whereas the Control, Hep and BMt groups remained 56%, 55% and 40% higher than baseline, respectively ($p < 0.05$).

By day 28, IL-1 had returned to baseline in PS, Sil and BMt groups, whereas elevated values persisted under Control and Hep treatment (IL-1 concentration profiles illustrated in Figure 1).

At day 7, the serum IL-6 levels were significantly increased over baseline only in the untreated control, PS and Sil groups. IL-6 levels remained significantly elevated through day 14 in all groups (by 26%, 42%, 32%, 14% and 13%, respectively).

By day 21, IL-6 had returned to baseline only in the PS group. By day 28, IL-6 level was above the baseline in control and Hep groups, and IL-6 concentrations in PS, Sil and BMt were within the normal range.

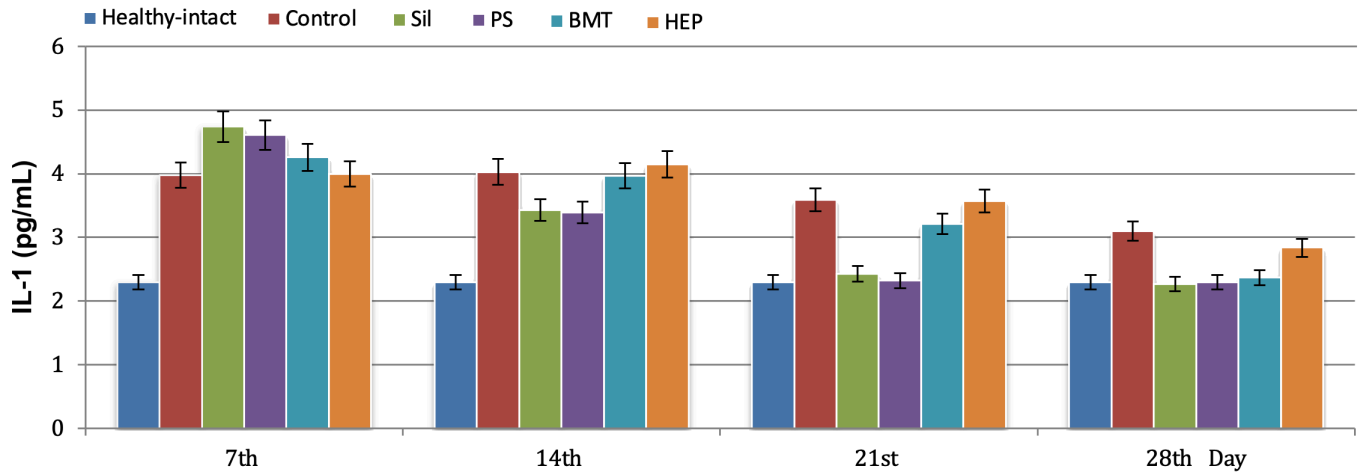


Figure 1. Concentrations of IL-1 in healthy, control, and treated rats across the duration of the study

Table 1. Concentrations of IL-1 (pg/mL) in healthy, control and treated rats

Treatment group	Day 7	Day 14	Day 21	Day 28
Healthy (uninjured)	2.30 ± 0.38	2.30 ± 0.38	2.30 ± 0.38	2.30 ± 0.38
Control (wounded and untreated)	3.98 ± 0.34*	4.03 ± 0.41*	3.59 ± 0.37*	3.10 ± 0.28*
PS-based preparation treatment	4.61 ± 0.53*	3.39 ± 0.45*	2.32 ± 0.44	2.30 ± 0.38
Sil-based preparation treatment	4.74 ± 0.26*	3.43 ± 0.49*	2.43 ± 0.46	2.27 ± 0.43
Betamethasone (BMT) treatment	4.26 ± 0.41*	3.97 ± 0.51*	3.21 ± 0.18*	2.37 ± 0.62
Hep-based preparation treatment	4.00 ± 0.20*	4.15 ± 0.38*	3.57 ± 0.44*	2.84 ± 0.36*

To induce full-thickness wounds, the fur over the dorsal region was clipped, the skin surface disinfected with 70% ethanol, and circular excisional lesions were created aseptically. A continuous suture line, approximately 5 cm in length and spaced at 1 cm intervals, was then applied along the wound area. Each treatment group consists of 10 rats. *Two-way ANOVA demonstrated significant effects of treatment, time, and their interaction ($p < 0.05$). Concentrations are expressed in pg/mL (mean ± standard deviation). Abbreviations: Hep – heparin, PS – polysilicon-siloxane, Sil – silicone.

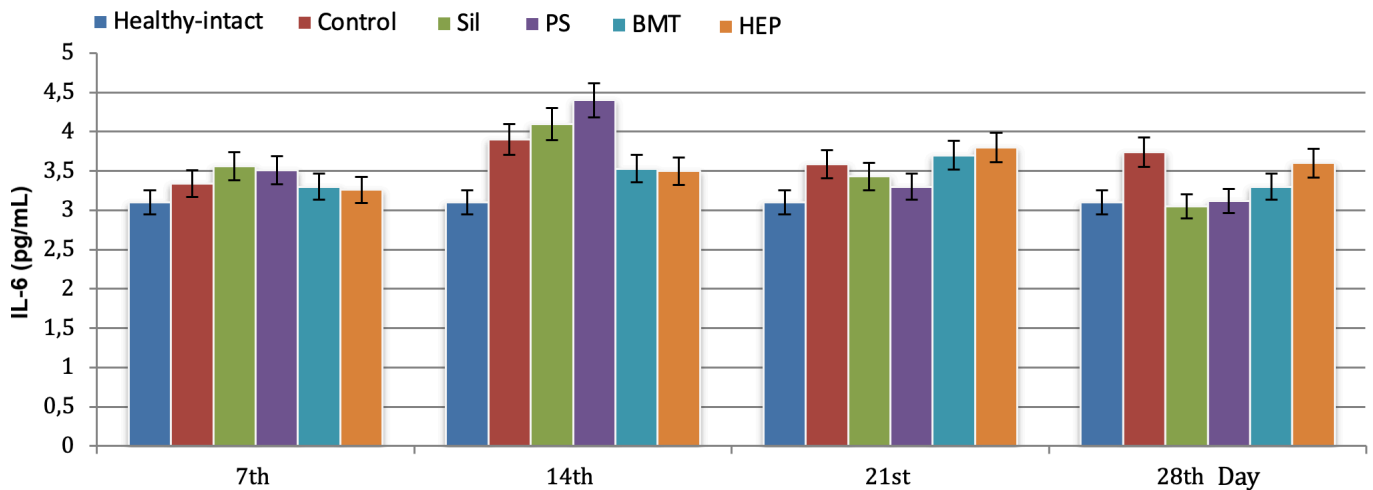


Figure 2. Concentrations of IL-6 in healthy, control, and treated rats across the duration of the study

Table 2. Concentrations of IL-6 (pg/mL) in healthy, control and treated rats

Treatment group	Day 7	Day 14	Day 21	Day 28
Healthy (uninjured)	3.10 ± 0.20	3.10 ± 0.20	3.10 ± 0.20	3.10 ± 0.20
Control (wounded and untreated)	3.34 ± 0.64*	3.90 ± 0.52*	3.59 ± 0.32*	3.74 ± 0.26*
PS-based preparation treatment	3.51 ± 0.50*	4.40 ± 0.70*	3.30 ± 0.50	3.12 ± 0.40
Sil-based preparation treatment	3.56 ± 0.40*	4.10 ± 0.90*	3.43 ± 0.60*	3.05 ± 0.40
Betamethasone (BMT) treatment	3.30 ± 0.40	3.53 ± 0.60*	3.70 ± 0.80*	3.30 ± 0.50
Hep-based preparation treatment	3.26 ± 0.40	3.50 ± 0.70*	3.80 ± 0.60*	3.60 ± 0.70*

To induce full-thickness wounds, the fur over the dorsal region was clipped, the skin surface disinfected with 70% ethanol, and circular excisional lesions were created aseptically. A continuous suture line, approximately 5 cm in length and spaced at 1 cm intervals, was then applied along the wound area. Each treatment group consists of 10 rats. *Two-way ANOVA demonstrated significant effects of treatment, time, and their interaction ($p < 0.05$). Concentrations are expressed in pg/mL (mean ± standard deviation). Abbreviations: Hep – heparin, PS – polysilicon-siloxane, Sil – silicone.

The sustained elevation of IL-6 in the PS and Sil groups coincided with the period of most active fibroblast proliferation and wound contraction observed in our histological analysis. This sustained IL-6 concentration in the most therapeutically successful groups (PS and Sil) suggests a prolonged signaling phase that promoted the enhanced fibroblast proliferation and re-epithelialization observed in our histological findings (IL-6 dynamics in all groups are shown in Figure 2. Concentrations of IL-1 and IL-6 are summarized in Tables 1 and 2).

In summary, the experiment demonstrated significant main effects of treatment and time, as well as a significant treatment $\times$ time interaction for both IL-1 and IL-6 levels ($p < 0.001$ for all comparisons). Early time points (day 7 and day 14) were characterized by elevated concentrations of both cytokines in control and Hep-treated groups, reflecting sustained inflammatory activity. In contrast, treatment with PS and Sil resulted in a progressive and statistically significant reduction of IL-1 and IL-6 levels over time. By days 21 and 28, cytokine concentrations in these groups approached values observed in healthy animals, indicating effective modulation of the inflammatory response and a transition toward tissue remodeling and regeneration. BMt treatment demonstrated an intermediate effect, with partial attenuation of cytokine levels that did not fully normalize by the end of the observation period.

Morphological assessment of wound healing images is presented in Figures 3-8. Histological evaluation revealed clear group-dependent differences in inflammatory response, granulation tissue formation, and extracellular matrix (ECM) organization at day 7 post-injury. Figure 3 demonstrates varying degrees of granulation tissue formation, inflammatory cell infiltration, and extracellular matrix (ECM) organization. The transition from the inflammatory phase to structural remodeling.

In the control group, wound sites were characterized by pronounced inflammatory cell infiltration, predominantly neutrophils and mononuclear cells. Granulation tissue was poorly organized, with loosely arranged, weakly stained collagen fibers indicating persistence of the inflammatory phase, delayed transition toward tissue remodeling, and matrix formation.

Treatment with Hep resulted in a partial attenuation of inflammation compared with controls. Granulation tissue appeared more structured, accompanied by moderately increased collagen deposition; however, collagen fibers remained irregular, and active angiogenesis was still evident, suggesting incomplete progression to the remodeling phase.

In the Sil group, inflammatory cell infiltration was markedly reduced. Granulation tissue was well developed, with more regularly aligned collagen fibers and increased presence of myofibroblasts, indicating enhanced wound contraction and advancement toward the reparative phase.

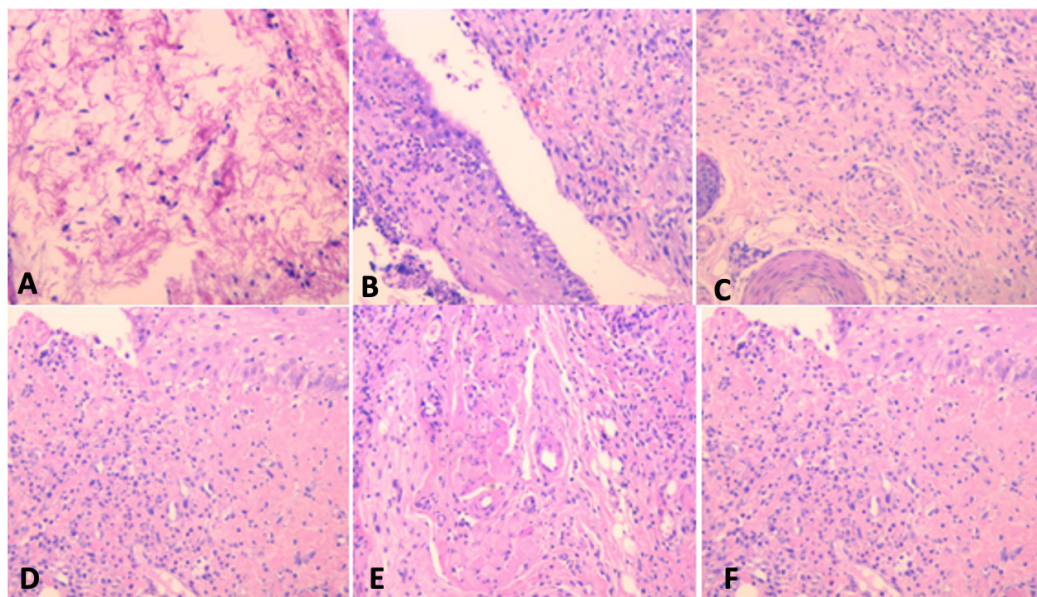


Figure 3. Morphological features of the skin across experimental groups (Day 7 post-injury, H&E, $\times 200$)

(A) Control group: Intense inflammatory cell infiltration, with abundant neutrophils and mononuclear cells. Irregularly formed Granulation tissue; collagen fibers disorganized and weakly stained. Numerous immature blood vessels. **(B)** Hep group: inflammatory cell infiltrations; more structured Granulation tissue with moderately increased collagen deposition. **(C)** Sil group: Well developed granulation tissue with more regularly arranged and parallel collagen fibers. An increased number of myofibroblasts. **(D)** BMt group: transitional morphology from the inflammatory to the remodeling phase; minimal inflammatory components; the extracellular matrix is relatively organized, collagen structure partially heterogeneous; moderate blood vessel density. **(E)** PS group: minimal inflammatory cells; dense and well organized granulation tissue; clearly aligned and intensely stained collagen fibers. **(F)** Intact/healthy skin: a normal skin architecture, with a well-organized epidermis and dermis, regularly arranged collagen and elastic fibers.

The BMt group exhibited a transitional morphological pattern between inflammation and remodeling. Inflammatory components were minimal, and ECM organization was improved relative to the control and Hep groups, although collagen fiber heterogeneity persisted. Vascular density was moderate, consistent with regulated angiogenesis.

The PS-treated group demonstrated the most advanced stage of healing. Histological sections showed minimal inflammatory infiltration, dense and well-organized granulation tissue, and clearly aligned, intensely stained collagen fibers, reflecting active ECM remodeling and tissue maturation. Re-epithelialization was nearly complete, closely resembling normal skin architecture.

The intact skin displayed a preserved epidermal and dermal structure with regularly arranged collagen and elastic fibers and absence of inflammatory cells.

In summary, the control group displays sparse, thin, and irregularly distributed collagen fibers, indicating delayed matrix formation. Hep treatment results in a moderate increase in collagen deposition with heterogeneous organization. The Sil group shows enhanced collagen density with improved fiber alignment. The BMt group exhibits intermediate collagen accumulation, reflecting a transitional remodeling stage. The PS-treated group demonstrates dense, well-organized collagen bundles resembling mature dermal architecture.

Day 7 histological sections stained with Masson's Trichrome illustrating collagen deposition and ECM organization across experimental groups, are presented in Figure 4.

In the control group collagen deposition was sparse and irregular. Collagen fibers appeared thin, loosely arranged, and unevenly distributed within the granulation tissue, indicating delayed matrix formation and incomplete progression toward the remodeling phase.

The Hep-treated group exhibited a moderate increase in collagen deposition compared to controls, although fibers remain discontinuous and irregular. Blue-stained collagen fibers were more apparent but remained disorganized and heterogeneously distributed, suggesting partial stimulation of ECM synthesis without adequate structural maturation.

In the Sil group, collagen deposition was markedly enhanced. Collagen fibers appeared denser and more uniformly distributed, with a tendency toward parallel alignment, indicating improved matrix organization and advancement of the reparative phase.

The BMt group demonstrated intermediate collagen accumulation. Although collagen fibers were more abundant than in the control and Hep groups, their organization remained partially heterogeneous, reflecting a transitional state between granulation tissue formation and early remodeling.

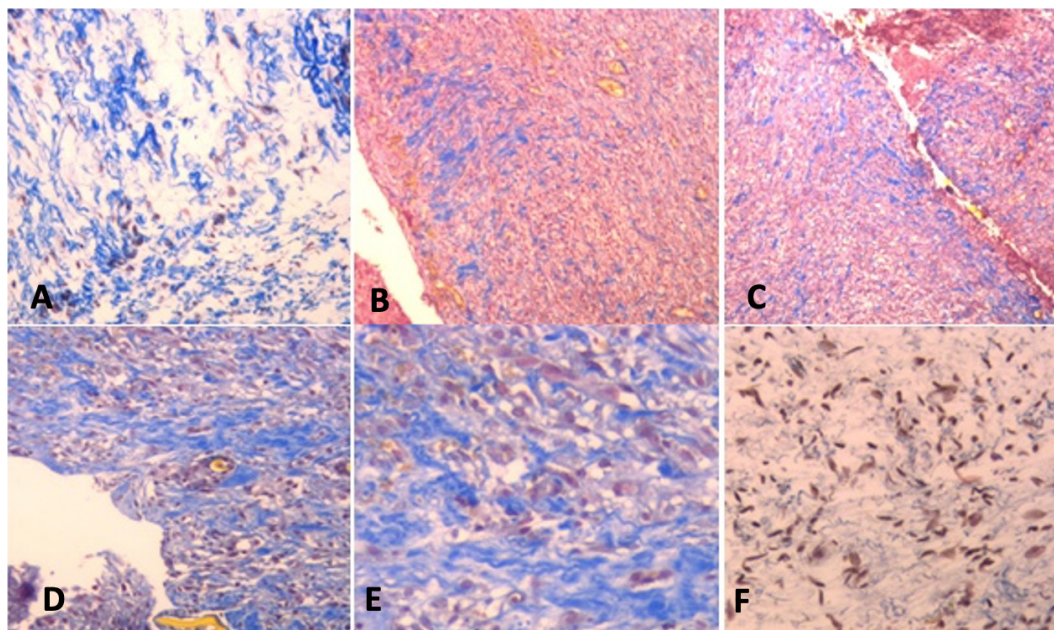


Figure 4. Collagen deposition during wound healing (Day 7 post-injury, Masson's Trichrome staining, $\times 100$ / $\times 200$)

(A) Control group ($\times 200$): sparse and irregular collagen deposition; thin Collagen fibers, loosely arranged, and unevenly distributed within the granulation tissue. Collagen fibers are stained blue, while cytoplasm and muscle fibers appear red/pink. **(B)** Hep group ($\times 100$): collagen deposition; disorganized and heterogeneously distributed Blue-stained collagen fibers. **(C)** Sil group ($\times 100$): enhanced collagen deposition; dense and more uniformly distributed Collagen fibers, with a tendency toward parallel alignment. **(D)** BMt group ($\times 200$): intermediate and partially heterogeneous collagen accumulation. **(E)** PS group ($\times 200$): pronounced and organized collagen deposition; densely packed and well aligned thick, intensely stained collagen bundles. **(F)** Intact/healthy skin ($\times 200$): well-organized, dense, and uniform arranged collagen fibers within the dermis, serving as a reference for optimal collagen architecture and structural integrity.

The PS-treated group showed the most pronounced and organized collagen deposition. Thick, intensely stained collagen bundles were densely packed and well aligned, closely resembling the architecture of mature dermal tissue. This pattern indicates accelerated ECM remodeling and tissue maturation.

In intact skin, the collagen fibers displayed a well-organized, dense, and uniform arrangement within the dermis. Enhanced collagen deposition and improved fiber organization observed in the PS group suggest that this treatment most effectively promotes extracellular matrix remodeling during the early stages of wound healing. The microscopic qualitative similarities between PS-treated wounds and intact skin further support its role in accelerating tissue maturation and restoring normal dermal architecture.

Histological sections stained with Weigert's elastic stain illustrating elastic fiber distribution and organization across experimental groups revealed that the control group shows sparse, fragmented, and poorly organized elastic fibers, indicating delayed elastic matrix restoration. Hep treatment results in a slight increase in elastic fiber presence, although fibers remain discontinuous and irregular. The Sil group demonstrates improved elastic fiber density with partial structural organization. The BMt group exhibits a transitional pattern, with moderately restored but heterogeneous elastic fibers. The PS-treated group displays more continuous and organized elastic fibers, more closely resembling normal dermal architecture. Intact skin shows mature elastic fiber organization (Figure 5).

Morphological features of the skin during the wound healing process (day 21 post-injury, Figure 6) show a direct correlation between early fiber restoration and late-stage tissue maturation. Groups like PS and Sil, which showed superior elastic fiber organization by day 7, also exhibited more organized fibroblast and vascular structures by day 21. In contrast, the Control group showed persistent delays in both fiber matrix restoration and cellular organization. Compared to the treated groups, Group A shows sparse, fragmented, and poorly organized elastic fibers, which indicates a delayed restoration of the elastic matrix. The PS and Sil groups show well-formed, mature microvessels, indicating efficient blood supply restoration to the healing tissue.

A significant presence of active, spindle-shaped fibroblasts is evident, particularly in the PS group, where they are engaged in the final stages of collagen matrix synthesis. Compared to earlier stages, there is a marked reduction in inflammatory cell infiltrate (neutrophils and macrophages) in the therapeutically successful groups, signifying a healthy transition from the inflammatory phase to permanent tissue restoration.

The dermal layer shows improved integration with the surrounding healthy skin, with a more organized cellular distribution than that observed in the untreated control group.

Histological sections illustrate the resolution of the acute inflammatory response. The PS group exhibits a sophisticated dermal morphology with spindle-shaped activated fibroblasts and mature, patent microvessels. In contrast, untreated sections maintain residual cellularity and less structured stromal organization.

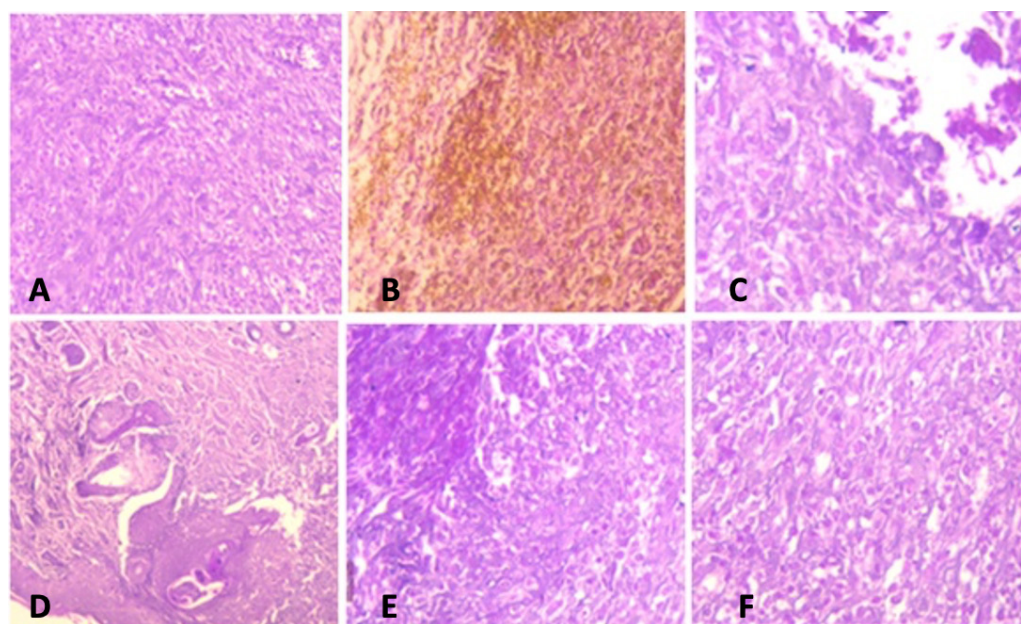


Figure 5. Elastic fiber dynamics during the wound healing process (Day 7 post-injury, Weigert's stain, x100)
(A) Control group: sparse, fragmented, and poorly organized elastic fibers. **(B)** Hep group: discontinuous and irregular elastic fiber. **(C)** Sil group: Dense and structurally organized elastic fibers. **(D)** BMt group: moderately restored and heterogeneous elastic fibers. **(E)** PS group: continuous and organized elastic fibers, approaching normal dermal architecture. **(F)** Intact/healthy skin: mature elastic fiber organization.

Figure 7 illustrates the state of collagen fibers during the wound healing process at day 21 post-injury, utilizing Van Gieson staining. While the control group represents the natural healing progression with potentially more disorganized fibers, the PS and Sil groups show microscopic morphological patterns that reflect a more structured and mature collagen matrix, moving closer to the intact architecture.

In the control group, the granulation tissue is irregularly formed, reflecting a slower maturation process where fibers appear fragmented or sparse.

The hep group shows a moderately increased deposition of collagen compared to the control. While the fibers are more structured, some inflammatory cell infiltration is still present within the matrix.

Sil group is characterized by well-developed granulation tissue where collagen fibers are arranged in a regular, parallel fashion. This group shows significant progress in fiber alignment and structural integrity.

BMt group shows a relatively organized extracellular matrix with minimal remaining inflammatory components. The collagen structure is transitioning toward maturity, though it is still partially heterogeneous in density.

PS group exhibits the most advanced healing with dense, well-organized granulation tissue. The collagen fibers are clearly aligned and intensely stained, indicating high maturity and approaching the quality of normal dermal architecture. Intact/ healthy skin shows perfectly organized and mature collagen networks. The fibers are dense, regular, and show the natural architecture of uninjured skin.

Figure 8 illustrates the restoration of elastic fibers 28 days post-injury. The control group is characterized by a significantly delayed healing profile. At day 21, it shows intense inflammatory infiltration (neutrophils and mononuclear cells), irregularly formed granulation tissue, and disorganized, weakly stained collagen. By day 28, elastic fibers remain sparse and fragmented.

The Hep group shows moderate improvement over the control. While it exhibits more structured granulation tissue and increased collagen deposition by day 21, persistent inflammatory infiltrations remain. Elastic fiber restoration by day 28 is still discontinuous and irregular.

The Sil group demonstrates a strong regenerative response. By day 21, it features well-developed granulation tissue with collagen fibers arranged in a regular, parallel fashion and an increased count of myofibroblasts. Elastic fibers show improved density and partial structural organization.

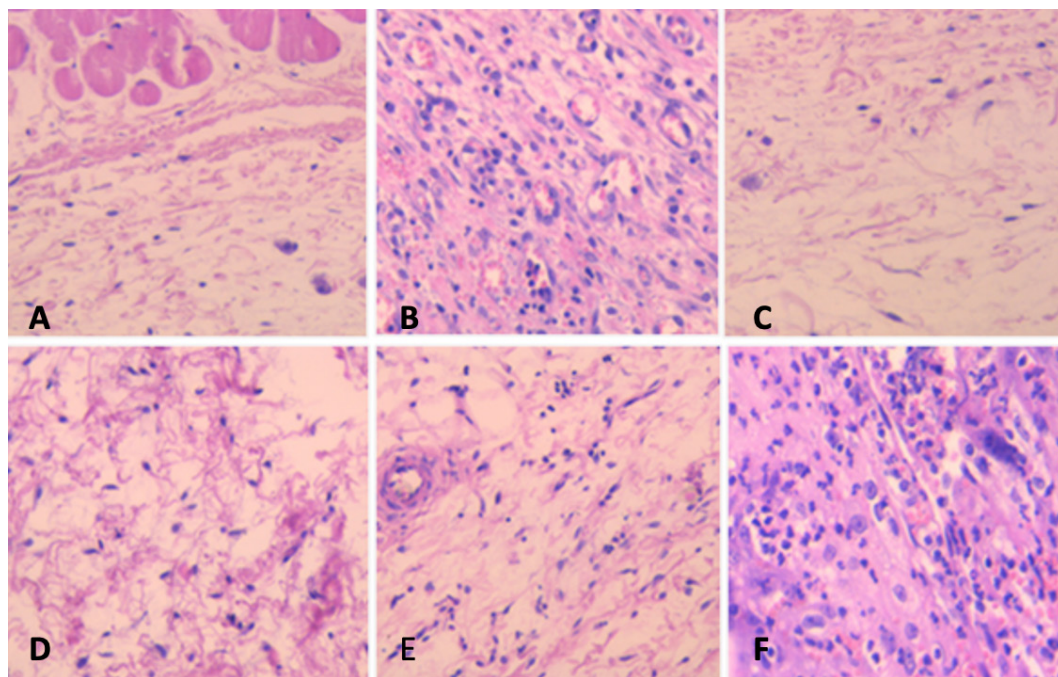


Figure 6. Morphological features of the skin across experimental groups (Day 21 post-injury, H&E staining, x200)

(A) Control group: Intense inflammatory cell infiltration with neutrophils and mononuclear cells. Irregularly formed granulation tissue. The collagen fibers are disorganized. Sparse, fragmented, and poorly organized elastic fibers. residual cellularity and less structured stromal organization. **(B)** Hep group: persistent inflammatory cell infiltrations, the granulation tissue is more structured. collagen deposition is moderately increased. **(C)** Sil group: Well developed granulation tissue with more regularly arranged collagen fibers. An increased number of myofibroblasts. Well-formed, mature microvessels. **(D)** BMt group: minimal Inflammatory components; the extracellular matrix is relatively organized, collagen structure partially heterogeneous; moderate blood vessel density. **(E)** PS group: minimal Inflammatory cells; dense and well organized granulation tissue; clearly aligned and intensely stained collagen fibers. Well-formed, mature microvessels. **(F)** Intact/healthy skin: a normal skin architecture, with a well-organized epidermis and dermis, regularly arranged collagen and elastic fibers.

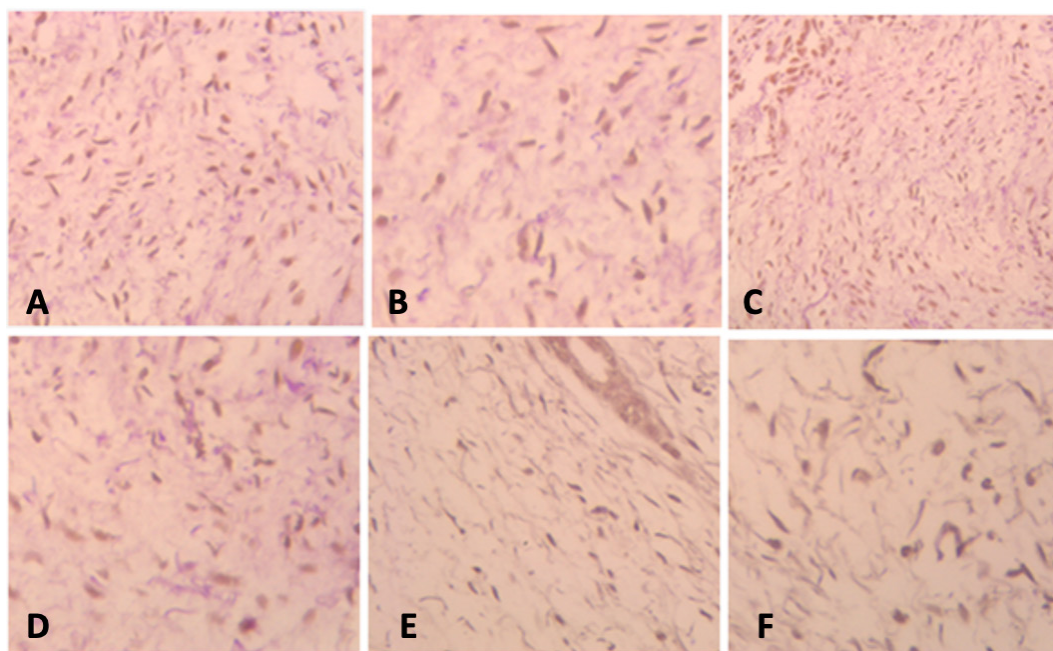


Figure 7. Collagen fibers during wound healing (Day 21 post-injury, Van Gieson staining, ×200)

(A) Control group: disorganized and weakly stained collagen fibers. The granulation tissue is irregularly formed, fibers are fragmented. **(B)** Hep group: moderately increased deposition of collagen. The fibers are more structured, some inflammatory cell infiltration still present within the matrix. **(C)** Sil group: well-developed granulation tissue where collagen fibers are arranged in a regular, parallel fashion. Significant progress in fiber alignment and structural integrity. **(D)** BMt group: relatively organized extracellular matrix with minimal remaining inflammatory components. The collagen structure is transitioning toward maturity, partially heterogeneous in density. **(E)** PS group: well-organized granulation tissue. The collagen fibers are clearly aligned and intensely stained (bright red). **(F)** Intact/Healthy Skin: organized and mature collagen networks. The fibers are dense, regular, and show the natural architecture of uninjured skin.

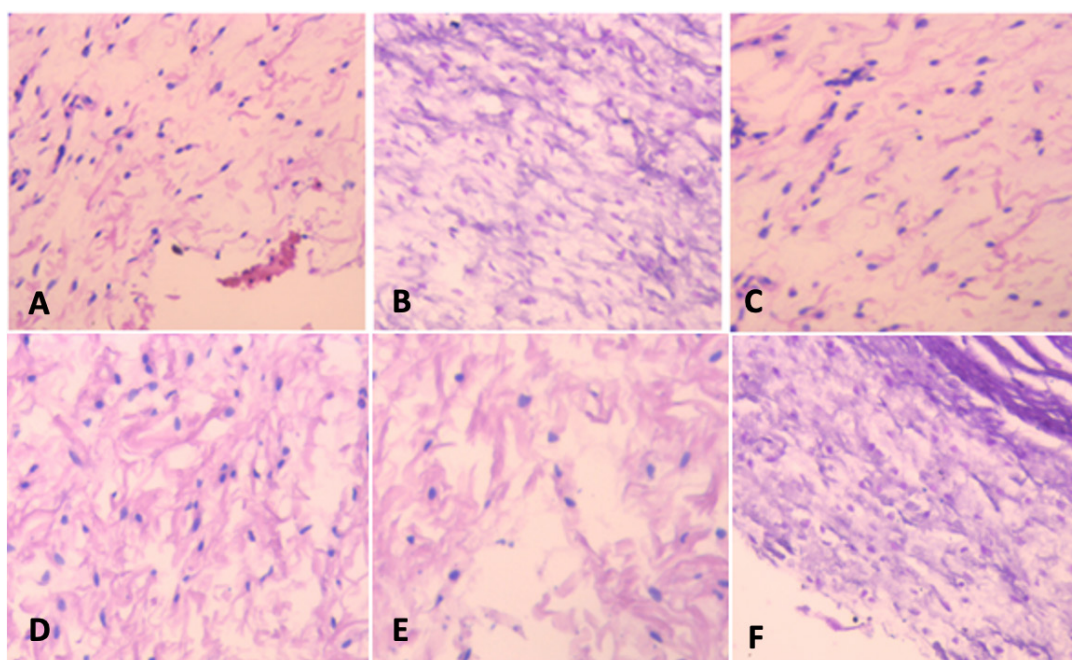


Figure 8. Elastic fiber restoration during the wound healing process (Day 28 post-injury, Weigert's stain, x200)

(A) Control group: sparse, fragmented, and poorly organized elastic fibers. **(B)** Hep group: slight increase in the presence of elastic fibers. Fibers remain largely discontinuous and irregular. **(C)** Sil group: This modality demonstrates improved elastic fiber density. The fibers exhibit a partial structural organization, showing significant progress over the control. **(D)** BMt group: transitional pattern of healing. The elastic fibers are moderately restored but remain heterogeneous in their distribution. **(E)** PS group: the most advanced recovery, with more continuous and organized elastic fibers. The tissue architecture approaching normal dermal architecture. **(F)** Intact/healthy skin: mature elastic fiber organization typical of healthy tissue.

The BMt group displays a transitional morphology. By day 21, it moves from the inflammatory to the remodeling phase with minimal inflammatory components and moderate blood vessel density. Elastic fiber is heterogeneous.

The PS group consistently shows the most advanced healing results. At day 21, it exhibits dense, well-organized granulation tissue with clearly aligned and intensely stained collagen fibers. By Day 28, its elastic fiber architecture is continuous and organized, closely approaching the architecture of normal dermal tissue. Intact Skin shows the well-organized epidermis, dermis, and regularly arranged fibers.

Collectively, early vascular proliferation was common across all groups. Vessel density resolved rapidly in PS-treated wounds (day 14), followed by Sil (day 21), whereas BMt, Hep and controls retained pronounced vascularity through day 28. Myofibroblast and inflammatory cell infiltration peaked at day 7 in all groups. PS showed the fastest normalization (day 21), while Sil and controls maintained moderate infiltration throughout healing. Collagen and Elastic Fiber Formation: Initial collagen scarcity gradually improved. PS initiated fiber deposition by day 14 and maintained organized bundles thereafter. Sil and BMt achieved normal collagen density by day 21, while Hep only reached comparable levels on day 28. Elastic fibers reappeared progressively, with complete restoration by day 21 in PS-treated animals and by day 28 in Sil.

These findings indicate that PS treatment most effectively accelerates the resolution of inflammation and promotes ECM organization, thereby facilitating the transition from the inflammatory to the remodeling phase of wound healing. The reduced inflammatory cell presence and enhanced collagen alignment observed in the PS group are consistent with improved tissue maturation and may underlie the superior functional and structural recovery compared with other treatment modalities.

Scar characteristics at different time points (7th, 14th, 21st, and 28th days) for each treatment group according to the Vancouver Scar Scale are shown in Table 3. VSS demonstrated improvement in scar pliability and height for the PS and Sil groups starting from day 14. While the BMt group showed reduced vascularity, it did not achieve the same level of overall structural maturation as the silicone-based treatments.

DISCUSSION

The Cutaneous repair progresses through a coordinated series of events beginning with coagulation, followed by inflammation, tissue formation, and ultimately structural remodeling [28,29]. In the present work, the healing response to four therapeutic agents—PS, Sil, BMt, and Hep—was examined by tracking cytokine behavior (IL-1, IL-6), microvascular changes, fibroblast distribution, collagen maturation, elastic fiber reorganization, and external scar quality.

Among the molecular mediators studied, IL-1 and IL-6 are especially central to early wound physiology. IL-1 generally peaks shortly after injury, driving leukocyte recruitment and amplifying inflammatory signaling before gradually diminishing as tissue stabilizes [30-31]. IL-6 expression also rises during the acute phase but often extends into proliferation, where it contributes to fibroblast activation, extracellular matrix synthesis, and overall tissue reconstruction [32-33]. When persistently elevated, however, these mediators can hinder resolution, prolong inflammation, and predispose tissue to delayed remodeling or hypertrophic scarring.

All treatment arms demonstrated an expected rise in IL-1 by the first week post-injury, reflecting the initiation of the inflammatory cascade. A faster return to baseline was observed in PS- and Sil-treated rats by day 21, whereas BMt required an additional week to reach

Table 3. Scar aspect during skin healing in healthy, control, and treated rats (The Vancouver Scar Scale)

Scar appearances		Vascularity (range 0-3)				Pigmentation (range 0-2)				Pliability (range 0-5)				Height (range 0-3)			
The Vancouver Scar Scale		Normal (0p) Pink (1p) Red (2p) Purple (3p)				Normal (0p) Hypopigmentation (1p) Hyperpigmentation (2p)				Normal (0p) Supple (1p) Yielding (2p) Firm (3p) Ropes (4p) Contracture (5p)				Flat (0p) < 2 mm (1p) 2-5 mm (2p) >5 mm (3p)			
Day post-injury		7th	14th	21st	28th	7th	14th	21st	28th	7th	14th	21st	28th	7th	14th	21st	28th
1	Healthy	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	Control	2	3	2	2	1	1	1	2	3	3	4	3	2	2	2	1
3	PS	2	1	0	0	0	1	1	0	2	2	1	0	1	1	1	0
4	Sil	2	2	1	1	0	2	1	1	3	2	2	1	2	1	1	1
5	BMt	2	2	2	1	1	2	1	1	3	3	2	1	2	1	1	1
6	Hep	2	3	2	2	1	2	2	1	3	3	3	2	2	2	1	1

Each study group consisted of 10 rats. Data are presented as the mean Vancouver Scar Scale (VSS) score of the study group. Abbreviations: BMt – betamethasone, Hep – heparin, PS – polysilicon-siloxane, Sil – silicone.

comparable values. In contrast, IL-1 clearance was markedly slower in the Hep group, implying persistent inflammatory signaling. These patterns suggest that PS, Sil and to a lesser extent BMt accelerate suppression of acute inflammation more effectively than Hep-based therapy.

Our results showed that PS and Sil treatments limited the IL-1 peak to approximately 74–75% of the untreated control maximum. This early attenuation of the pro-inflammatory response is critical; as noted by Mirza et al. [30], excessive or prolonged IL-1 beta activity can stall wounds in the inflammatory phase and lead to hypertrophic scarring. By blunting this initial cytokine spike, the polysilicon-siloxane and silicone treatments likely prevented secondary tissue damage, thereby facilitating a more rapid transition to the proliferative phase of healing.

IL-6 behavior followed a slightly delayed trajectory. Peak expression occurred around day 14 for all treatments, but reductions to baseline were evident by day 28 only in PS, Sil and BMt-treated wounds. Persistent elevation in both control and Hep groups indicates prolonged inflammatory activation and potentially slower progression into the proliferative and remodeling phases. The inability of Hep to reduce IL-6 within the same timeframe highlights its limited immunomodulatory impact during early healing.

Collectively, the cytokine profiles imply that PS, Sil and BMt promote a more timely resolution of inflammation, whereas Hep demonstrates a weaker regulatory influence on early immune responses.

A notable observation in this study was that IL-6 levels in the PS and Sil groups remained higher than those in untreated controls during the first 14 days of healing. Although this may initially appear paradoxical given the superior clinical outcomes of these groups, it aligns with the known dual role of IL-6 in tissue repair. Unlike the purely pro-inflammatory peak of IL-1, sustained IL-6 signaling is a prerequisite for the initiation of the proliferative phase. As demonstrated by Lin et al. [33], the absence of IL-6 leads to impaired leukocyte infiltration and a marked reduction in granulation tissue formation. In our study, the prolonged elevation of IL-6 in the most therapeutically beneficial groups (PS and Sil) likely served as a physiological bridge, stimulating the robust fibroblast activity and organized collagen deposition observed histologically. This suggests that these treatments do not simply suppress inflammation, but rather modulate the cytokine environment to favor active structural remodeling over a prolonged period.

The biological significance of this sustained IL-6 signaling is clearly reflected in the histological outcomes. The high levels of IL-6 served as a physiological driver for neovascularization, as evidenced by the prominent blood vessel density observed in H&E staining (Figures 3 and 6). This

enhanced vascular supply provided the metabolic foundation for robust fibroblast activation. Consequently, as early as Day 7, Masson's Trichrome staining (Figure 4) revealed an accelerated deposition of the collagen scaffold.

By the final stages of the study (Days 21–28), the impact of early cytokine optimization became structurally manifest. The Van Gieson staining (Figure 7) demonstrated that the PS and Sil groups achieved a mature dermal architecture characterized by dense, parallel collagen bundles, unlike the disorganized fibers seen in untreated controls. Furthermore, the Weigert's stain (Figures 5 and 8) confirmed a superior restoration of the elastic fiber network, which is critical for the tensile strength and functional flexibility of the resulting tissue.

Ultimately, our data suggest that the superior clinical performance of PS and Sil treatments is not due to simple immune suppression, but rather a sophisticated modulation of the IL-1/IL-6 axis. By attenuating the degradative effects of IL-1 and optimizing the regenerative signaling of IL-6, these treatments orchestrate a transition from disorganized granulation tissue to a structurally and functionally sound skin matrix.

Neovascular development also plays a pivotal role in repair, as microvessels supply oxygen and metabolic substrates essential for regeneration [34–35]. Therefore, earlier normalization of vascularity can be interpreted as a marker of efficient inflammatory control and successful transition toward matrix rebuilding [36].

Sustained vascular density through day 28 in untreated animals indicates a prolonged inflammatory milieu, which may interrupt the progression toward healthy matrix formation and re-epithelialization. Conversely, vascular normalization occurred markedly earlier in the PS-treated group (day 14) and subsequently with Sil (day 21), signifying a more efficient inflammatory shutdown. Elevated vessel counts in BMt- and Hep-treated wounds throughout the study imply slower transition from inflammation to repair.

The accelerated recovery observed with PS treatment is likely attributable to its regulatory influence on cytokine release and matrix remodeling. Sil appears to exert both anti-microbial and anti-inflammatory activity, which may explain the improved vascular regression seen in this group.

Myofibroblasts and inflammatory cell infiltration are expected components of early contraction and wound stabilization [37,38]. Their persistence, however, is associated with fibrosis and excessive scar tissue. On day 7, PS and control wounds demonstrated high cellularity, but only PS-treated tissue reached baseline cellular levels by day 21. Sil-treated animals retained moderate but controlled cellular activity, indicating a steady healing response without excessive fibrosis.

BMt- and Hep-treated wounds exhibited extended inflammatory cell presence and sustained myofibroblast activity, conditions that can hamper timely re-epithelialization and predispose to more rigid scarring.

Collagen deposition is fundamental to wound strength [30], though overproduction increases the risk of hypertrophic or keloidal tissue formation.

On day 7, collagen fibers were scarce in all groups, reflecting early-stage matrix formation. By day 14, PS-treated wounds displayed clear collagen development that continued steadily through the study, pointing to accelerated matrix assembly and effective tissue reconstruction. Sil and BMt reached comparable collagen density roughly one week later, indicating adequate but slower synthesis. Hep-treated wounds showed substantial fiber accumulation only by day 28.

The early collagen deposition observed with PS treatment suggests efficient progression into the proliferative phase and may account for improved remodeling outcomes. Sil also supported matrix formation, though with more gradual tissue organization. BMt's delayed fiber accumulation may be explained by its immunosuppressive influence, which tempers cellular activity. While Hep ultimately produced abundant collagen, this late surge may be less advantageous for early-phase healing, though potentially helpful in reducing hypertrophic growth at later stages.

Elastic fiber behavior followed a similar progression. Moderate levels were identified initially, with PS-treated wounds achieving full restoration by day 21. Sil-supported matrix repair required more time, normalizing by day 28. In comparison, BMt and Hep groups displayed slower elastic fiber reorganization, which may contribute to greater stiffness in mature scar tissue.

The rapid reappearance of elastic fibers in PS-treated wounds highlights its positive effect on extracellular matrix remodeling and may explain the improved pliability and overall scar quality observed in this group.

- Scar quality, assessed through the four VSS domains—vascularity, pigmentation, pliability, and height—differed substantially between treatment approaches.
- Vascularity: PS-treated animals demonstrated the most accelerated decline in vessel prominence, reflecting rapid suppression of inflammatory activity. Sil and BMt produced intermediate improvements, while wound sites in the control and Hep groups retained higher vascular density for longer periods.
- Pigmentation: Color uniformity returned earliest and most consistently in PS and Sil groups. More variable pigmentation in the control and Hep groups likely corresponds to the extended inflammatory window observed in cytokine analysis.

- Pliability: PS generated the most flexible scar tissue, whereas Sil and BMt produced more moderate softening. Reduced pliability in the control and Hep groups indicates suboptimal remodeling and denser matrix formation.

- Height: Scar elevation resolved quickly with PS, becoming flat by day 14. Sil and BMt improved gradually, and the slowest reductions occurred in the untreated and Hep groups.

Integrating cytokine trends with histological and VSS outcomes, PS produced the most favorable global healing profile—rapid inflammatory clearance, timely matrix deposition, efficient elastic fiber return, and optimal cosmetic and biomechanical scar features. These qualities support PS as the most effective intervention for early-stage wound care.

Sil also performed well, particularly in harmonizing inflammation and collagen synthesis, suggesting suitability for wounds susceptible to infection or requiring balanced rather than aggressive modulation.

BMt displayed slower early improvements, likely attributable to immunosuppressive action, yet may remain beneficial where excessive inflammation is the primary concern.

Hep, despite delayed but strong collagen buildup, appears better suited to later-phase scar modulation rather than acute wound intervention. Its tendency to maintain inflammatory signaling longer may hinder early closure but could restrain excessive scarring once remodeling has begun.

Despite the significant findings regarding cytokine modulation and tissue remodeling, several limitations of this study must be acknowledged. First, while the rat model used in this research is a standard for wound healing studies, rodent skin heals primarily through wound contraction rather than the re-epithelialization characteristic of human skin, which may limit the direct translatability of these results to clinical practice. Second, the current study focused specifically on serum concentrations of IL-1 and IL-6; however, local cytokine levels within the wound microenvironment and the expression of other critical growth factors (such as TGF-beta or VEGF) were not quantified, which could provide a more comprehensive view of the repair process. Additionally, the experimental duration was limited to 28 days; a longer observation period would be beneficial to assess the long-term mechanical strength and stability of the resulting scar tissue. Finally, while environmental conditions were strictly controlled, the potential influence of individual versus group housing on stress-induced healing variations warrants further investigation in larger-scale studies.

CONCLUSIONS

The findings of this work highlight the value of choosing wound-management strategies according to the healing stage and biological response. Among the evaluated treatments, PS and Sil produced the most rapid improvement, demonstrated by earlier reductions in IL-1 and

IL-6 levels and clearer histological evidence of controlled vascularity, organized collagen deposition, and reduced inflammatory cell presence. BMt achieved moderate progress, but at a slower pace, while Hep and untreated controls showed the most prolonged inflammatory profile and later tissue remodeling.

Overall, the PS treatment delivered the most complete regenerative outcome, combining fast cytokine normalization with favorable scar physiology. Sil also proved effective, particularly in maintaining a balanced inflammatory environment and supporting progressive tissue restoration. BMt and Hep contributed to healing but were comparatively slower to induce matrix organization and scar refinement.

The differences in treatment effects observed in this study underline the need for individualized selection of therapeutic approaches—rapid modulation of early inflammation appears critical for optimal scar quality, while agents acting at a later-phase may be beneficial where fibrosis control or collagen stabilization is required. Tailoring intervention to wound biology may therefore yield superior clinical outcomes.

ABBREVIATIONS

ANOVA – analysis of variance
 BMt – betamethasone
 BSA – bovine serum albumin
 CI – confidence interval
 ECM – extracellular matrix
 ELISA – enzyme-linked immunosorbent assay
 FFPE – formalin-fixed paraffin-embedded
 H&E – hematoxylin and eosin
 Hep – heparin-based preparation
 HOCl – hypochlorous acid
 IL-1 – interleukin-1
 IL-6 – interleukin-6
 NaOCl – sodium hypochlorite
 PBS – phosphate-buffered saline
 PS – polysilicon–siloxane–based preparation
 RT – room temperature
 Sil – silicone-based preparation
 UV – ultraviolet
 VSS – Vancouver scar scale
 SPSS – statistical package for the social sciences

ACKNOWLEDGEMENT

None.

AUTHORS' CONTRIBUTION

NK: data curation, investigation, validation, writing (original draft).
 SG: supervision, project administration, writing (review & editing).
 LG: funding, resources, supervision, project administration.
 KG: methodology, formal analysis, validation.

NS: funding, resources, software.

TD: data acquisition, data interpretation, writing (original draft, review & editing).

NG: methodology, investigation, writing (original draft, review & editing).

VK: investigation, formal analysis, visualization, writing (original draft, review & editing).

LR: methodology, investigation, writing (original draft, review & editing).

All authors have read and approved the final version of the manuscript.

CONFLICT OF INTEREST

None to declare.

Publisher's Note: The Editorial Office stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Copyright: © 2026 by the authors. Submitted for possible open access publication under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

REFERENCES

1. Baroni A, Buommino E, De Gregorio V, Ruocco E, Ruocco V, Wolf R. Structure and function of the epidermis related to barrier properties. *Clin Dermatol.* 2012;30(3):257-262. DOI: 10.1016/j.clindermatol.2011.08.007
2. Ramos-e-Silva M, de Moura Castro Jacques C. Epidermal barrier function and systemic diseases. *Clin Dermatol.* 2012;30(3):277-279. DOI: 10.1016/j.clindermatol.2011.08.025
3. Proksch E, Brandner JM, Jensen JM. The skin: an indispensable barrier. *Exp Dermatol.* 2008;17(12):1063-1072. DOI: 10.1111/j.1600-0625.2008.00786.x
4. Bayat A, McGrouther DA, Ferguson MWJ. Skin scarring. *BMJ.* 2003;326:88-92. DOI: 10.1136/bmj.326.7380.88
5. Choudhary V, Choudhary M, Bollag WB. Exploring skin wound healing models and the impact of natural lipids on the healing process. *Int J Mol Sci.* 2024;25:3790. DOI: 10.3390/ijms25073790
6. Eming SA, Krieg T, Davidson JM. Inflammation in wound repair: molecular and cellular mechanisms. *J Invest Dermatol.* 2014;134(9):2350-2356.
7. Gurtner GC, Werner S, Barrandon Y, Longaker MT. Wound repair and regeneration. *Nature.* 2008;453(7193):314-321. DOI: 10.1038/nature07039
8. Han G, Ceilley R. Chronic wound healing: a review of current management and treatments. *Adv Ther.* 2017;34(3):599-610. DOI: 10.1007/s12325-017-0478-y

9. Martin P, Nunan R. Cellular and molecular mechanisms of repair in acute and chronic wound healing. *Br J Dermatol*. 2015;173(2):370-378. DOI: 10.1111/bjd.13954
10. Reinke JM, Sorg H. Wound repair and regeneration. *Eur Surg Res*. 2012;49(1):35-43. DOI: 10.1159/000339613
11. Dinarello CA. Immunological and inflammatory functions of the interleukin-1 family. *Annu Rev Immunol*. 2009;27:519-550. DOI: 10.1146/annurev.immunol.021908.132612
12. Ren C, Kumar S, Chanda D, Chen J, Mountz JD, Ponnazhagan S. Therapeutic potential of mesenchymal stem cells producing interferon-alpha in a mouse melanoma lung metastasis model. *Stem Cells*. 2008 Sep;26(9):2332-2338. DOI: 10.1634/stemcells.2008-0084
13. Wynn TA, Vannella KM. Macrophages in tissue repair, regeneration, and fibrosis. *Immunity*. 2016;44(3):450-462. DOI: 10.1016/j.immuni.2016.02.015
14. Dunn LK, Schechter LN. Management of hypertrophic scars and keloids. *Plast Reconstr Surg*. 2012;130(3):447e-458e.
15. Huang L, Wu Z, Liu D, Li G. Hypochlorous acid: an effective and safe alternative approach to control surgical site infections. *Front Microbiol*. 2020;11:737.
16. MacNeil S. Progress and opportunities for tissue-engineered skin. *Nature*. 2007;445(7130):874-880. DOI: 10.1038/nature05664
17. Wang F, Li X, Wang X, Jiang X. Efficacy of topical silicone gel in scar management: A systematic review and meta-analysis of randomised controlled trials. *Int Wound J*. 2020;17(3):765-773. DOI: 10.1111/iwj.13337
18. Partsch H, Mortimer P. Compression for leg wounds. *Br J Dermatol*. 2015;173(2):359-369. DOI: 10.1111/bjd.13851
19. Radford K. Pain management in wound care. *Br J Nurs*. 2012;21(14 Suppl):S4-S5. DOI: 10.12968/bjon.2012.21.Sup16.S4
20. Shih B, Garside E. A systematic review of the effectiveness of silicone in hypertrophic scar and keloid management. *J Cutan Aesthet Surg*. 2014;7(3):141-146.
21. Sidgwick GP, McGeorge D, Bayat A. A comprehensive evidence-based review on the role of topicals and dressings in the management of skin scarring. *Arch Dermatol Res*. 2015;307(6):461-477. DOI: 10.1007/s00403-015-1572-0
22. Woo KY, Coutts PM. Advanced wound dressings. *Wound Healing Skin Integr*. 2015;3(2):102-118.
23. Zamboni WA, Roth AC, Russell RC. The effect of hyperbaric oxygen on revascularization of a rabbit ear chamber. *Plast Reconstr Surg*. 2000;105(3):990-996.
24. Park JW, Koh YG, Shin SH, Choi Y, Kim W, Yoo HH, et al. Review of scar assessment scales. *Med Lasers*. 2022;11:1-7. DOI: 10.25289/ML.2022.11.1.1
25. Fearmonti R, Bond J, Erdmann D, Levinson H. A review of scar scales and scar measuring devices. *Eplasty*. 2010;10:e43.
26. ChooAMH, OngYS, IssaF. Scar assessment tools: how do they compare? *Front Surg*. 2021;8:637821. DOI: 10.3389/fsurg.2021.643098
27. Percie du Sert N, Hurst V, Ahluwalia A, Alam S, Avey MT, Baker M, et al. The ARRIVE guidelines 2.0: updated guidelines for reporting animal research. *PLoS Biol*. 2020;18(7):e3000410. DOI: 10.1371/journal.pbio.3000410
28. Rodrigues M, Kosaric N, Bonham CA, Gurtner GC. Wound healing: a cellular perspective. *Physiol Rev*. 2019;99(1):665-706. DOI: 10.1152/physrev.00067.2017
29. Takeo M, Lee W, Ito M. Wound healing and skin regeneration. *Cold Spring Harb Perspect Med*. 2015;5(1):a023267. DOI: 10.1101/cshperspect.a023267
30. Mirza RE, Fang MM, Ennis WJ. Blocking interleukin-1 β induces a healing-associated wound macrophage phenotype and improves healing in type 2 diabetes. *Diabetes*. 2013;62(7):2579-2587. DOI: 10.2337/db12-1450
31. Arango Duque G, Descoteaux A. Macrophage cytokines: involvement in immunity and infectious diseases. *Front Immunol*. 2014;5:491. DOI: 10.3389/fimmu.2014.00491
32. Dinarello CA. Interleukin-1 in the pathogenesis and treatment of inflammatory diseases. *Blood*. 2011;117(14):3720-3732. DOI: 10.1182/blood-2010-07-273417
33. Lin ZQ, Kondo T, Ishida Y, Takayasu T, Mukaida N. Essential involvement of IL-6 in the skin wound-healing process as evidenced by delayed wound healing in IL-6-deficient mice. *J Leukoc Biol*. 2010;88(5):863-875.
34. Tonnesen MG, Feng X, Clark RA. Angiogenesis in wound healing. *J Invest Dermatol Symp Proc*. 2000;5(1):40-46. DOI: 10.1046/j.1087-0024.2000.00014.x
35. Madhusudhan DK, Agarwal T, Chatterjee K. Role of growth factors in therapeutic angiogenesis for chronic wound healing. *Tissue Eng Regen Med*. 2015;12(5):311-325.
36. Darby IA, Laverdet B, Bonté F, Desmoulière A. Fibroblasts and myofibroblasts in wound healing. *Clin Cosmet Investig Dermatol*. 2014;7:301-311. DOI: 10.2147/CCID.S50046
37. Hinz B, Phan SH, Thannickal VJ, Prunotto M, Desmoulière A, Varga J, et al. Recent developments in myofibroblast biology: paradigms for connective tissue remodeling. *Am J Pathol*. 2012 Apr;180(4):1340-55. DOI: 10.1016/j.ajpath.2012.02.004