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Assessment of the Therapeutic Effects of Topical Short-Acting Insulin on Experimental Wound Healing in Rabbits Receiving Panthenol

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ABSTRACT: Wound healing is a complex, dynamic biological process aimed at restoring tissue integrity and normal function following injury; it involves a sequential series of cellular and molecular interactions encompassing the stages of hemostasis, inflammation, proliferation, and tissue remodeling. The efficiency of this process depends on the balance between factors that promote and those that inhibit healing; consequently, research efforts focus on developing therapeutic interventions capable of accelerating wound healing, improving the quality of regenerated tissue, and minimizing complications. The present study was conducted to evaluate the role of topical insulin—prepared as a carbomer-based gel at two different concentrations—in accelerating the healing of induced wounds in laboratory rabbits, as well as to assess the effect of combining it with panthenol on the wound-healing process. The animal study involved 42 male rabbits, in which surgical wounds measuring 2 cm² were created (one wound on each side). The rabbits were divided into seven equal groups (6 rabbits per group):The first group received no treatment, while the second was treated with gel. The third group was treated with topical 5% panthenol, whereas the fourth and fifth groups were treated with topical insulin at low (0.1 IU/mL) and high (0.5 IU/mL) concentrations, respectively. Finally, the sixth and seventh groups were treated with a mixture of panthenol and insulin at low and high concentrations, respectively. Treatment continued across all groups for 14 days, with wound size and contraction rate assessed on days 3, 7, 10, and 14 of the experiment. Additionally, levels of hydroxyproline, interleukin-6 (IL-6), TNF-alpha, catalase, and MDA were measured in the wound tissue, and histological changes in skin biopsies taken from the wounds were evaluated using Masson's trichrome stains. The results demonstrated significant differences among the experimental groups ($P \leq 0.05$). Groups 1 and 2 exhibited the least improvement in wound size, contraction rate, hydroxyproline, and catalase levels, alongside elevated levels of Interleukin-6, TNF-alpha, and MDA. In contrast, the use of panthenol alone resulted in only limited improvement in these parameters compared to Groups 1 and 2. Conversely, topical insulin treatment led to significant improvements across these metrics; the 0.5 IU dose outperformed the 0.1 IU dose, indicating a dose-dependent response in stimulating collagen synthesis, as well as improvements in antioxidant status, inflammatory markers, and wound contraction capacity. The results demonstrated that the combination of topical insulin and panthenol achieved the greatest reduction in wound size and the highest rate of wound contraction. Additionally, this combination led to increased levels of hydroxyproline and catalase, alongside a significant decrease in levels of Interleukin-6, TNF-alpha, and MDA compared to all other groups; notably, there was no significant difference between the two insulin dosages when combined with panthenol regarding hydroxyproline measurements. These findings were corroborated by the histological analysis, which clearly illustrated the role of topical

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insulin—at both concentrations—in accelerating wound healing, particularly when used with topical panthenol. This indicates a synergistic effect between the two substances in enhancing collagen deposition and improving the reorganization of regenerating tissue. This effect is attributed to insulin's ability to stimulate fibroblast proliferation and increase the synthesis of structural proteins, as well as to the role of panthenol in supporting cell regeneration and improving the wound-healing environment. These results indicate that topical insulin is highly effective in accelerating wound healing in laboratory rabbits and that its combination with panthenol further enhances this efficacy, making it a promising therapeutic approach for improving wound healing and accelerating the restoration of the natural structure and function of injured tissues.

INTRODUCTION

Wound healing is a complex biological process that restores tissue integrity after injury. It generally occurs through four overlapping phases: haemostasis, inflammation, proliferation, and remodelling. Haemostasis involves vasoconstriction and clot formation to control bleeding and protect the wound. During the inflammatory phase, immune cells such as neutrophils and macrophages migrate to the wound site to remove microorganisms and damaged tissue **(Gurtner *et al.*, 2008)**. During the proliferative phase, fibroblasts and keratinocytes contribute to new tissue formation, while angiogenesis and collagen deposition support tissue regeneration. Finally, during the remodelling phase, collagen fibres are reorganized and strengthened to improve the mechanical properties of the repaired tissue **(Singer & Clark, 1999)**.

Insulin is a peptide hormone produced by the beta cells of the pancreas and is primarily known for its important role in glucose metabolism. Beyond its metabolic functions, insulin may contribute to wound healing by promoting cellular proliferation and migration, which are essential for tissue repair and regeneration. Insulin may also modulate the inflammatory response and promote angiogenesis, thereby improving blood flow and oxygen delivery to the wound site **(Kahn *et al.*, 2014)**.

Recent studies have investigated the effects of topical insulin in animal models. NPH-insulin ointment was evaluated in an alkali-induced corneal burn model in rabbits, with improved clinical healing, better histological findings, and reduced oxidative stress compared with control treatment **(Kurt *et al.*, 2024)**. These findings suggest that topical insulin may enhance tissue repair in rabbit wound models.

Rodent studies have provided complementary evidence. Topical insulin cream accelerated cutaneous wound closure in rats, improved re-epithelialization, and increased the expression of angiogenic factors such as vascular endothelial growth factor (VEGF) and endothelial nitric oxide synthase (eNOS) **(Lima *et al.*, 2012)**. Similarly, insulin eye drops were reported to accelerate corneal epithelial wound healing in streptozotocin-induced diabetic mice, suggesting that insulin may have beneficial effects in impaired wound-healing conditions **(Chen *et al.*, 2024)**. Nanocarrier-based formulations have also been investigated to improve topical insulin delivery by increasing insulin stability and providing sustained release, which may further enhance wound repair.

Experimental studies conducted at the **College of Veterinary Medicine, University of Baghdad** have also evaluated different locally applied materials and biological approaches for wound healing in rabbits. Banana leaf was investigated as a poultice in experimentally induced rabbit wounds **(Al-Mutheffer, 2013)**. Bovine pericardial and amniotic membranes were compared for the treatment of skin wounds in rabbits, with both materials demonstrating applicability in the wound-healing process and no significant difference between them **(Al-Falahi *et al.*, 2018)**. Acellular bovine pericardium and dermal matrices were also evaluated in full-thickness cutaneous wounds in male rabbits using histopathological assessment **(Al-Bayati & Hameed, 2018)**. Furthermore, rabbit serum was investigated for its effect on skin wound healing, with histological evidence indicating improved tissue repair **(Majeed & Abood, 2019)**. Collectively, these studies support the use of rabbits as an experimental model for evaluating locally applied agents and biomaterials in wound healing.

Panthenol, also known as provitamin B5, is widely used in cosmetic and pharmaceutical preparations. It possesses moisturizing properties and acts as a humectant by attracting and retaining water in the skin. Adequate hydration is important during wound healing because it supports cellular activity and helps maintain skin barrier function **(Gorski et al., 2020)**.

Panthenol also possesses anti-inflammatory properties that may help reduce redness and irritation. Furthermore, it can promote skin barrier repair and facilitate the healing of minor wounds by supporting cellular proliferation and migration **(Proksch *et al.,* 2017)**.

Therefore, the present study aimed to investigate the effect of **local insulin application combined with panthenol on wound healing in rabbits**.

METHODOLOGY

Experimental Animals: Forty-two (42) male rabbits (New Zealand White) were used in this study. All rabbits were visibly healthy upon physical examination, with weights ranging between 1-1.5 kg and ages of approximately 8-9 months. The animals were divided randomly into seven groups, with Six rabbits in each group. The rabbits were housed individually in cages provided by the animal housing facility of physiology, Biochemistry and Pharmacology department, University of Baghdad / College of Veterinary Medicine to prevent interference with treatments. Throughout the experiment, pellets and water were provided. The housing environment was maintained under controlled ambient conditions, including a temperature range of 20–25 °C, proper venti lation, and a 12-hour light/dark cycle. The rabbits were allowed a 2-week adaptation period before the experiments were conducted from 11February 2026 to 12 February 2026. Ethical approval Ethical approval was granted through the local committee of animal care and uses at (University of Baghdad / College of Veterinary Medicine) NO 329 date 10 February 2026.

Rabbits were being divided randomly into seven groups (6 rabbits in each group). Treatments begin 24hrs after inducing wound 1. Group A: wounded without any treatment 2. Group B: wounded and treated with gel. 3. Group C: wounded and treated with local panthenol gel (5%) 4. Group D: wounded and treated with local insulin-H: 0.1 IU/mL 5. Group E: Wounded and treated with local insulin-H: 0.5 IU/m 6.Group (F): wounded and treated with local insulin-L:0.1 IU/mL panthenol gel (5%) 7.Group (G): wounded and treated with local insulin-H: 0.5 IU/mL and panthenol gel (5%)

Induction of Wounds in Rabbit: Rabbits' were anesthetize with 35 mg/kg of ketamine and 5 mg/kg of xylazine intra muscularly. **(Pandian, 2005)**. The dorsal area were be prepared by clipping and shaving to create (2 cm^2) full-thickness wounds **(Hameed, 2024).** As in figure 3-1The wound were treated twice daily for each group at a dose of ≈0.1 mL/cm^2:• Placebo / Insu lin-Low dose / Insulin-High dose / Panthenol 5% Follow-up until day 14 or until ≥95% closure. The diameters of wounds were measured by calliper and the Wound contraction percentage at day 3,7,10 and 14. Hydroxyproline, Malondialdehyde (MDA) and Catalase activity, pro-inflammatory cytokines, including Tumor Necrosis Factor-alpha (TNF-) and Interleukin-6 (IL-6), were quantified in the skin tissue to determine the ability of the treatments to modulate the inflammatory phase and reduce oxidative damage. Skin biopsies were processed for histological examination to assess the healing process in the end of the experiment.

COLLECTION OF SKIN BIOPSY SAMPLE FROM RABBIT WOUND

Skin biopsy sections were collected on day 14 f of treatment. The rabbits were anesthetized as previously mentioned, and the wounds were excised as a square area 2x2 cm^2 on the dorsal region, using a sterile surgical kit. Preservation of the skin section is initially attached using 10% formalin for 48 hours and sent to the Unit of Histopathology at the College of Veterinary Medicine, University of Baghdad. Following fixation, it undergoes dehydration using ethanol to eliminate water content. Subsequently, the alcohol agent is eliminated through the utilization of xylol. Subsequently, the skin sample is immersed in paraffin at 60°C for 2 hours, leading to solidification of the paraffin media. The specimen is cut into sections using a microtome (thickness 5 microns). The skin specimen undergoes staining processes with the mason stain. A light microscope is used for the examination of the stained skin section **(Suvarna et al., 2019)**

STATISTICAL ANALYSIS

Data were analyzed using IBM SPSS Statistics, employing a two-way Analysis of Variance (ANOVA) to evaluate the main and interaction effects of two independent variables—such as experimental groups and time periods—on studied parameters. While a one-way ANOVA assesses the impact of a single factor across multiple groups, a two-way ANOVA is utilized to examine how two independent factors, and their interaction, affect dependent variables. Following the ANOVA, Fisher's Least Significant Difference (LSD) post hoc test is used to identify specific pair-wise differences between means, with all findings evaluated at a $p < .05$ significance level. **(George and Mallery, 2019)**

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RESULTS AND DISCUSSION

1. Effect of local insulin 0.1IU, 0.5 IU and its combination with panthenol on Clouser time between different groups:

The experimental results demonstrate that topical insulin accelerates wound closure time in a dose-dependent manner, and its therapeutic efficiency is markedly enhanced when combined with panthenol, reducing wound closure time to a minimum of days. 9.67 ±0.88 these findings strongly agree with existing medical literature. Specifically, Topical insulin application has been shown to accelerate wound healing and re-epithelialization through activation of insulin-signaling pathways, particularly the PI3K/AKT and MAPK/ERK pathways **(Lima *et al.,* 2012)**. Furthermore, established physiological data indicate that panthenol serves as a key promoter of skin repair by inducing cell migration and preserving critical wound hydration **(Gorski *et al.,* 2020)**. The beneficial effects of topical treatments on wound healing have also been demonstrated in experimental animal models **(Al-Khayyat *et al.* 2008)** reported enhanced healing of experimentally induced skin wounds in rabbits following topical treatment, supporting the role of locally applied therapeutic agents in promoting tissue repair. Similarly, **(Al-Bayati *et al.* 2016)** observed improved wound contraction and re-epithelialization, together with increased cellularity, vascularization, and granulation tissue formation in treated cutaneous wounds. In the present study, the 0.5 IU insulin + panthenol combination achieved significantly better wound closure than either treatment alone, suggesting a potential synergistic effect between insulin and panthenol on the wound-healing process **(Liu *et al.,* 2021)**. By showing that the combination group (Insulin 0.5 + Panthenol) achieves statistically superior closure metrics compared to either monotherapy, these results expand upon documented clinical paradigms regarding synergistic, multi-targeted metabolic wound healing pathways **(Liu *et al.,* 2021)** as shown in Table 1.

Table 1: Effect of topical insulin (0.1 and 0.5 IU/mL) and its combination with panthenol on wound closure time among different groups:

Group	Mean ± SE of Closure time(day)
Control negative	19.00 ±0.36 a
Control positive	17.00 ±0.36 ab
Panthenol	16.83 ±0.31 ab
Insulin 0.1	14.83 ±0.94 bc
Insulin 0.5	11.83 ±0.79 de
Insulin 0.1+Panthenol	13.00 ±1.44 cd
Insulin 0.5+Panthenol	9.67 ±0.88 h
L.S.D. value	2.359 *
Means having with the different letters in same column differed significantly. * (P≤0.05).	

2.Effect of local insulin 0.1IU, 0.5 IU and its combination with panthenol on wound size and contraction Ratio of rabbit in different periods:

The experimental data demonstrates that all treatment interventions significantly accelerated wound healing over the 14-day period compared to the negative control, with combination therapies yielding the most profound efficacy. The combination of Insulin 0.5 IU + Panthenol achieved the highest therapeutic success, reducing wound size to a minimal (0.84 ±0.43 mm) by Day 14 (P≤0.05). This treatment significantly outperformed both the negative control (10.64 ±1.86 mm) and standard Panthenol monotherapy (8.02 ±0.33 mm). Insulin also exhibited a clear dose-dependent effect, as Insulin 0.5 IU alone (2.69 ±1.11 mm) induced significantly greater wound closure than Insulin 0.1 IU (5.38 ±1.12 mm) by the study's end. According to the Least Significant Difference (LSD = 3.188) and row-wise lowercase lettering, every group experienced statistically

significant temporal healing progression from Day 3 to Day 14. Ultimately, the unique column-wise uppercase lettering at Day 14 underscores that pairing higher-dose insulin with panthenol produces a powerful synergistic acceleration in tissue repair**. As shown in Table 2**

Table 2: Effect of local insulin 0.1IU, 0.5 IU and its combination with panthenol on wound size and contraction Ratio of rabbit in different period

	Day 3		**Day 7**		**Day 10**		**Day 14**		
Group	Wound size (mm)	Contraction ratio (%)	Wound size (mm)	Contraction ratio (%)	Wound size (mm)	Contraction ratio (%)	Wound size (mm)	Contraction ratio (%)	
Control Negative	19.18 ±0.17 A a	4.1	17.18 ±0.77 A a	14.1	13.49 ±1.38 A b	32.55	10.64 ±1.86 A b	46.8	
Control Positive	16.97 ±0.88 AB a	15.15	14.17 ±1.46 AB ab	29.15	11.03 ±0.96 AB b	44.85	7.15 ±0.42 BC c	64.25	
Panthenol	18.21 ±0.92 AB a	8.95	15.98 ±1.39 AB a	20.1	12.39 ±0.71 AB b	38.05	8.02 ±0.33 AB c	59.9	
Insulin 0.1	17.92 ±1.08 AB a	10.4	13.89 ±0.79 BC b	30.55	9.77 ±0.89 BC c	51.15	5.38 ±1.12 CD d	73.1	
Insulin 0.5	16.97 ±1.14 AB a	15.15	11.52 ±1.53 CD b	42.4	6.55 ±0.96 D c	67.25	2.69 ±1.11 DE d	86.55	
Insulin 0.1+panthenol	14.97 ±0.89 B a	25.15	10.88 ±1.31 CD b	45.6	7.21 ±1.11 CD c	63.95	3.27 ±1.49 DE d	83.65	
Insulin 0.5 +panthenol	14.82 ±0.79 B a	25.9	10.01 ±0.04 D b	49.95	5.10 ±1.09 D c	74.5	0.840 ±0.43 E d	95.8	

Wound size (mm) the LSD: 3.188 *.

Means having with the different big letters in same column and small letters in same row differed significantly.

*** (P≤0.05).**

Contraction Ratio (%) = $[(D_0 - D_t) / D_0] \times 100$

*** D_0 = Initial wound diameter (20 mm)**

*** D_t = Wound diameter at each observation day**

Topical administration of local insulin (0.1 IU and 0.5 IU) and panthenol, especially when used in combination, leads to an accelerated reduction in wound size and a pronounced enhancement of the tissue contraction ratio in rabbits. This therapeutic benefit can be attributed to the capacity of topical insulin to activate specific insulin receptors on keratinocytes and dermal fibroblasts, stimulating intracellular pathways that drive cellular proliferation, migration, and re-epithelialization across the wound bed, (**Wang and Xu 2020)** while panthenol acts as a structural and metabolic precursor to support active tissue regeneration and epidermal maturation **(Ebner *et al.,* 2002)**. These findings closely agree with established literature demonstrating that local insulin applications significantly upregulate collagen deposition, total protein accumulation, and tissue remodeling during the proliferative phase of healing **(Zeng *et al.,* 2016)**. Furthermore, the pronounced, dose-dependent rise seen in the combination groups matches advanced dermatological studies evaluating co-adjuvant healing matrices, confirming that dual-action formulations containing panthenol effectively optimize granular matrix accumulation and tissue tensile strength **(Proksch *et al.,* 2017)**.

3. Effect of local insulin 0.1IU, 0.5 IU and its combination with panthenol on Hydroxyproline Levels in Rabbit Wound

Based on the statistical analysis using the Least Significant Difference (L.S.D.) test ($P \leq 0.05$), the combination of Insulin and Panthenol produced a highly significant, synergistic increase in Hydroxyproline levels compared to all other groups. The highest values were recorded in Insulin 0.5 + Panthenol (649.35 ± 44.31) and Insulin 0.1 + Panthenol (548.15 ± 94.42) groups; both share the letter 'a', meaning they are statistically similar to each other but significantly superior to the standalone treatments. Standalone Insulin administration showed a dose-dependent upward trend, where the higher dose of Insulin 0.5 (275.46 ± 17.36), letter 'b') significantly outperformed the controls, while Insulin 0.1 (227.07 ± 7.60), letter 'bc') yielded an intermediate response. Conversely, the control negative (62.71 ± 9.15), control positive (87.15 ± 20.48), and standalone Panthenol (137.89 ± 17.59) groups all shared the letter 'd', indicating no statistically significant differences among them. These findings demonstrate that while individual applications of Panthenol or low-dose Insulin provide limited benefits, co-administering Insulin with Panthenol drastically enhances Hydroxyproline synthesis**.** As shown in **Table 3**

Table 3: Effect of local insulin 0.1IU, 0.5 IU and its combination with panthenol on Hydroxyproline Levels in Rabbit Wound

Group	**Mean ±SD of Hydroxyproline**
Control negative	62.71 ±9.15 d
Control positive	87.15 ±20.48 d
Panthenol	137.89 ±17.59 cd
Insulin 0.1	227.07 ±7.60 bc
Insulin 0.5	275.46 ±17.36 b
Insulin 0.1+Penthenol	548.15 ±94.42 a
Insulin 0.5+Penthenol	649.35 ±44.31 a
L.S.D. value	122.20 *
Note. Values are expressed as Mean ± SD; *(n = 6)* for each excremental design	
Means having the different letters in same column differed significantly. * (P≤0.05).	

Topical administration of local insulin (0.1 IU and 0.5 IU) and panthenol, especially when used in combination, leads to a profound increase in hydroxyproline levels within rabbit wounds. This elevated level of hydroxyproline is directly attributed to the stimulated proliferation of fibroblasts and subsequent accelerated synthesis of collagen fibers within the extracellular matrix. **(Wang and Xu, 2020)** Mechanistically, topical insulin enhances cellular metabolism, facilitates early cell migration, and induces angiogenesis via specific cellular signaling pathways **(Gorski *et al.,* 2020)**, while panthenol acts as a structural and metabolic precursor to support active tissue regeneration and epidermal maturation **(Ebner *et al.,* 2002)**. These findings closely agree with established literature demonstrating that local insulin applications significantly upregulate collagen

deposition, total protein accumulation, and tissue remodeling during the proliferative phase of healing **(Zeng *et al.,* 2016).** Furthermore, the pronounced, dose-dependent rise seen in the combination groups matches advanced dermatological studies evaluating co-adjuvant healing matrices, confirming that dual-action formulations containing panthenol effectively optimize granular matrix accumulation and tissue tensile strength **(Proksch *et al.,* 2017).**

4. Effect of local insulin 0.1 IU, 0.5 IU and its combination with panthenol in IL-6 (Interleukin 6) and Tumour Necrosis Factor Alpha TNF concentration in Rabbit Wound

Statistical analysis using the Least Significant Difference (L.S.D.) test ($P \leq 0.05$) demonstrates that the combination therapies achieved the most significant reduction in interleukin-6 (IL-6) concentrations compared to all other evaluated groups. The lowest IL-6 levels were recorded in the Insulin 0.5 + Panthenol (59.29 ± 0.56) and Insulin 0.1 + Panthenol (92.67 ± 7.78) groups, which both share the letter 'e', indicating they are statistically similar to each other but significantly superior in suppressing this inflammatory marker compared to standalone treatments. Among the monotherapies, a dose-dependent anti-inflammatory effect was observed for Insulin, where the higher dose of Insulin 0.5 (160.12 ± 8.44, letter 'd') significantly outperformed Insulin 0.1 (217.31 ± 27.05, letter 'c'). Interestingly, standalone Insulin 0.1 and standalone Panthenol (219.32 ± 7.23) shared the letter 'c', revealing no statistical difference between their respective capabilities to lower IL-6. Conversely, the highest inflammatory responses were observed in the untreated groups, with that treated with gel exhibiting the peak concentration (543.69 ± 16.83, letter 'a') followed by the untreated group (489.11 ± 39.05, letter 'b'). Ultimately, these findings reveal that while standalone treatments moderately decrease IL-6, co-administering Insulin with Panthenol triggers a powerful synergistic effect that drastically suppresses IL-6 concentration, as fully detailed in **Table 4**

Table 4: Effect of local insulin 0.1 IU, 0.5 IU and its combination with panthenol in IL-6 (Interleukin 6) and TNF (Tumour Necrosis Factor Alpha) concentration in Rabbit Wound

Group	Mean ±SE of IL-6 (pg/ml)	Mean ±SE of TNF (pg/ml)
Control negative	489.11 ±39.05 b	106.97 ±3.71 a
Control positive	543.69 ±16.83 a	111.59 ±2.32 a
Panthenol	219.32 ±7.23 c	45.80 ±0.71 b
Insulin 0.1	217.31 ±27.05 c	47.91 ±6.15 b
Insulin 0.5	160.12 ±8.44 d	37.38 ±1.53 c
Insulin 0.1+Penthenol	92.67 ±7.78 e	30.37 ±1.01 cd
Insulin 0.5+Penthenol	59.29 ±0.56 e	27.24 ±1.15 d
L.S.D. value	47.523 *	8.134 *

Note. Values are expressed as Mean ± SD; *(n = 6)* for each excremental design

Means having the different letters in same column differed significantly.

* ($P \leq 0.05$).

The results demonstrate that topical administration of local insulin (0.1 IU and 0.5 IU) and panthenol, especially when used in combination, results in a profound, dose-dependent downregulation of Interleukin-6 (IL-6) concentrations within rabbit wounds compared to both control groups. The significant decrease in the level of interleukin-6 may be attributed to the complementary anti-inflammatory properties of both active agents; topical insulin effectively modulates the early cellular inflammatory cascade, downregulating pro-inflammatory cytokine expression while attenuating local oxidative damage inside the injury bed. At the same time, panthenol acts as a structural and metabolic coadjuvant, optimizing cellular bioenergetics and inhibiting over-activated regional macrophage infiltration to prevent prolonged acute tissue stress. These findings closely agree with established contemporary literature confirming that localized insulin therapies systematically restrict elevated inflammatory mediators like IL-6 and TNF-α, allowing the cellular framework to transition into the proliferative and remodeling phases of tissue repair **(Wang and Xu, 2020).** Furthermore, this pronounced synergistic decline aligns perfectly

with advanced dermatological studies establishing that active panthenol-containing matrix matrices optimize extracellular tissue recovery while suppressing deleterious inflammatory markers **(Gorski *et al.,* 2020).**

Statistical analysis using the Least Significant Difference (L.S.D.) test ($P \leq 0.05$) reveals that all treatment applications significantly reduced Tumor Necrosis Factor Alpha (TNF-α) concentrations compared to the first and second groups. The control positive (111.59 ± 2.32) and control negative (106.97 ± 3.71) groups shared the letter 'a', representing the highest baseline inflammatory status. Standalone treatments with Panthenol (45.80 ± 0.71) and Insulin 0.1 (47.91 ± 6.15) both shared the letter 'b', showing an identical, moderate capacity to lower TNF-α, whereas increasing the standalone dose to Insulin 0.5 (37.38 ± 1.53, letter 'c') caused a significantly greater reduction. The most pronounced anti-inflammatory effect was achieved by the combination groups; Insulin 0.5 + Panthenol (27.24 ± 1.15, letter 'd') led to the lowest absolute TNF-α concentration, while Insulin 0.1 + Panthenol (30.37 ± 1.01, letter 'cd') shared statistical similarity with both the high-dose combination and standalone Insulin 0.5. These results confirm that while individual therapies effectively lower tissue inflammation, co-administering insulin with panthenol provides the maximum suppression of TNF-α levels, as shown in **Table 4**

The significant decrease in the level of Tumor Necrosis Factor-alpha (TNF-α) observed across the treated groups may be attributed to the capacity of local insulin to downregulate the over-activated acute inflammatory cascade, suppressing the recruitment of pro-inflammatory macrophages and downstream cytokine signaling pathways within the injured tissue framework. Simultaneously, panthenol works alongside insulin by acting as a cellular energy precursor that reduces localized oxidative stress and helps transition the microenvironment from an active inflammatory phase into a proliferative tissue remodeling phase. These findings closely agree with established contemporary literature demonstrating that localized low-dose insulin applications systematically restrict elevated inflammatory mediators like TNF-α and IL-6, thereby preventing chronic wound stress and accelerating overall epidermal closure (**Wang and Xu, 2020)**. Furthermore, this pronounced synergistic reduction aligns perfectly with advanced dermatological studies establishing that topically applied panthenol downregulates key pro-inflammatory gene matrices to support early fibroblastic activity and restore extracellular matrix stability (**Gorski *et al.,* 2020)**.

5. Effect of local insulin 0.1 IU, 0.5 IU and its combination with panthenol in CAT (Catalase) and MDA (Malondialdehyde) concentration in Rabbit Wound

Statistical analysis using the Least Significant Difference (L.S.D.) test ($P \leq 0.05$) demonstrates that the combination therapies achieved the most significant increase in Catalase (CAT) concentrations compared to all other evaluated groups. The absolute highest antioxidant activity was recorded in the Insulin 0.5 + Panthenol group (360.34 ± 13.56), which uniquely holds the letter 'a', making it statistically superior to all other treatments. The Insulin 0.1 + Panthenol group (298.69 ± 4.74), letter 'b') also demonstrated an exceptional capacity to elevate CAT levels, significantly outperforming all monotherapies. Among the standalone treatments, a clear dose-dependent response was observed for Insulin, where Insulin 0.5 (260.71 ±12.30) Custom letters 'c' group) significantly surpassed Insulin 0.1 (218.09 ± 5.30), letter 'd'). Conversely, the lowest Catalase concentrations were observed in the negative control (102.46 ±2.02), positive control (95.59 ± 2.75), and standalone Panthenol (108.61 ± 4.33) groups. These three groups all shared the letter 'e', indicating no statistically significant differences among them. Ultimately, these tabulated findings reveal that while individual Panthenol application provides no benefit to antioxidant levels and standalone Insulin offers moderate improvements, co-administering Insulin with Panthenol triggers a powerful synergistic effect that drastically maximizes Catalase concentration**.** As shown in **Table 5**

Table 5 Effect of local insulin 0.1 IU, 0.5 IU and its combination with panthenol in CAT (Catalase) and MDA (Malondialdehyde) concentration in Rabbit Wound

Group	Mean ±SE of CAT (Pg/ml)	Mean ±SE of MDA (Pg/ml)
Control negative	102.46 ±2.02 e	505.81 ±87.70 b
Control positive	95.59 ±2.75 e	927.99 ±147.09 a
Panthenol	108.61 ±4.33 e	323.36 ±30.49 bc
Insulin 0.1	218.09 ±5.30 d	186.68 ±4.97 cd
Insulin 0.5	260.71 ±12.30 c	158.63 ±10.64 cd

Insulin 0.1+Penthenol	298.69 ±4.74 b	127.79 ±5.92 cd
Insulin 0.5+Penthenol	360.34 ±13.56 a	90.62 ±13.55 d
L.S.D. value	37.625 *	207.74 *
Note. Values are expressed as Mean ± SD; *(n = 6)* for each excremental design Means having the different letters in same column differed significantly. * (P≤0.05).		

The significant increase in the level of Catalase (CAT) observed across the treated groups may be attributed to the capacity of local insulin to actively stimulate the cellular enzymatic antioxidant defines network. This pathway directly upregulates endogenous scavenging enzymes to mitigate excessive accumulation of reactive oxygen species (ROS) and hydrogen peroxide (H2O2) at the injury site, thereby minimizing tissue degradation **(Wang and Xu, (2020).** Concurrently, panthenol works in a complementary manner by acting as a structural and energetic precursor that reduces local oxidative stress, prevents lipid peroxidation, and protects cellular membranes from oxidative damage during active tissue repair **(Gorski et al., 2020).**These findings closely agree with contemporary literature establishing that topical insulin applications enhance endogenous antioxidant defenses including catalase and superoxide dismutase by modulating intracellular signaling pathways to shift the wound environment out of prolonged oxidative stress and into active proliferation (**Ramírez-GarcíaLuna *et al.,* 2023)**. Furthermore, this pronounced synergistic elevation aligns perfectly with recent dermatological studies demonstrating that modern co-adjuvant healing formulations effectively upregulate key cytoprotective matrices and scavenging mechanisms, which stabilizes the extracellular framework and ensures cell survival during the matrix remodeling phase **(Comino-Sanz *et al.*, 2021)**

Statistical analysis using the Least Significant Difference (L.S.D.) test ($P \leq 0.05$) demonstrates that all treatment applications substantially reduced Malondialdehyde (MDA) concentrations compared to the first and second groups, signaling a significant reduction in lipid peroxidation and oxidative stress. The group treated with gel (927.99 ± 147.09) exhibited the absolute peak concentration of MDA and held the letter 'a', which significantly differed from the untreated group (505.81 ± 87.70, letter 'b'). Standalone Panthenol treatment (323.36 ± 30.49) shared the letters 'bc', indicating an intermediate reduction that overlapped statistically with the control untreated group. Conversely, standalone Insulin doses (Insulin 0.1 and Insulin 0.5) and the combination therapies induced the lowest levels of MDA, all sharing the letter 'd' (or 'cd'). The absolute lowest MDA accumulation was achieved by the Insulin 0.5 + Panthenol group (90.62 ± 13.55), which statistically outperformed the Panthenol monotherapy and the controls. Ultimately, these findings reveal that while individual treatments—particularly insulin—effectively suppress oxidative damage, combining a higher dose of insulin with panthenol provides the most robust reduction in MDA production, as fully detailed in **Table 5**

The significant decrease in the level of Malondialdehyde (MDA) may be attributed to the combined antioxidant and cytoprotective properties of both active agents; topical insulin downregulates lipid peroxidation, protects vulnerable cell membrane lipid bilayers, and actively suppresses the over-activation of the acute tissue necrotic cascade at the injury site **(Wang and Xu, 2020)**. Concurrently, panthenol works synergistically as a structural co-adjuvant and metabolic precursor to Coenzyme A, elevating local bioenergetic pathways, reducing free radical accumulation, and neutralizing toxic reactive oxygen species (ROS) that induce severe lipid damage **(Gorski *et al.,* 2020).** These findings closely agree with contemporary literature establishing that topical insulin therapy minimizes local oxidative stress biomarkers and curbs elevated membrane lipid breakdown to shift the tissue out of chronic inflammation and into successful active proliferation **(Wang and Xu, 2020)**. Furthermore, this pronounced synergistic decline aligns perfectly with recent dermatological studies demonstrating that modern d-panthenol protective matrices effectively reduce lipid degradation products, like MDA, while upregulating endogenous cellular defenses to preserve matrix integrity during the tissue remodeling phase **(Gorski *et al.,* 2020)**.

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HISTOPATHOLOGICAL STUDY

1. Healthy skin before wound induction

The histopathological section of skin in a healthy Rabbit clearly delineates the distinct layers of the epidermis (E) and the underlying dermis (D). Within the stratified squamous epidermis, the sequential specialized layers are highlighted by the white line, demonstrating the expected differentiation from the deeper stratum basal up to the superficial stratum corneum. Beneath the dermal-epidermal junction, denoted by the black arrow, the dermis is populated by standard structural features, including regular loose and dense irregular connective tissue networks. Furthermore, healthy skin appendages are well-preserved, showcasing clearly defined sebaceous glands (SG) and robust hair follicles (HF) embedded within the dermal matrix, as shown in **Figure 1**

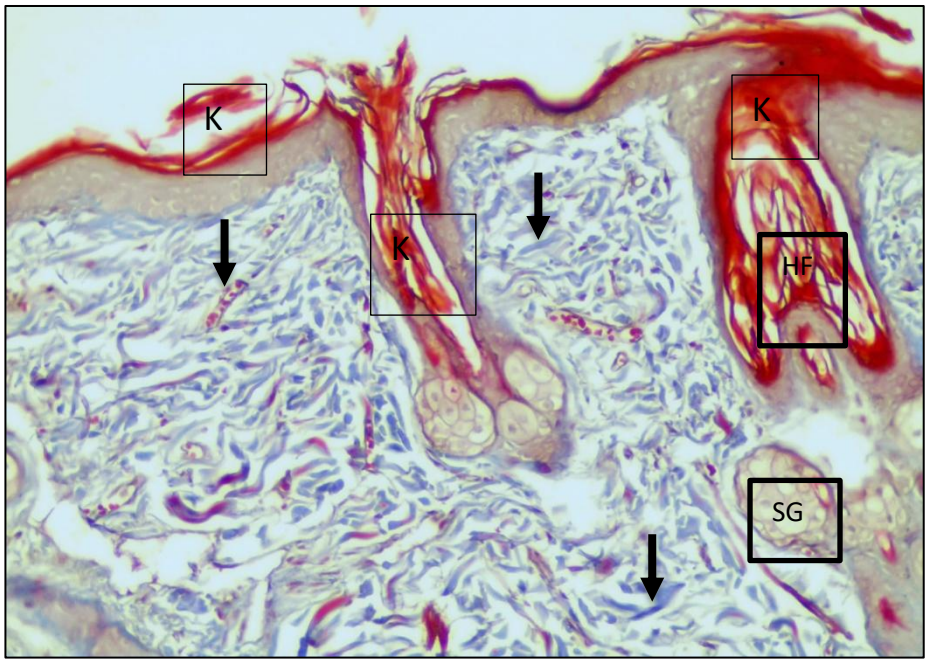

Figure 1. Representative histological image of unwounded skin of rabbit stained with Masson's trichrome stain shows normal epidermis with distinct, red-stained keratin layers (K). The dermis consists of wavy collagen bundles stained blue (blue arrow), and the dermal blood vessel walls, hair follicles (HF), and sebaceous glands presenting with bright red cytoplasm. MT, 20X.

2. Histopathological Rabbit untreated wounded skin

The histopathological evaluation of the untreated wounded rabbit skin using Masson's Trichrome (MT) staining at 20X magnifications reveals a highly vascularized dermal layer undergoing active repair. The dermis is heavily occupied by an abundance of vascular granulation tissue featuring a dense network of newly formed capillaries and localized inflammatory activity. Crucially, the MT stain clearly differentiates extracellular matrix components: immature collagen fibers and newly synthesized blood vessels are stained distinctively in red, while the irregular, unorganized wavy collagen fibrils stain a contrasting light bluish hue. Anchored at the uppermost margin of this healing tissue, a heavy layer of dark, red-stained necrotic and cellular debris remains present, outlining the unmodulated progression of the superficial wound boundary **as shown in Figure 2.**

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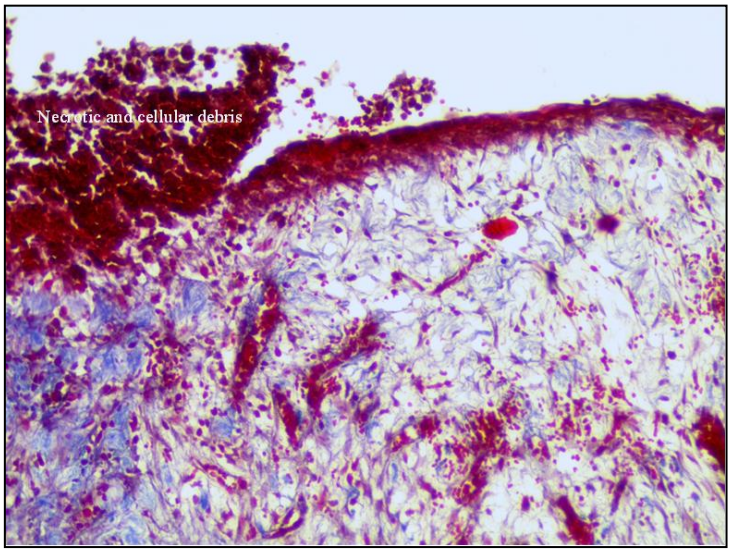

Figure 2. Representative histopathological image of untreated wounded skin group stained with MT shows the dermis occupied by large amount of vascular granulation tissue rich with newly formed capillaries and irregular wavy collagen fibrils that gave light bluish with MT stain. 20X.

Note: Immature collagen and blood vessels fibers stained with red color.

3. Histopathological features of rabbit wounded skin treated with carbomer gel

Histopathological examination using Masson's Trichrome (MT) staining at 20X magnifications highlights the structural remodeling profile of the untreated wound in . The lost dermal architecture is heavily replaced by hyalinized collagen bundles and dense vascular granulation tissue. Abundant newly formed capillaries appear prominently within the red-stained superficial healing zones. Directly beneath this vascular matrix, immature, unorganized wavy collagen fibrils stain a light blue hue, indicating disorganized fibroblastic deposition. Deeper baseline tissue displays moderate-to-strong blue coloration, marking intact, mature host collagen bundles unaffected by the primary injury. Together, these distinct staining patterns demonstrate a highly vascularized but poorly consolidated structural matrix characteristic of unmodulated healing. **Figure 3**

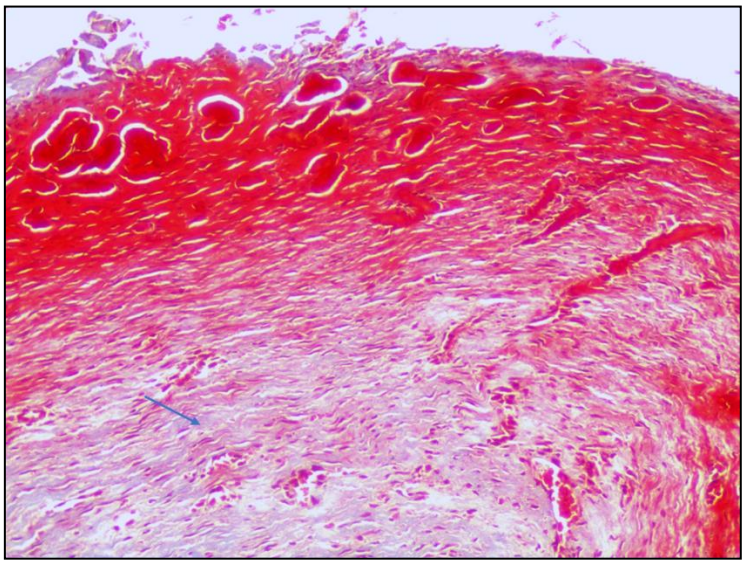

Figure 3. Representative histopathological image of untreated wounded skin of rabbit stained with MT shows the lost dermis was occupied by hyalinized collagen bundles and large amount of vascular granulation tissue rich with newly formed blood capillaries (red area). Irregular wavy collagen fibrils stained with light blue (blue arrow). MTS 20X

4. Histopathological features of rabbit wounded skin treated with Panthenol

The histopathological evaluation of wounded rabbit skin treated with Panthenol using Masson's Trichrome (MT) staining at 20X magnifications illustrates the specific structural remodeling and collagen matrix architecture of the healing zone. The analysis confirms that the lost dermis is heavily occupied by a dense superficial layer of necrotic and cellular debris integrated with hyalinized collagen bundles. Directly beneath this damaged boundary, a moderate amount of vascular granulation tissue has formed, which is heavily populated by newly developing capillaries. Furthermore, the stain differentiates a mild amount of immature, irregular, wavy collagen fibrils that take on a characteristic light blue coloration . Taken together, these findings demonstrate that while initial fibroblastic matrix deposition and angiogenesis have begun, the structural foundation remains poorly organized and weakly consolidated, which is highly indicative of an unmodulated, slow-progressing wound healing process as Shawon in **Figure 4**

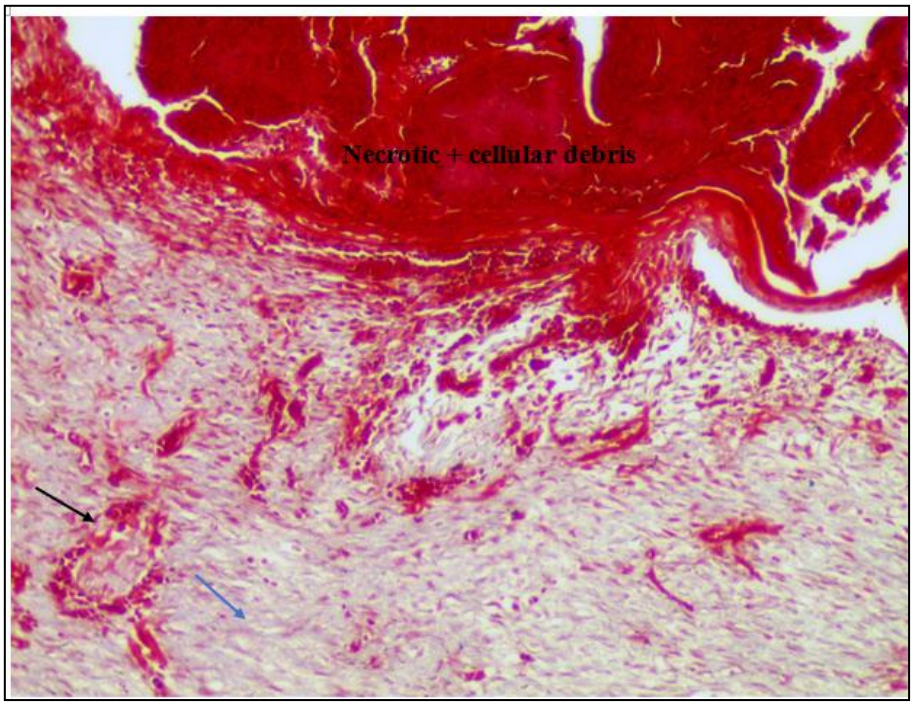

Figure 4. Representative histopathological image of wounded rabbit skin treated with Panthenol stained with MT shows the lost dermis was occupied by necrotic and cellular debris with hyalinized collagen bundles. Moderate amount of vascular granulation tissue (black arrows) with mild amount of irregular wavy collagen fibrils stained with light blue (blue arrow). MTS 20X.

5. Histopathological features of rabbit wounded skin treated with Insulin 0.1IU

The histopathological examination wounded skin of rabbits treated with Insulin 0.1IU using Masson's Trichrome (MT) staining at 20X magnifications highlights a distinct structural matrix remodelling profile. Within the healing zone, the stain reveals only a mild amount of irregular, wavy collagen fibrils that present with a faint light blue coloration. This weak hue signifies highly disorganized fibroblastic deposition and an incomplete structural reconstruction at the primary site of injury. In contrast, the surrounding undamaged, deeper tissue margins demonstrate a clear line of demarcation, displaying strongly stained, dense host mature collagen bundles highlighted in a deep blue tone . Taken together, these findings confirm that while early structural fiber deposition has initiated, the wound matrix remains weak, poorly consolidated, and largely reliant on the uninjured native tissue framework for mechanical support.as shown in **Figure 5**

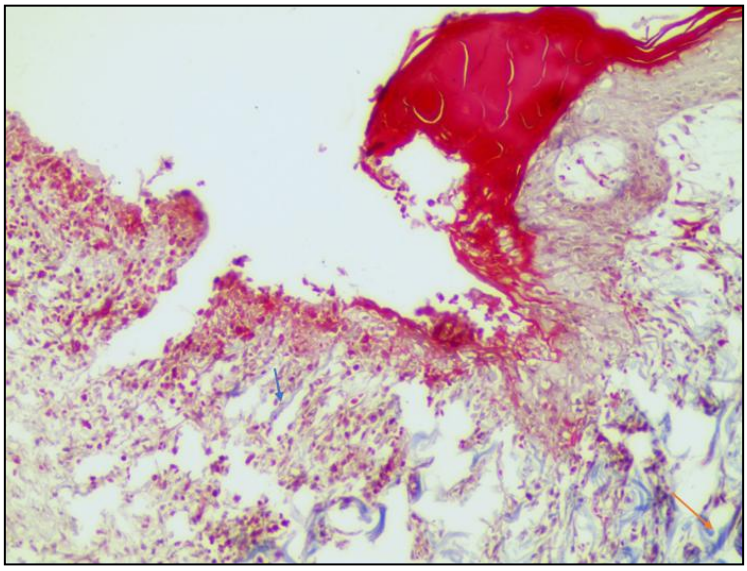

Figure 5. Representative histopathological image of wounded skin of rabbits treated with Insulin 0.1IU of rabbit stained with MT shows mild amount of irregular wavy collagen fibrils stained with light blue (blue arrow), with evidence of strong stained host mature collagen bundles (orange arrow). MTS 20X.

6. Histopathological features of rabbit wounded skin treated with Insulin 0.5 IU

The histopathological evaluation of wounded rabbit skin treated with insulin 0.5 IU using Masson's Trichrome (MT) staining at 20X magnifications confirms a highly advanced structural remodelling and tissue maturation profile. The superficial dermal layer demonstrates only a mild-to-moderate presence of residual vascular granulation tissue, indicating a successful down-regulation of acute angiogenic activity. Crucially, the underlying dermis is dominated by a dense deposition of parallelly aligned fibrous connective tissue. These newly synthesized extracellular matrix components are composed of organized, irregular, wavy collagen bundles that take on a characteristic mild blue color under MT staining. Taken together, these findings verify that the wound architecture in this group has effectively transitioned into a mature remodelling phase, characterized by a well-consolidated structural foundation and organized collagen deposition As shown in **Figure** 6

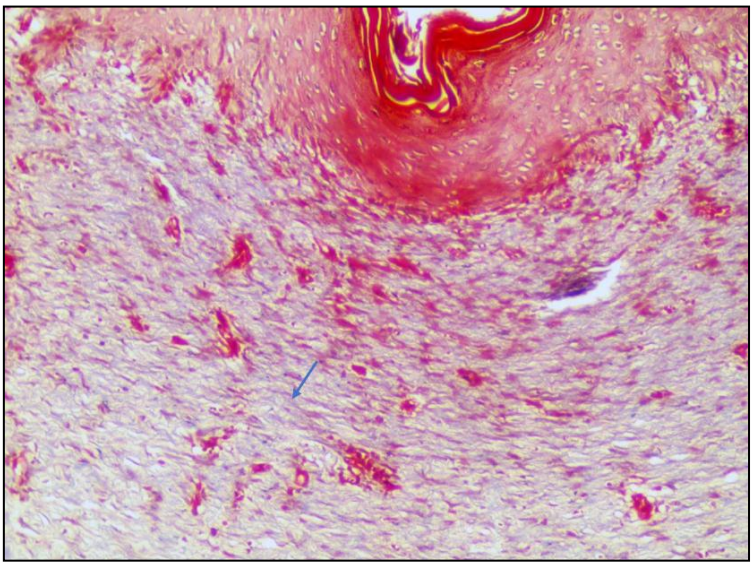

Figure 6. Representative histopathological image of wounded rabbit skin treated with Insulin 0.5 IU of rabbit stained with MT shows mild-moderate vascular granulation tissue at the superficial dermal layer with dense amount of parallel aligned fibrous connective that composed of irregular wavy collagen bundles stained with mild blue color (blue arrow). MTS 20X.

7. Histopathological features of rabbit wounded skin treated with Insulin 0.1 IU and Panthenol combination

The histopathological examination of wounded skin rabbit treated with Insulin 0.1 IU and Panthenol combination using Masson's Trichrome (MT) staining at 20X magnifications confirms an advanced stage of structural matrix consolidation and dermal maturation. The superficial dermal layer exhibits only mild vascular granulation tissue, indicating that the acute angiogenic phase has successfully resolved. Crucially, the underlying dermis is filled with a dense amount of parallelly aligned fibrous connective tissue. This tissue consists of well-organized, irregular, wavy collagen bundles that take on a prominent, moderate-to-marked blue coloration. Taken together, these findings demonstrate that wounded skin rabbit treated with Insulin 0.1 IU and Panthenol combination has successfully synthesized a dense, highly stable, and well-consolidated extracellular matrix framework

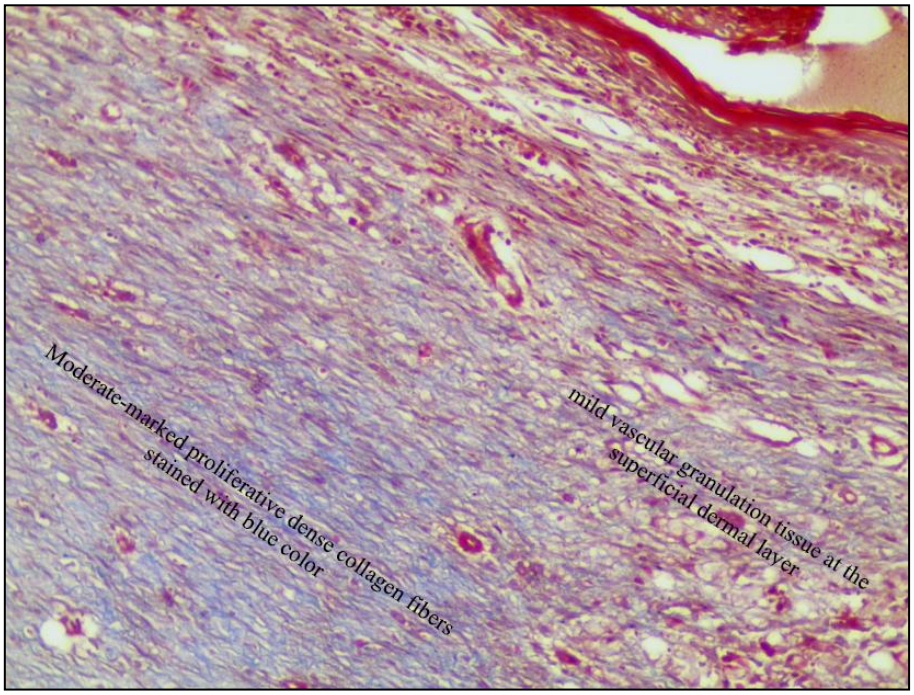

Figure 7. Representative histopathological image wounded skin rabbit treated with Insulin 0.1 IU and Panthenol combination stained with MT shows mild vascular granulation tissue at the superficial dermal layer with dense amount of parallel aligned fibrous connective that composed of irregular wavy collagen bundles stained with moderate-marked blue color. MTS 20X.

8. Histopathological features of rabbit wounded skin treated with Insulin 0.5 IU and Panthenol combination

The histopathological examination of wounded skin rabbits treated with Insulin 0.5 IU and Panthenol combination using Masson's Trichrome (MT) staining at 20X magnifications highlights a highly advanced structural remodelling and matrix stabilization process. The superficial dermal layer exhibits only mild vascular granulation tissue, indicating that the acute inflammatory and hyper-angiogenic phases have successfully resolved. Crucially, the sub-epidermal zone is filled with a dense amount of parallelly aligned fibrous connective tissue composed of irregular, wavy collagen bundles stained with a moderate blue colour. Meanwhile, the deeper dermal layer exhibits strongly blue-stained, mature collagen bundles. Together, these distinct staining patterns demonstrate excellent matrix maturation, showcasing a well-consolidated structural foundation that tightly integrates newly synthesized tissue with the native host dermis as shown in **Figure 8.**

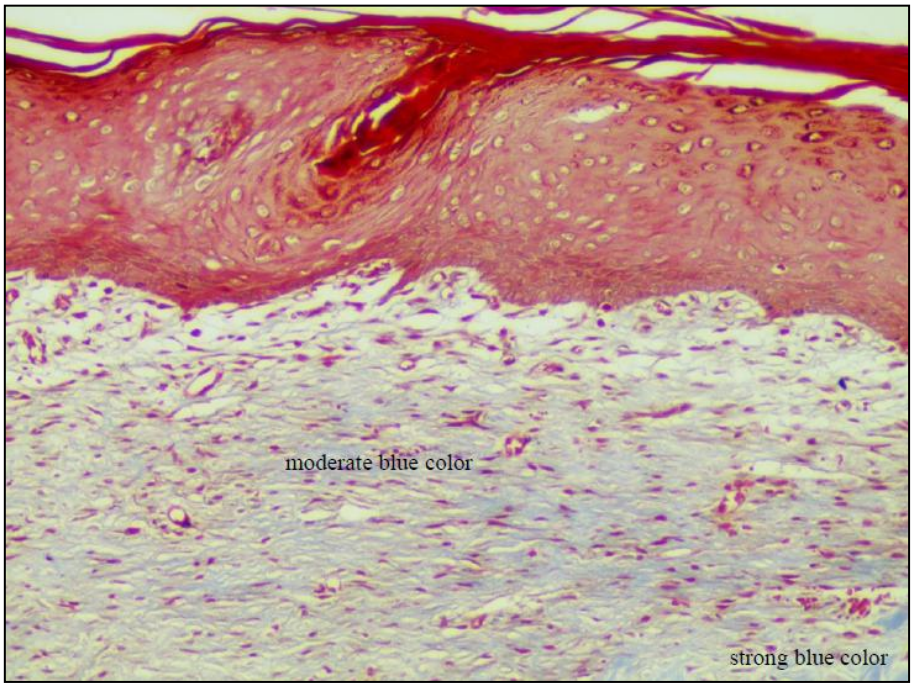

Figure 8. Representative histopathological image of wounded skin rabbits treated with Insulin 0.5 IU and Panthenol combination and stained with MT shows mild vascular granulation tissue at the superficial dermal layer with dense amount of parallel aligned fibrous connective that composed of irregular wavy collagen bundles stained with moderate blue color at the superficial dermal layer, while the collagen bundles of the deep dermal layer were strongly blue-stained. MTS 20X.

CONCLUSIONS

Topical insulin played an important role in accelerating the wound-healing process and the combination of insulin and panthenol produced greater wound-healing effects than either treatment alone, indicating a synergistic interaction.

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