P-ISSN 1991-8941
E-ISSN 2706-6703
Vol. 20, No. 1 (2026)

Journal of University of Anbar for Pure Science
(JUAPS)

journal homepage: juaps.uoanbar.edu.iq

Open Access

Original Paper

The potential wound healing and antimicrobial effects of silver nanoparticles and hyaluronic acid in animal models

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ARTICLE INFO

Received: 18/06/2025
Accepted: 24/08/2025
Available online: 01/03/2026
April Issue
10.37652/juaps.2025.161691.1447

Cite @ JUAPS

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ABSTRACT

This study aimed to investigate the wound healing properties and antimicrobial activity of silver nanoparticles, hyaluronic acid, and their combination in animal models. Twenty rabbits were divided into five groups (n = 4): group 1, the control group; group 2, the induction group; group 3, the group treated with 1% silver nanoparticle ointment (1% SNO); group 4, the group treated with hyaluronic acid ointment (HAO); and group 5, the combination-treated group. Skin wounds were induced in the latter four groups, contaminated with multidrug-resistant Pseudomonas aeruginosa, and treated for 15 days. The healing process was evaluated based on gross and histopathological findings. Histopathological scoring was used to compare the groups. Results showed that wound healing improved in all treated groups compared with the induction group. The 1% SNO-treated group showed better results than the HAO-treated group in reducing inflammation, while the HAO-treated group also showed improvement compared with the induction group. The 1% SNO group showed a greater reduction in inflammation, whereas the HAO group exhibited better epidermal regeneration. The most significant acceleration of wound healing was observed in the combination-treated group (group 5). It was also noted that this group had the lowest score (0) for inflammation and granulation tissue formation and the highest scores (4) for the regeneration of skin appendages, collagen deposition, and re-epithelialization compared with other groups. In conclusion, combining HAO and SNO may be more effective than using either treatment alone. To our knowledge, this is the first study to use a combination of SNO and HAO for treating skin wounds.

Keywords: *Hyaluronic acid, Nanosilver, Skin wound, Wound healing*

1 INTRODUCTION

Wound healing is a complex process that involves interactions among many cell types and an appropriate extracellular microenvironment. It includes coordinated sequential events such as coagulation, inflammation, proliferation, and tissue remodeling. Because of their role in wound healing and broad-spectrum antimicrobial activity, silver compounds have been widely used for hygienic and healing purposes [1, 2]. In the 17th and 18th centuries, silver nitrate was used to treat ulcers, and since 1960, silver has been employed in wound management. Recently, due to rising antibiotic resistance and advances in polymer technology, interest in silver has been renewed. Many silver-containing dressings are commercially available and widely used in burn

treatment, either as silver-impregnated bandages or silver sulfadiazine creams. Silver-based products are considered essential in burn management [3].

Multiple types of silver preparations, such as silver-based dressings, are widely available today. Most are fibers, impregnated scaffolds, or products coated with silver salts or metallic silver nanoparticles. All exhibit broad-spectrum antibacterial activity against both Gram-negative and Gram-positive microbes [4, 5]. The mechanisms by which silver exerts antimicrobial activity include effects on the bacterial cell wall and DNA, as well as the ability to block respiratory enzyme pathways. This antimicrobial activity has been demonstrated even against multidrug-resistant microbes [6, 7]. Several clinical studies have shown the safety and lower systemic toxicity of silver-containing products [8].

Particles with a size of 100 nm or less are considered nanoparticles. Due to their unusual physical, chemical, and biological properties, silver nanoparticle-containing dressings have been widely used in vitro. Several recent studies have shown that silver nanoparticle dressings possess broad-spectrum antimicrobial activity and are non-cytotoxic; however, there are a limited number of in vivo studies to confirm this fact [9–14]. Some researchers have reported cytotoxicity for fibroblasts and keratinocytes; however, these studies demonstrated this only in vitro. This could be due to decreased mitochondrial function [15,16], production of reactive oxygen species (ROS), and DNA damage in human mesenchymal stem cells [17].

Hyaluronic acid belongs to glycosaminoglycans (GAGs), which are major components of the extracellular matrix. The hyaluronic acid molecule consists of D-glucuronic acid and N-acetyl-D-glucosamine linked by β-glycosidic bonds. It has unique features that distinguish it from other GAGs, including its structure as a very long linear polymer of simple molecular units repeated thousands of times, its large molecular size (approximately 5×10^6 kDa) [18, 19], and the fact that it does not attach to a core protein or undergo modification after synthesis. It is widely hypothesized that the molecular size of hyaluronic acid significantly influences its biological activities and tissue functions. For example, high-molecular-weight hyaluronic acid (HMWHA) exhibits anti-inflammatory and immunosuppressive properties, while low-molecular-weight hyaluronic acid (LMWHA) has potent pro-inflammatory properties [20].

The sequential events in wound healing aim to repair injured tissue, with the extracellular matrix playing a crucial role at all stages, including cellular migration, inflammation, angiogenesis, remodeling, and scar formation. It is well documented that hyaluronic acid is involved in various signaling pathways within the wound microenvironment during healing. Additionally, as an important extracellular matrix component with unique properties, hyaluronic acid helps promote tissue regeneration [21, 22].

This study aims to explore the antimicrobial and wound-healing properties of a combination of silver nanoparticle ointment (SNO) and hyaluronic acid ointment (HAO) compared with their individual applications.

2 MATERIALS AND METHODS

2.1 Study setting

The study was conducted in the Department of Pathology and Forensic Medicine, College of Medicine, Misan University, Maysan, Iraq.

2.2 Animals

Animals included in the study were obtained from the National Center for Drug Control and Research. They were housed in individual cages maintained at 23–26 °C and 40%–50% humidity, with regular light–dark cycles. The animals were provided with standard pellet food and water ad libitum. These procedures followed the guidelines for the care and use of experimental animals in the laboratory.

2.3 Experimental animals and study design

A total of twenty adult rabbits, twenty weeks old and weighing 1–1.5 kg, were used in the experiment. The animals were divided into five groups (4 rabbits each). Group 1 served as the control; group 2 as the induction group; group 3 was treated with 1% silver nanoparticle ointment; group 4 was treated with hyaluronic acid; and group 5 received a combination of nanosilver and hyaluronic acid. Silver nanoparticles were purchased from Areej Al-Furat Company, Baghdad, Iraq, while hyaluronic acid ointment was obtained from Al-Urjuan Pharmacy, Maysan, Iraq. The bacterial isolates used to inoculate the wound were multidrug-resistant strains of Pseudomonas aeruginosa, isolated from patients with burn injuries in the burn care unit at Al-Sader Teaching Hospital, Maysan, Iraq. A bacterial suspension was prepared by incubating the isolates in an enrichment medium to obtain a suspension matching the 0.5 McFarland scale standard.

2.4 Preparation of a 1% silver nano-particle ointment (1% SNO)

Silver nanoparticles were obtained as a pre-prepared powder consisting of pure silver with a size of 20 nm, as verified by the manufacturer through a scanning electron micrograph in the leaflet enclosed with the product package. One gram of nanosilver powder was mixed with 3 mL of castor oil and stirred well until fully homogenized. The volume was then adjusted to 100 mL with white petroleum jelly to prepare a 1% nanosilver ointment. The characteristics of the ointment, including viscosity, spreadability, and pH, were estimated in our previous study [23].

2.5 Induction of experimental wound

A 5 cm incisional wound was created using a sterile scalpel on the skin of the rabbits' thighs in the study groups under anesthesia, except for the control group. The incisions were infected with 100 µL [24] of P. aeruginosa suspension and then closed with sutures. Wound healing was evaluated every five days over a 15-day period. During this time, healing was visually observed, and data were recorded and photographed. Assessment of healing included measuring wound size, scab exfoliation, and the appearance of granulation tissue.

2.6 Study groups and surgical procedure

Animals in the study groups (except those in the control group) were anesthetized by intramuscular injection of both xylazine (0.15 mg/kg) and ketamine (15 mg/kg). A 5 cm surgical incision was made, involving the full thickness of the thigh skin. The incision was sutured using 3/0 sutures.

The study groups were organized as follows: group 1 served as the negative control; group 2 as the induction group; group 3 received 1% nanosilver ointment; group 4 received hyaluronic acid; and group 5 received a combination of 1% nanosilver and hyaluronic acid ointments. All groups received topical applications of the ointments under study. Specifically, group 2 was treated with a mixture of white petroleum jelly and castor oil, both of which were used to prepare the tested ointments. Group 3 received 1% SNO, group 4 was treated with hyaluronic acid, and group 5 was treated with a combination of 1% SNO and hyaluronic acid ointments. Wound treatment was continued once daily for 14 days, and on day 15, the incision site was harvested and processed for histopathological study.

2.7 Histopathological preparation

Skin samples were fixed in formalin for 48 hours. Fixed samples were dehydrated using an ascending series of alcohol concentrations: 70%, 80%, 90%, and 100%, with the last two doubled. Tissues were cleared with xylene and embedded in paraffin. Samples were sectioned at 5 µm using a microtome, mounted on slides, and stained with hematoxylin and eosin [25].

2.8 Scoring of the histopathological findings

Histopathological findings were scored to improve comparison between groups and to accurately measure tissue improvement caused by each treatment; this was performed as described in a previous study [26], as shown in Table 1. The scoring parameters included inflammation, granulation tissue formation, re-epithelialization, and regeneration of skin appendages.

Table 1 Scoring Parameters

S	Range of scores	Score	Value of change
1	0	0	No change
2	1-25%	1	The maximum average of the change is up to 25%.
3	26-50%	2	The maximum average of the change is between 26% and 50%.
4	51-75%	3	The maximum average of the change is between 51% and 75%.
5	> 75%	4	The maximum average of the change is > 75%.

2.9 Statistical analysis

Statistics were analyzed using SPSS. A one-way ANOVA was used to compare histopathological findings, and results were presented as means ± standard errors.

3 RESULT AND DISCUSSION

3.1 Gross findings

After wound induction, all groups exhibited similar wound features during the first three days. These included swelling, redness, and clot formation at the wound site, especially along the incision edges. In this study, rabbits served as an experimental model to evaluate wound-healing effectiveness, as they closely mimic the human wound-healing process [27].

The gross appearance of the wound showed significant differences between the induction and treated groups throughout the study period. The induction group displayed signs of wound infection by day five after induction of the infected incision. After 10 days, a thick, creamy discharge became visible and persisted until day 15. Minimal granulation tissue was observed at the wound

edges, and the wound showed no signs of healing by the end of the experiment (Figure 1A). In the hyaluronic acid ointment-treated group, the wound showed similar signs of purulent discharge; however, granulation tissue was more prominent than in the induction group (Figure 1B). The 1% SNO-treated group showed complete wound closure (Figure 1C). The combination group demonstrated complete wound union with minimal remaining granulation tissue, along with noticeable shrinking and a significant reduction in wound size (Figure 1D).

Hemostasis and inflammation are the initial stages of healing, beginning within minutes to hours after injury [28]. Hemostasis occurs first, followed by inflammation, which is vital for healing. Inflammation is a natural and well-coordinated process that removes dead tissue, debris, and bacteria, while also promoting the growth of new blood vessels and the recruitment and activation of fibroblasts in the injured area [29]. The inflammatory phase typically begins within 24 hours after injury, peaks between 24 and 48 hours, and can last for several days or longer, depending on the severity of the injury [30]. The primary goal of wound healing is to facilitate faster recovery with minimal scarring. Chronic wounds may result from prolonged inflammation that impairs the healing process. Many factors contribute to protracted inflammation, including infection [31]. Therefore, reducing inflammation and controlling infection are essential for improving wound healing. In this study, the induced wound was contaminated with multidrug-resistant P. aeruginosa, and silver nanoparticles and hyaluronic acid were used as ointments, both individually and in combination, to assess their effects on wound healing.

Silver nanoparticles were prepared as a 1% silver ointment, and their characteristics, including homogeneity, viscosity, and spreadability, were consistent with those reported in a previous study [23]. The 1% SNO-treated group showed complete wound closure. The microscopic view revealed complete re-epithelialization of the epidermal layer; these findings align with those reported by [23]. The well-known antimicrobial activity of silver nanoparticles, compared with other salts, can be attributed to their large surface area, which enhances contact with microorganisms. Silver nanoparticles penetrate bacteria by attaching to the cell membrane. They interact with bacterial cell components, such as sulfur-containing proteins and phosphorus-containing structures, such as DNA. Inside the bacteria, they disrupt the respiratory chain by interacting with thiol groups on respiratory enzymes, thereby hindering cell division and ultimately leading to cell death. Silver nanoparticles also release silver ions within bacterial cells, further enhancing their bactericidal effect [32–35].

In contrast to the induction and hyaluronic acid-treated groups, the SNO-treated group showed no pus, demonstrating silver's ability to modulate the inflammatory response, a crucial component of the wound-healing process. Various inflammatory mediators are involved in the routine process of wound healing. The balance between pro- and anti-inflammatory cytokines is vital for successful wound repair and epithelial regeneration, and it must be tightly regulated in vivo, as prolonged inflammation contributes substantially to impaired wound healing [36].

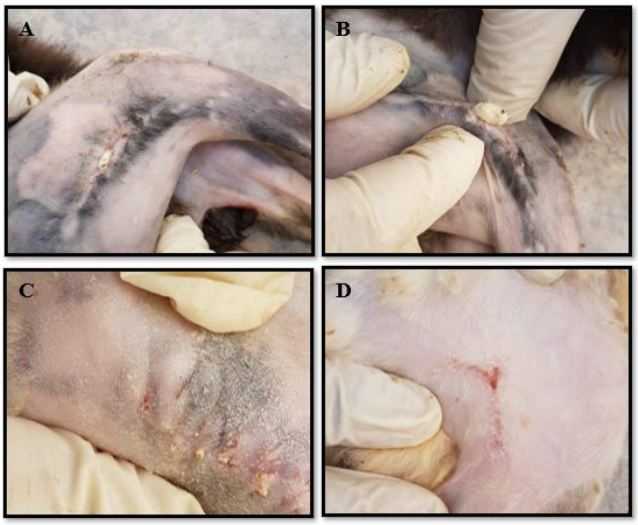

Fig. 1 Gross findings of the wound: A) no wound closure with pus formation, B) partial wound closure with minimal pus at the wound site, C) complete wound closure with small abscesses, D) complete wound closure with no scab formation; however, re-epithelialization of the epidermal layer was observed.

3.2 Histopathological findings

The skin section of the negative control group appeared within normal limits. The epidermal layer consisted of a superficial keratin layer overlying normal stratified squamous epithelium with an intact basement membrane, showing a clear boundary between the epidermis and dermis. The dermis contained well-organized skin appendages (e.g., hair follicles, sebaceous glands, sweat glands) surrounded by collagen fibers, as shown in Figure 2.

The induction group exhibited significant acute inflammation at the wound site, characterized by hemorrhage and liquefactive necrosis (Figure 3). No collagen deposition was observed in the area, and no evidence of granulation tissue formation or epithelial regeneration in the epidermal layer was observed. Various inflammatory mediators are involved in the routine process of wound healing. The balance between pro- and anti-inflammatory cytokines is vital for successful wound repair and epithelial regeneration, and it must be tightly regulated in vivo, as prolonged inflammation significantly contributes to impaired wound healing [36].

IL-10 is an essential anti-inflammatory mediator produced by keratinocytes. Its unique action is to suppress pro-inflammatory cytokines, including IL-6. IL-10 also inhibits the synthesis of monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-1a (MIP-1a), thereby reducing leukocyte migration to the wound site [37, 38].

The hyaluronic acid-treated group showed significant collagen buildup, extensive granulation tissue formation, and partial regeneration of skin appendages. The epidermal layer displayed regeneration as a single layer of epithelial cells, as shown in Figure 4. Hyaluronic acid was used in this study to enhance and accelerate wound healing. We observed that it could boost dermal repair, as shown by increased collagen deposition. This finding aligns with [39], which reported that hyaluronic acid promotes fibroblast migration, thereby facilitating collagen deposition at the wound site. Additionally, it supports the regeneration of skin appendages, which agrees with the results of [40]. Furthermore, there was significant formation of new blood vessels in the dermal layer, consistent with [41], who found that hyaluronic acid breakdown products are pro-angiogenic.

The present study demonstrated regeneration of a monolayer of epidermal epithelial cells, in agreement with the findings of [42]. They reported that exogenous hyaluronic acid application enhances mitosis and cellular proliferation. Price et al. found that exogenous hyaluronic acid promotes the proliferation of corneal keratinocytes both in vitro and in vivo [43]. However, the hyaluronic acid ointment-treated group did not exhibit full-thickness regeneration. We believe this is due to hyaluronic acid's lack of antimicrobial efficacy, which hampers efficient epithelial regeneration in contaminated wounds.

Compared with the SNO-treated group, this group showed notable full-thickness epithelial regeneration in the epidermal layer, with well-formed superficial keratin. Additionally, significant collagen buildup was seen in the dermal layer; however, multiple abscesses were present at the wound site, as shown in Figure 5. Therefore, combining 1% SNO with hyaluronic acid could enhance wound healing and strength. This may be achieved through the antimicrobial activity of silver nanoparticles and hyaluronic acid's ability to modulate fibroblast migration, collagen deposition, and regeneration of skin appendages. To the best of our knowledge, this is the first study to use silver nanoparticles in combination with hyaluronic acid for full-thickness wound healing.

The combination group showed completely normal skin, with a full-thickness epidermis and a substantial superficial keratin layer. The dermal layer displayed well-developed skin appendages, including hair follicles, sebaceous glands, and sweat glands, at the wound site, as shown in Figure 6.

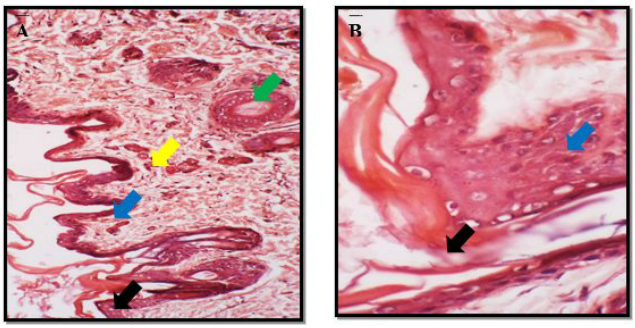

Fig. 2 Skin of the negative control group shows a normal superficial keratin layer (black arrow), a normal epidermal layer (blue arrow), and normal skin appendages: hair follicles (green arrow) and sweat glands (yellow arrow). H&E A) 10X B) 40X

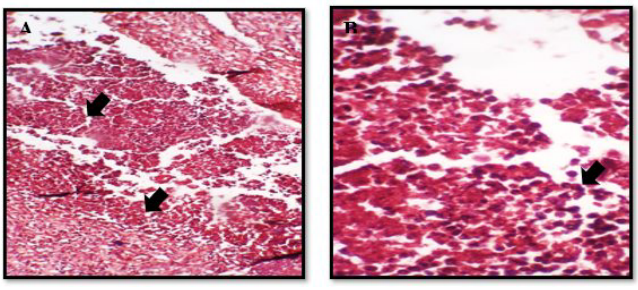

Fig. 3 Skin of the positive control group shows intensive acute inflammation (black arrow) in the site of the wound, hemorrhage (green arrow), and necrotic tissue (yellow arrow). H&E A) 10X, B) 40X

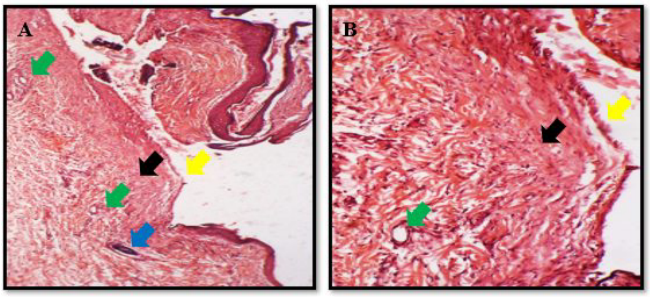

Fig. 4 Skin of the hyaluronic acid-treated group shows intensive collagen deposition (black arrow), newly generated hair follicles (blue arrow) with newly generated blood vessels (green arrow), and a monolayer of epithelial cells (yellow arrow) at the wound site. H&E A) 4X, B) 10X

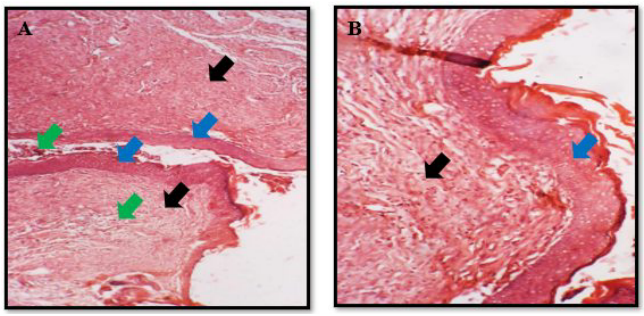

Fig. 5 Skin of Nano-silver treated group shows intensive collagen deposition (black arrow), a fully mature epidermal layer overlying the collagen (blue arrow) at the wound site, and small areas of abscesses are also present (green arrow). H&E A) 4X, B) 10X

3.3 Results of the scoring

The scoring results are shown in Table 2 and Figure 8. It is necessary to indicate the degree of the healing process based on all scoring parameters, as they complement each other.

3.3.1 Scoring of inflammation

The negative control group was assigned a score of 0 for inflammation and granulation tissue; however, it received a score of 4 for other parameters, as the skin sections of this group showed no changes. Inflammation was 90±2.43% in the induction group; therefore, it was scored as 4. In the hyaluronic acid ointment-treated group, inflammation was 43±1.661%, scored as 2. In the SNO-treated group, inflammation was 9±0.011%, scored as 1. In the combination group, there was no inflammation, scored as 0. The 1% SNO-treated and combination-treated groups showed no statistically significant differences compared with the negative control group (P>0.05). In contrast, both the induction and hyaluronic acid ointment-treated groups showed significant differences from the other groups ($P \leq 0.01$ and $P \leq 0.05$, respectively).

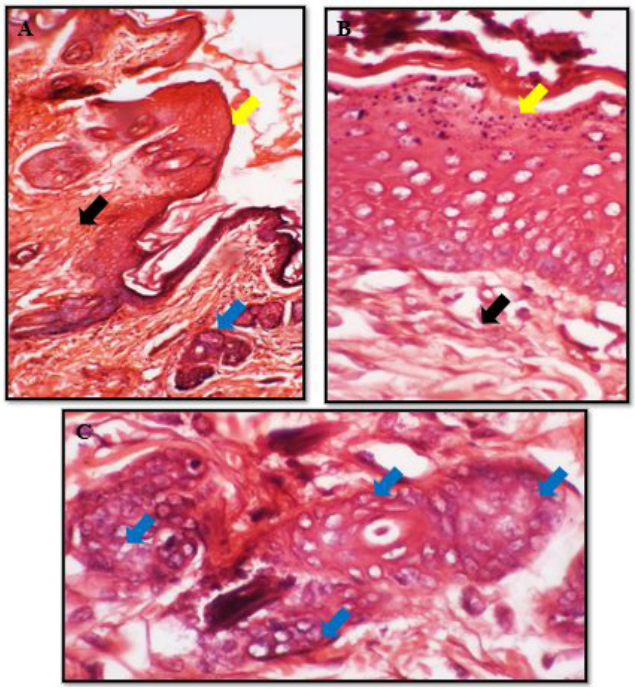

Fig. 6 Skin of the combination-treated group shows intensive collagen deposition in the site of the wound (black arrow), newly developed, well-organized hair follicles (blue arrow), and fully regenerated epidermal epithelium (yellow arrow). H&E A) 10X, B) &C) 40X

3.3.2 Scoring of granulation tissue formation

The presence of granulation tissue should be carefully evaluated to assess the progression of healing. It is essential to distinguish between the absence of granulation tissue in non-healing wounds and its absence during complete healing. However, re-epithelialization indicates complete healing, accompanied by the formation of granulation tissue. In the present study, the thickness of granulation tissue was as follows: induction group, 0.937±0.03%, score (0); hyaluronic acid ointment group, 31.415±1.58%, score (2); SNO group, 21.109±3.772%, score (3); and the combination group, where no granulation tissue was observed, score (0). Both hyaluronic acid and 1% SNO showed significant differences (P≤0.05) compared with the other groups.

3.3.3 Scoring of skin appendages regeneration

Regeneration of skin appendages was scored to evaluate the degree of healing among the study groups. The scoring was as follows: the induction group showed no skin appendage regeneration (score 0); the hyaluronic acid ointment group scored 3.01±0.18% (score 1); the SNO group had no observed skin appendages (score 0); and the combination group scored 4 (100%). The hyaluronic acid ointment and 1% SNO-treated groups showed no significant difference compared with the negative control group (P>0.05), whereas significant differences were observed when compared with the induction group.

3.3.4 Scoring of collagen deposition

Collagen deposition is a sign of healing, as it involves replacing the non-regenerative component of tissue; it is compensatory but non-functional. Therefore, extensive collagen deposition and an underdeveloped dermis indicate that healing is still in the early stages. In this study, the collagen percentages were as follows: induction group, 12.91±3.22% (scored 1); hyaluronic acid group, 73.09±0.43% (scored 3); SNO group, 79.45±3.81% (scored 4); and the combination group, 84.5±1.16% (scored 4). No significant differences were observed between the treated groups (P>0.05), but a notable difference was found between the treated groups and both the negative control and induction groups (P≤0.05) (Figure 7).

3.3.5 Scoring of re-epithelialization

In the present study, the degree of re-epithelialization is considered an indicator of wound closure. At the same time, the thickness of the epithelial tissue helps indicate whether partial or complete healing has occurred. Epithelial thickness was measured and scored for this purpose as follows: the induction group showed no epithelial tissue, scored (0); the hyaluronic acid ointment group had a thickness of 7.16±0.37µm, scored (1); the SNO group had 100 µm (OR %), scored (4); and the combination group had 100 µm (or %), scored (4). No significant differences were observed between the control, 1% SNO, and combination groups (P>0.05). However, both the induction and hyaluronic acid ointment groups showed significant differences compared with the control group and other treatment groups (P ≤ 0.01).

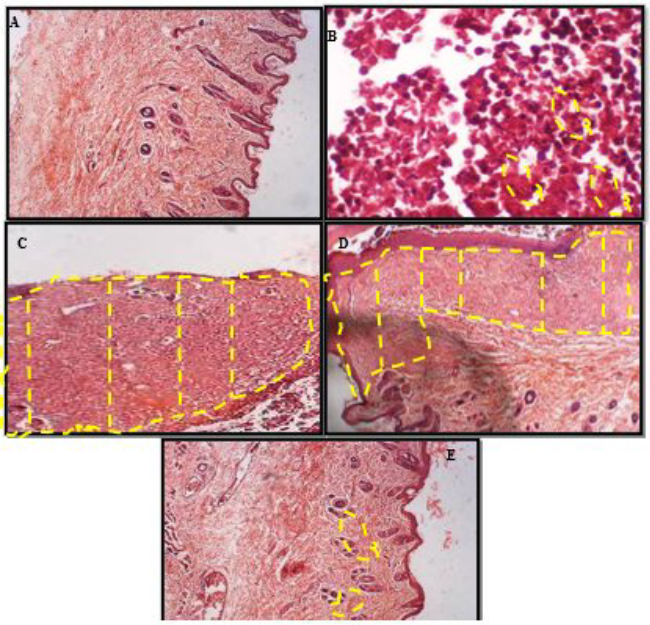

Fig. 7 Histopathological findings of the wound; A) no wound in the negative control group, B) little fibrous tissue and intensive inflammation C) complete wound closure with intensive fibrosis D) complete closure with intensive fibrosis in the wound site E) complete wound closure with no scab formation; however, re-epithelialization of the epidermal layer was observed, the fibrosis is illustrated by area with dash line.

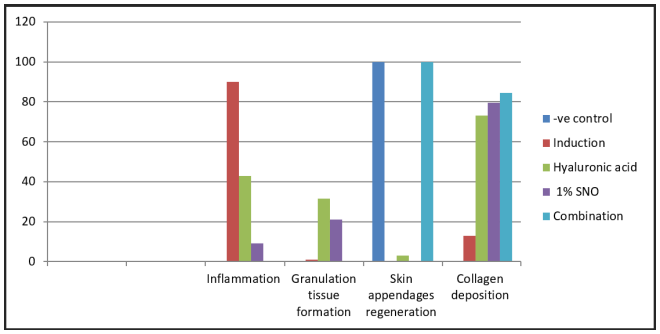

Fig. 8 Shows the scores of histopathological changes of wound healing.

incorporation of advanced hybrid architectures.

4 CONCLUSION

In conclusion, combining hyaluronic acid with silver nanoparticles resulted in improved wound healing compared with using either hyaluronic acid or silver nanoparticle ointments alone.

Table 2 Table of revealed scoring for the histopathological changes

Parameter	-ve control		Induction		Hyaluronic acid		1% SNO		Combination	
	V	S	V	S	V	S	V	S	V	S
Inflammation	0 A	0	90 ± 2.43 B	4	43 ± 1.661 C	2	9 ± 0.011 A	1	0 A	0
Granulation tissue formation	0 A	0	0.937 ± 0.03 A	0	31.415± 1.58 B	2	21.109± 3.772 B	1	0 A	0
Skin appendage regeneration	100 A	4	0 B	0	3.01 ± 0.18 B	1	0 B	0	100 A	4
Collagen deposition	0 A	0	12.91 ± 3.2 2 B	1	73.09 ± 0.43 C	3	79.45 ± 3.81C	4	84.5± 1.16 C	4
Re-epithelialization	100 A	4	On B	0	7.16 ± 0.37 B	1	100A	4	100A	4

V: refers to the Value, S: refers to the score. The values in the table are expressed as a mean ± standard error (SE). Capital letters refer to the statistical status between the rows of the table; difference in the letters refers to the statistical differences.

Acknowledgement

Authors of this article would like to acknowledge the staffs of department of pathology and forensic medicine as well as those of department of microbiology in the college of medicine/University of Misan for their kind help in accomplishing this research.

Funding source

No funds received.

Data availability

N/A

DECLARATIONS

Conflict of interest

Authors declare that no conflict of interest to be declared.

Consent to publish

N/A

Ethical approval

The study was conducted by ethical approval from the Ethics Committee in the College of Medicine, University of Misan (No. 101/2024).

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How to cite this article

Ramadhan MA, Abahadly WKY, Shamikh HF, Al-Rawi KF. The potential wound healing and antimicrobial effects of silver nanoparticles and hyaluronic acid in animal models. Journal of University of Anbar for Pure Science. 2026; 20(1):64-73. doi:10.37652/juaps.2025.161691.1447