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Research Article

Effects of Silver Nanoparticles and *Aloe vera* Extract on Wound Closure and Bacterial Reduction in a Mouse Wound Model

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ABSTRACT

Introduction: Microbial resistance and poor tissue repair in chronically infected wounds motivate exploring silver nanoparticles as broad-spectrum antibacterials, combined with natural anti-inflammatory and reparative compounds to improve treatment. The present study aimed to assess the synergistic effect of silver nanoparticles and *Aloe vera* extract on wound closure and bacterial load reduction in mice.

Methods and materials: A total of 32 male mice, weighing 25-30 grams and aged 4 weeks, were randomly assigned to four equal groups (n = 8). The four groups were an untreated control group, a group treated with alcoholic extract of *Aloe vera* (300 mg/mL), a group treated with silver nanoparticles (3.5 mg/mL), and a combined group treated with silver nanoparticles (3.5 mg/mL) and *Aloe vera* extract (300 mg/mL). An 8-mm-diameter, full-thickness skin wound was created on the dorsal region, and mice were treated for 14 days. Wound healing was assessed by measuring the wound surface area on days 0, 3, 7, 10, and 14. Bacterial colony counts (CFU/mL), histological changes, and collagen formation were evaluated on days 0, 3, 7, 10, and 14.

Results: Wound closure on day 14 was 71.4% in the control group, 82.6% in the *Aloe vera* group, 86.9% in the silver nanoparticle group, and 94.8% in the combined group. The combined group demonstrated a significant reduction in wound area compared with the control group. The bacterial load in the combined group was 1.8×10^3 CFU/mL, a 99.9% reduction compared with the control group (4.6×10^6 CFU/mL). Histological examination demonstrated that the combined group had increased granulation tissue formation, higher organization of collagen fibers, and decreased inflammatory cell infiltration at days 3, 7, and 14 compared with the control group.

Conclusion: The present findings indicated that the combination of silver nanoparticles with *Aloe vera* extract could support the development of novel wound-healing therapies by accelerating wound closure and reducing microbial load.

1. Introduction

The skin is the largest organ of the body and plays an important role in physical integrity, protection, and homeostasis[1]. Surgery, burns, trauma, and chronic diseases can damage the skin and impair the natural wound-healing process, leading to complications such as infection, prolonged inflammation, and delayed tissue regeneration[2]. Wound healing is a complex, multistep process that includes hemostasis, inflammation, cell proliferation, and tissue

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remodeling, and it is controlled by many cellular, molecular, and environmental factors[3].

Bacterial infection is a major limiting factor in wound healing[2,4]. Microbial growth and proliferation at the injury site can lead to further inflammation, extracellular matrix degradation, and hindered new tissue formation[5]. The increase in bacterial resistance to traditional antibiotics has increased the need for alternative treatments with strong antimicrobial efficacy[6]. Therefore, nanomaterials with special properties have been developed as a new approach to control infection and boost healing[2,7]. Silver nanoparticles (AgNPs) are among the most widely used nanomaterials in regenerative medicine because of their high surface activity and ability to provide antibacterial effects against a wide variety of microorganisms[8]. Silver nanoparticles are effective in inhibiting pathogen growth through mechanisms including production of reactive oxygen species (ROS), disruption of bacterial cell membranes, and inhibition of metabolic processes[9]. Moreover, AgNPs can promote wound healing by modulating the inflammatory response and supporting tissue regeneration[10]. However, the use of AgNPs is limited due to concern over cytotoxicity, dose-dependent effects, and possible disruption of reparative cell activity despite the potential benefit[11]. Thus, incorporating AgNPs with natural bioactive materials is a promising approach to improve therapeutic efficacy and minimize possible adverse effects[12].

Plant agents rich in bioactive compounds such as flavonoids, polyphenols, and antioxidants have a high potential to modulate inflammation, induce cell proliferation, and promote tissue regeneration[13]. *Aloe vera* is a well-known medicinal plant used in wound healing and is reported to have anti-inflammatory, antioxidant, and reparative properties due to its broad spectrum of bioactive compounds[14,15]. The *Aloe vera* gel components such as polysaccharides, vitamins, and phenolic compounds are known to stimulate skin regeneration by promoting fibroblast migration, increasing collagen production, and reducing oxidative stress[16,17]. In addition, the antibacterial activity of *Aloe vera*, combined with AgNPs, can help control microbial contamination at the wound site[18,19].

Given the importance of identifying combination therapies for infected and complex wounds, simultaneously investigating nanomaterials and natural compounds could open new avenues for developing novel wound dressings and therapeutic approaches[20-22]. Although the individual effects of AgNPs and *Aloe vera* extract on wound healing have been well studied, data on their combined effect in a laboratory animal model remained limited. Therefore, the present study aimed to assess the combined effects of AgNPs and *Aloe vera* extract on wound closure, bacterial load reduction, and tissue regeneration in a mouse model.

2. Methods and materials

2.1. Ethical approval

All experimental procedures were performed in compliance with the ethical guidelines for laboratory animal use at Mashhad University of Medical Sciences, Mashhad, Iran (IR.BMSU.AEC.1401.014). The study protocol was in accordance with the ARRIVE guidelines.

2.2. Silver nanoparticles

Silver nanoparticles used in this study were purchased as a ready-to-use colloidal suspension from Zist Shimi Azma Roshd (Nano Zino, Tehran, Iran). The product was supplied as a colloidal silver nanoparticle solution (Catalog No.: NanoZino-Ag-1000; Lot No.: AG-1402-XX), with a manufacturer-reported concentration of 1000 ppm. Prior to use, the physicochemical properties of the AgNPs were verified in the central laboratory of Mashhad University of Medical Sciences, Mashhad, Iran. The hydrodynamic diameter, polydispersity index, and zeta potential were determined by dynamic light scattering using a Malvern Zetasizer Nano ZS (Malvern Instruments, UK) at 25°C. Transmission electron microscopy (Philips CM120, Netherlands, operating at 80 kV) was used to examine morphology. The UV-Vis absorption spectrum was recorded in the 300-700 nm range using a BioTek Epoch microplate spectrophotometer to confirm the characteristic surface plasmon resonance (SPR) band of AgNPs, typically observed around 400-420 nm. The stock suspension was sonicated for 10 minutes in an ultrasonic bath before each application to ensure homogeneity. The 1000 ppm stock suspension was diluted with sterile distilled water to a final working concentration of 3.5 mg/mL immediately before each topical application[23].

2.3. Aloe vera extract

The amount of 100 g of fresh leaves of *Aloe vera* (L.) Burm. f. (*Aloe barbadensis Miller*) was obtained from Gino Vera Co. (Gino Kar Aaveh Cooperative, Tehran, Iran). The leaves were washed thoroughly with distilled water, and the outer green rind was carefully removed to collect the inner clear gel. The gel was homogenized using a Heidolph SilentCrusher M homogenizer at 10,000 rpm for 3 minutes at 4°C to obtain a uniform slurry. The homogenate was filtered through Whatman No. 1 filter paper, and the filtrate was centrifuged at 10,000 × g for 20 minutes at 4°C to remove insoluble debris. The supernatant (pure gel extract) was collected, stored in sterile amber vials at 4°C in the dark, and used within 7 days to minimize degradation of bioactive compounds. For the alcoholic extract, the dried leaf powder was macerated in 70% ethanol (1:30 w/v) at room temperature (25°C) for 24 hours with continuous shaking. The mixture was filtered through Whatman No. 1 filter paper, and the filtrate was concentrated under reduced pressure using a rotary evaporator at 40°C to obtain a viscous extract. The concentrated alcoholic extract was stored in sterile amber vials at 4°C in the dark until use. The extract concentration was expressed on a dry-weight basis (mg/mL). The total phenolic content of the extract was quantified using the Folin-Ciocalteu method with gallic acid as the standard, as previously described, and expressed as µg gallic acid equivalents (GAE) per mg of dry extract[24]. The pure gel extract was adjusted to a final working concentration of 300 mg/mL (dry weight basis) for topical application[25].

2.4. Experimental animals

A total of 32 male BALB/c mice weighing 25-30 g were purchased from the Razi Institute, Iran. The mice were housed under established laboratory conditions with controlled temperature (22 ± 2°C) and a 12-hour light/dark cycle, and had access to water and standard feed *ad libitum*. The mice acclimated to the laboratory environment for one week before the experiments.

2.5. Wound model creation and animal grouping

A full-thickness skin wound model was created under general anesthesia with an intraperitoneal injection of ketamine (80 mg/kg; Alfasan, Netherlands) and xylazine (10 mg/kg; Alfasan, Netherlands) under sterile conditions[26]. The dorsal area was shaved and disinfected, and a circular full-thickness wound (6 mm diameter) was created using a sterile punch biopsy instrument, extending through the epidermis and dermis to the level of the panniculus carnosus (excluding the fascia)[2]. To establish an infected wound model, the wounds were inoculated with a standardized bacterial suspension of *Staphylococcus aureus* (*S. aureus*; ATCC 43300; 5 × 107 CFU/mL), and infection was confirmed 24 hours post-inoculation by quantitative bacterial culture[2]. Following wound creation, mice were randomly allocated into four groups (n = 8 per group). The control group received no topical treatment and only routine wound cleaning with sterile saline (Group 1). The second group received topical application of the prepared *Aloe vera* extract (300 mg/mL), delivered as 50 µL per wound (Group 2). The third group received topical application of AgNPs (3.5 mg/mL) in suspension, delivered as 50 µL per wound (Group 3). The final group received a combined topical formulation of *Aloe vera* extract (300 mg/mL) and AgNPs (3.5 mg/mL; Group 4). These concentrations were selected based on previous studies reporting the minimum inhibitory concentration of *Aloe vera* extract against *S. aureus* (60-100 mg/mL) and of AgNPs against *S. aureus* (6.25-12.5 µg/mL), with the combination concentrations adapted from a prior study on *Aloe vera*–AgNPs wound treatment[23]. Treatments were initiated immediately after wound creation (day 0) and applied once daily for 14 consecutive days until the end of the study period.

The mice (n = 8 per group) were euthanized on day 14 post-wounding by cervical dislocation under deep anesthesia. The entire wound bed, including a 2-mm margin of surrounding intact skin and the underlying panniculus carnosus, was excised from the dorsal region of each animal. Each excised wound specimen was divided into two equal halves. One half was fixed in 10% neutral buffered formalin for histological evaluation (H&E and Masson's trichrome staining). For quantitative bacterial load assessment, the other half was weighed, homogenized in one mL sterile PBS, and serially diluted 10-fold; 100 µL of each dilution was spread onto tryptic soy agar (TSA) plates (MirMedia, Iran), and the plates were incubated at 37°C for 24 hours. Colonies were counted on plates yielding 30-300 colonies, and the bacterial load was expressed as CFU/g of tissue. Thus, one specimen per animal and eight specimens per group were analyzed for each endpoint.

2.6. Wound closure assessment

Standardized digital images were captured using a fixed-distance photobox setup with consistent lighting and camera positioning, and a graduated ruler was included in each image as a scale reference. Wound areas were measured using ImageJ software (version 1.53; National Institutes of Health, USA). Briefly, the scale was calibrated by drawing a 10-mm line over the ruler in each image (Analyze to Set Scale), and the wound margin was then outlined and quantified using the polygon/freehand selection tool[27]. The percentage of wound closure was calculated as Formula 1.

Wound closure (%) = ([Initial wound area − Current wound area] / Initial wound area) × 100 (Formula 1)

Changes in wound area over time were compared across different groups to determine the effect of the treatments on the rate of skin regeneration.

2.7. Bacterial and histological analysis

To evaluate the antibacterial effect of the treatments, wound exudate samples were collected at designated time points (days 0, 3, 7, and 14) using sterile cotton swabs. The swabs were immediately immersed in 1 mL of sterile phosphate-buffered saline (PBS) and vortexed for one minute to release bacteria. Serial 10-fold dilutions were prepared in sterile PBS, and 100 µL of each dilution was spread onto tryptic soy agar (TSA; Merck, Germany) plates and mannitol salt agar (MSA; Merck, Germany) for selective isolation of S. aureus. Plates were incubated at 37°C for 24 hours, and the number of colony-forming units (CFU) was counted on plates showing 30-300 colonies[28].

2.8. Statistical analysis

All quantitative data were reported as mean ± standard deviation (Mean ± SD). Statistical analysis was performed using SPSS (version 31). One-way ANOVA was used for comparisons between multiple groups, and two-way ANOVA was used to examine time-dependent changes in the wound closure process. Where significant differences were observed, the Tukey post-hoc test was performed for multiple comparisons. A P-value less than 0.05 was considered statistically significant.

3. Results

3.1. Wound closure

In the present study, wound healing was monitored over a 14-day period in male mice. While all treatment groups demonstrated a progressive reduction in wound area after induction, Group 4 exhibited a clearly accelerated closure

rate compared with all other groups. Specifically, Group 4 demonstrated a greater reduction in wound area than the control group as early as day 3, with the divergence becoming more pronounced on days 7 and 10. By the end of the observation period, Group 4 produced the greatest epithelialization and wound contraction. On day 14, the wound closure percentages were 71.4 ± 5.8% in the control group, 82.6 ± 4.7% in Group 2, 86.9 ± 3.9% in Group 3, and 94.8 ± 2.6% in Group 4. Group 4 demonstrated a statistically significant enhancement in wound closure compared with other treatment groups (Tables 1 and 2; $p < 0.05$).

Table 1. Effects of *Aloe vera* extract and silver nanoparticles on wound closure in male mice over 14 days

Treatment groups \ Days	Day 3 (%)	Day 7 (%)	Day 10 (%)	Day 14 (%)
Group 1	18.6 ± 3.4^{a}	39.8 ± 4.6^{a}	57.2 ± 5.1^{a}	71.4 ± 5.8^{a}
Group 2	24.7 ± 3.8^{b}	52.5 ± 5.2^{b}	69.4 ± 4.9^{b}	82.6 ± 4.7^{b}
Group 3	27.9 ± 4.1^{b}	58.7 ± 4.8^{c}	74.8 ± 4.3^{c}	86.9 ± 3.9^{c}
Group 4	33.8 ± 4.5^{c}	68.9 ± 5.1^{d}	84.7 ± 3.6^{d}	94.8 ± 2.6^{d}

Group 1: Control group, Group 2: *Aloe vera* extract at 300 mg/mL, Group 3: AgNPs at 3.5 mg/mL, Group 4: *Aloe vera* extract (300 mg/mL) and AgNPs (3.5 mg/mL). Values are presented as mean ± SD. ^{a,b,c,d} Mean different superscript letters within each column differ significantly ($p < 0.05$).

Table 2. Effects of *Aloe vera* extract and silver nanoparticles on remaining wound area in male mice over 14 days

Treatment groups \ Days	Day 0 (mm^2)	Day 3 (mm^2)	Day 7 (mm^2)	Day 14 (mm^2)
Group 1	50.0 ± 0.0	40.7 ± 1.7^{c}	30.1 ± 2.3^{d}	14.3 ± 2.9^{d}
Group 2	50.0 ± 0.0	37.7 ± 1.9^{b}	23.8 ± 2.6^{c}	8.7 ± 2.4^{c}
Group 3	50.0 ± 0.0	36.1 ± 2.1^{b}	20.6 ± 2.4^{b}	6.6 ± 2.0^{b}
Group 4	50.0 ± 0.0	33.1 ± 2.2^{a}	15.6 ± 2.5^{a}	2.6 ± 1.3^{a}

Group 1: Control group, Group 2: *Aloe vera* extract at 300 mg/mL, Group 3: AgNPs at 3.5 mg/mL, Group 4: *Aloe vera* extract (300 mg/mL) and AgNPs (3.5 mg/mL). Values are presented as mean ± SD. ^{a,b,c,d} Mean different superscript letters within each column differ significantly ($p < 0.05$).

3.2. Bacterial load

To evaluate the antibacterial efficacy of the topical treatments, viable bacterial counts at the wound site were quantified at the end of the 14-day treatment period in mice. The results showed that microbial load was significantly reduced in groups 2 and 3 compared with the control group ($p < 0.05$); however, the greatest reduction was observed in Group 4. Viable bacterial counts were 4.6×10^6 CFU/mL in the control group, 8.2×10^4 CFU/mL in Group 2, 2.7×10^4 CFU/mL in Group 3, and 1.8×10^3 CFU/mL in Group 4. Group 4 produced a statistically significant reduction in bacterial load relative to the control group (Table 3; $p < 0.05$). Group 4 achieved a 3.40-log reduction in bacterial load (99.96%) compared with the control group, surpassing the reductions attained by *Aloe vera* (1.75 log; 98.2%) and AgNPs (2.23 log; 99.4%) alone.

3.3. Comparison of the combined treatment with individual treatments

A direct inter-group comparison revealed that the concurrent administration of AgNPs and *Aloe vera* extract was superior to either group 2 or 3 in accelerating wound closure and suppressing bacterial proliferation. Group 4 exhibited the most rapid reduction in wound area at all assessed time points and the lowest residual bacterial load at the end of the study (Table 4).

Table 3. Effects of *Aloe vera* extract and silver nanoparticles on viable bacterial load at the wound site in mice on day 14 post-wounding

Treatment groups	Bacterial count (CFU/mL)	Log_{10} (CFU/mL)	Reduction compared with control
Group 1	4.6×10^{6a}	6.66	—
Group 2	8.2×10^{4b}	4.91	98.2%
Group 3	2.7×10^{4c}	4.43	99.4%
Group 4	1.8×10^{3d}	3.26	99.96%

Group 1: Control group, Group 2: *Aloe vera* extract at 300 mg/mL, Group 3: AgNPs at 3.5 mg/mL, Group 4: *Aloe vera* extract (300 mg/mL) and AgNPs (3.5 mg/mL). ^{a,b,c,d} Mean different superscript letters within each column differ significantly ($p < 0.05$).

Table 4. Comparative analysis of the therapeutic efficacy of *Aloe vera* extract, silver nanoparticles, and their combination on wound healing and bacterial reduction in mice on day 14 post-wounding

Treatment groups	Wound closure at day 14 (%)	Remaining wound area at day 14 (mm^2)	Bacterial load (CFU/mL)	Overall therapeutic response
Group 1	71.4 ± 5.8^{a}	14.3 ± 2.9^{d}	4.6×10^{6c}	Baseline
Group 2	82.6 ± 4.7^{b}	8.7 ± 2.4^{c}	8.2×10^{4d}	Moderate improvement
Group 3	86.9 ± 3.9^{c}	6.6 ± 2.0^{b}	2.7×10^{4b}	Strong improvement
Group 4	94.8 ± 2.6^{d}	2.6 ± 1.3^{a}	1.8×10^{3a}	Highest efficacy

Group 1: Control group, Group 2: *Aloe vera* extract at 300 mg/mL, Group 3: AgNPs at 3.5 mg/mL, Group 4: *Aloe vera* extract (300 mg/mL) and AgNPs (3.5 mg/mL). Values are presented as mean ± SD. ^{a,b,c,d} Mean different superscript letters within each column differ significantly ($p < 0.05$).

4. Discussion

Wound healing is a complex, multi-stage process involving infection control, regulation of the inflammatory response, and restoration of skin architecture[29-31]. Growing microbial resistance to conventional antibiotics has intensified the investigation of alternative strategies that can simultaneously control infection and promote tissue

repair[32]. The current results demonstrated that the combined formulation was more effective in both accelerating wound closure and inhibiting bacterial growth than either agent administered alone.

The combination of *Aloe vera* and AgNPs achieved the highest wound closure rate on day 14 (94.8 ± 2.6%), compared to other groups. Moreover, the combination of *Aloe vera* and AgNPs exhibited the smallest residual wound area and the lowest bacterial load. These findings indicated that combining a nanomaterial with potent antibacterial activity and a plant-derived compound with antioxidant and reparative properties constitutes an efficient strategy for improving the wound microenvironment. The effects observed with AgNPs in the present study could be attributed to their unique physicochemical properties. Silver nanoparticles inhibit the growth of a broad range of microorganisms by disrupting bacterial cell membranes, increasing ROS production, and interfering with metabolic pathways[33]. In the present study, AgNPs alone enhanced wound closure and reduced bacterial load relative to the control group, with bacterial counts decreasing from 4.6×10^6 CFU/mL in the control group to 2.7×10^4 CFU/mL in the AgNP group. This observation was consistent with the role of AgNPs in controlling wound infection and promoting healing. The AgNPs possess potent antibacterial activity and have been shown to accelerate wound healing in animal models[34]. Morones et al.[35] reported that AgNPs inhibit a wide range of Gram-positive and Gram-negative bacteria, an effect related to particle size and silver ion release. These findings support the notable reduction in microbial load observed following AgNP treatment in the current study.

The beneficial effects of *Aloe vera* extract may be ascribed to its bioactive constituents, including polysaccharides, flavonoids, and phenolic compounds[36,37]. Wound closure was remarkably higher in the *Aloe vera* group (82.6%) than in the control. Other studies have similarly reported *Aloe vera*'s ability to promote skin regeneration by reducing oxidative stress, modulating inflammation, and stimulating fibroblast activity[38]. For instance, Hamman[38] explored the potential of *Aloe vera* bioactive compounds in dermatological applications and tissue repair and reported their ability to alleviate skin injury conditions.

The combination group outperformed all other groups, suggesting a synergistic interaction between AgNPs and *Aloe vera*. The AgNPs act primarily by controlling infection and reducing microbial load, whereas *Aloe vera* facilitates healing by creating a favorable environment for tissue regeneration and attenuating deleterious inflammatory responses. Recent studies have increasingly focused on hybrid nano-botanical systems for wound treatment; for instance, combining natural agents with AgNPs in bioactive dressings has been shown to reduce wound size and enhance antibacterial efficacy[39-41]. From a translational perspective, the present results suggested that the combination of AgNPs and *Aloe vera* was a promising candidate in developing topical products such as gels, creams, or advanced wound dressings.

5. Conclusion

The present study demonstrated that topical treatment with a combination of AgNPs (3.5 mg/mL) and *Aloe vera* extract (300 mg/mL) improved the wound healing process and significantly decreased the bacterial load in a murine cutaneous wound model. Treatment with AgNPs or *Aloe vera* extract alone also improved wound healing, but the combination was superior in terms of wound closure and control of microbial growth. This effect is probably due to the synergy between the antibacterial activity of the AgNPs and the bioactive, antioxidant, and tissue repair-supporting features of *Aloe vera*. However, this study is limited by its reliance on a single animal model with a short follow-up, the absence of molecular analyses of inflammatory and regenerative pathways, and the lack of data on cytotoxicity, silver ion release kinetics, and optimal dosage. Given these results, this combination is a promising candidate for developing novel topical wound therapies; nonetheless, further studies are essential to address these limitations and to evaluate efficacy in more advanced models and clinical trials.

Declarations

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Authors' contributions

Ali Heydari conceived and designed the study and supervised the project. Nima Salimpour and Mansooreh Miri Moghaddam performed animal handling, wound model creation, and bacterial culture and CFU counting. Fateme Gholami prepared and characterized the *Aloe vera* extract. Vahid Salahirad prepared and characterized the silver nanoparticles. Anahita Gharagozlou performed wound imaging and image analysis. Hooman Javidi conducted the statistical analysis. Parham Tavangar carried out histological processing and evaluation. Negar Nickkar drafted the manuscript, administered the project, and served as the corresponding author. Mohamadreza Jahantabi provided materials and technical support. All authors critically revised and approved the final edition of the manuscript for publication in the present journal.

Availability of data and materials

All datasets are available upon request from the corresponding author.

Competing interests

The authors declared no competing interests.

Ethical consideration

All the authors confirmed that ethical concerns, such as plagiarism, permission to publish, research misconduct, data fabrication or falsification, duplicate submissions, and

redundant publication, have been thoroughly reviewed. The authors declare that they used artificial intelligence (AI) tools (Grammarly) solely for language polishing and grammatical correction during the preparation of this manuscript. No AI tools were employed for data generation, analysis, interpretation, or scientific decision-making. The authors have critically reviewed and verified all content and take full responsibility for the accuracy, originality, and integrity of the final manuscript, including all data, figures, and conclusions. This responsibility applies to the initial submission, all revisions, and the final publication. The authors confirm that no unattributed content has been included and that all sources are properly acknowledged.

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