Synergistic effects of hyaluronic acid and azelaic acid in cutaneous wound healing: A histopathological study

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Abstract

Cutaneous wounds pose significant clinical challenges by disrupting the body's protective barrier, necessitating optimized healing strategies to improve patient outcomes. Hyaluronic acid (HA) facilitates tissue repair, while azelaic acid (AzA) exhibits anti-inflammatory and antibacterial properties. This study evaluated the synergistic effects of topical HA and AzA on wound healing in a rabbit model. Standardized full-thickness wounds (6 mm diameter, 2 mm depth) were created using a skin punch. Treatments with HA and AzA were applied every 12 hours for 14 days, while control wounds received a placebo solution. Tissue samples were collected on days 7 and 14 for histopathological examination using hematoxylin & eosin and Masson's trichrome staining. The treatment group showed complete epidermal coverage, well-organized granulation tissue, enhanced collagen deposition, and reduced inflammation compared to controls, which exhibited incomplete regeneration and disorganized cellular structures. These findings demonstrate that combined topical application of HA and AzA significantly accelerates cutaneous wound healing, highlighting its potential clinical utility for improved tissue repair.

Keywords: Rabbit, Hyaluronic Acid, Azelaic Acid, Wound Healing, Pathology

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Introduction

The skin, as the body's largest and most visible organ, serves as the primary defense against external threats, functioning as a crucial barrier against physical trauma and microbial pathogens. Effective recovery from cutaneous wounds is paramount for maintaining overall body health. Given the skin's vital role in preventing bacterial and foreign body invasion into the bloodstream, the application of advanced techniques and technologies for wound management is essential. These methods should aim to eliminate surface bacteria, accelerate wound healing, and preserve skin homeostasis, thereby preventing the development of secondary complications resulting from underlying systemic conditions (Abou-Okeil *et al.,* 2018; Maheswary *et al.,* 2021). Hyaluronic acid (HA), a naturally occurring carbohydrate polymer, exhibits exceptional bioadhesive properties, rendering it a valuable biomaterial in both medical and cosmetic applications. As a key component of the extracellular matrix, HA demonstrates superior biocompatibility compared to synthetic polymers (Wei *et al.,* 2018). In skin, HA constitutes 50% or more of the body's total HA content. Due to its distinctive viscoelasticity, biocompatibility, biodegradability, and non-immunogenicity, HA is widely used in dermatology for its beneficial effects, including anti-aging, anti-wrinkle, and skin hydration properties, as well as in tissue regeneration and overall skin rejuvenation (Zhu *et al.,* 2020; Chylińska and Maciejczyk, 2025). The introduction of azelaic acid (AzA) in dermatology dates back to the 1970s, when significant depigmentation was observed in pityriasis versicolor lesions by a dermatologist in Rome (Feng *et al.,* 2024). AzA, a naturally occurring organic dicarboxylic acid, received FDA approval in 1996 for the topical treatment of acne (Rosso and Bhatia, 2011). Compared to alternative anti-acne treatments, such as isotretinoin, antibiotics, and contraceptives, AzA demonstrates a superior safety profile, with no reported antimicrobial resistance to date. It is recognized as a promising active ingredient in the treatment of acne vulgaris (Xing *et al.,* 2021). The conventional process of cutaneous wound healing encompasses an initial inflammatory phase, followed by tissue regeneration involving epithelialization, angiogenesis, collagen deposition, and extracellular matrix remodeling (Eming *et al.,* 2014; Thapa *et al.,* 2020). Hyaluronic acid, a versatile macromolecule, promotes tissue engineering and wound healing through its diverse forms and non-antigenic nature, enhancing angiogenesis and converting chronic wounds. Azelaic acid, a dicarboxylic acid with antikeratinizing, antibacterial, and anti-inflammatory properties, effectively treats acne and rosacea by inhibiting bacterial growth and neutralizing free oxygen radicals. Both compounds demonstrate significant potential in dermatological applications, particularly in improving wound healing outcomes via distinct mechanisms (Price *et al.,*

2005; Pasca *et al.,* 2022). This study aims to assess the efficacy of a cream containing combination azelaic acid and hyaluronic acid on the healing of open wounds in a rabbit model.

Material and methods

Azelaic acid, hyaluronic acid, glycerin, citric acid, and distilled water were obtained from Danapharmed Company (Tehran, Iran). Ketamine 10% was supplied by Bremer Pharma Co. (Germany), and xylazine 2% was provided by the Pharmaceutical Company of Serumwerk Bernburg AG (Germany). All the other chemicals used were of reagent grade. To prepare 100 mL of the final formulation, 10 g of azelaic acid, 5 mL of glycerin, 1 mL of hyaluronic acid, and 0.1 mL of phenoxyethanol (as a preservative) were combined using standard methods. Initially, water and glycerin were subjected to indirect heating in a water bath for 30 minutes. After cooling, the powdered ingredients were incorporated, and the pH was adjusted. The preservative was then added. The final volume was brought to 100 mL with distilled water. To adjust the pH to the natural pH range of skin (5.4-5.9), citric acid was added dropwise. The in vivo study was conducted in six healthy adults (6-12 months) New Zealand white rabbits (n=6) of male sex procured from the Laboratory Animals Research (LAR) section, Rastegar laboratory, faculty of veterinary medicine, Tehran, Iran. The rabbits were acclimatized for two weeks before the initiation of the study and maintained under uniform managerial conditions (12-hour light/dark cycle and constant temperature/humidity) throughout the study period. In addition, the rabbits were given continuous access to a standard diet and ad libitum water for drinking. The authors declare that this study was approved by the Ethics Committee of the Faculty of Veterinary Medicine at the University of Tehran and conducted in accordance with their guidelines (ID: IR.UT.VETMED.REC.1403.065).

Initially, rabbits were anesthetized via intramuscular injection with xylazine hydrochloride 2% (4 mg/kg) and ketamine hydrochloride 10% (40 mg/kg). Following induction of anesthesia, the rabbits were positioned on the operating table, and the dorsal skin was scrubbed and prepared. Four 6-mm diameter, 2-mm deep cutaneous punch biopsies were then performed on each rabbit along the spine in the dorsal region, 2 cm lateral to the midline. All wounds were left to heal by secondary intention (unsutured), with complete removal of the epidermis, dermis, and hypodermis, via excisional wounding. A control solution was applied to two wounds on the right side, while a combined formulation of hyaluronic acid (HA) and azelaic acid (AZ) was applied to two wounds on the left side, with both treatments administered every 12 hours. The formulation was applied for seven days to the upper two wounds and for fourteen days to the lower two wounds. Sampling was performed from the upper two wounds at the end of day

seven and from the lower two wounds at the end of day fourteen, after which the rabbits were euthanized. The wound healing process was subsequently studied following the sampling. Histopathological evaluations of the recovered wound tissues were performed using different staining procedures. Initially, the skin tissues excised from the healed wound areas were fixed in 10% neutral buffered formalin, routinely processed, dehydrated, embedded in paraffin wax, sectioned at 5 μm in thickness (Rotary Microtome RM2 145; Leica, Wetzlar, Germany) and stained with Haematoxylin and Eosin (HandE) and Masson's trichrome. Sections were examined using a light microscope (Motic, BA310 Epi-LED FL) and representative images were taken. The histological assessment included evaluation of the following tissue characteristics: epithelialization, collagen deposition, inflammatory cell infiltration, and neovascularization.

Results

Microscopic examination of normal rabbit skin tissue revealed a keratinized stratified squamous epithelium in the epidermal layer. Beneath the epidermis, the dermis was observed, containing sections of sebaceous glands, hair follicles, blood vessels, and scant connective tissue.

Microscopic examination of control skin tissue samples, seven days post-injury, revealed an immature, newly formed epidermis with disorganized cellular arrangement, minimal thickness, and an absent stratum corneum. re-epithelization was limited to the marginal areas of the wound. On the wound was covered with crust (amorphous eosinophilic materials containing Aggregates of fibrin strands, blood cells, neutrophils, and necrotic and debris cells). A large granulation tissue was present beneath the defect, containing blood vessels perpendicular to the wound surface, along with fibrocytes, fibroblasts, and collagen fibers. Higher magnification revealed significant infiltration of predominantly mononuclear inflammatory cells (lymphocytes and plasma cells with few neutrophils), accompanied by interstitial edema within the granulation tissue. Multifocal moderate hemorrhages were also observed within the granulation tissue. Furthermore, some microabscesses (focal accumulations of neutrophils and necrotic cells) were observed in the sections from two rabbits (Fig. 1).

Microscopic examination of treatment skin tissue samples, 7 days post-injury induction, revealed an immature, newly formed epidermis characterized by disorganized cellular arrangement, minimal thickness without stratum corneum. Notably, this epidermis completely covered the wound surface. In the granulation tissue, mild edema and angiogenesis were observed. These new blood vessels were exhibited round cross-sections, along with fibrocytes, fibroblasts, and collagen fibers that were somewhat parallel to the wound surface. Higher magnification revealed significant infiltration of

predominantly mononuclear inflammatory cells, including lymphocytes and plasma cells, along with a few neutrophils. Multifocal and moderate hemorrhages were also noted in the granulation tissue (Fig. 2).

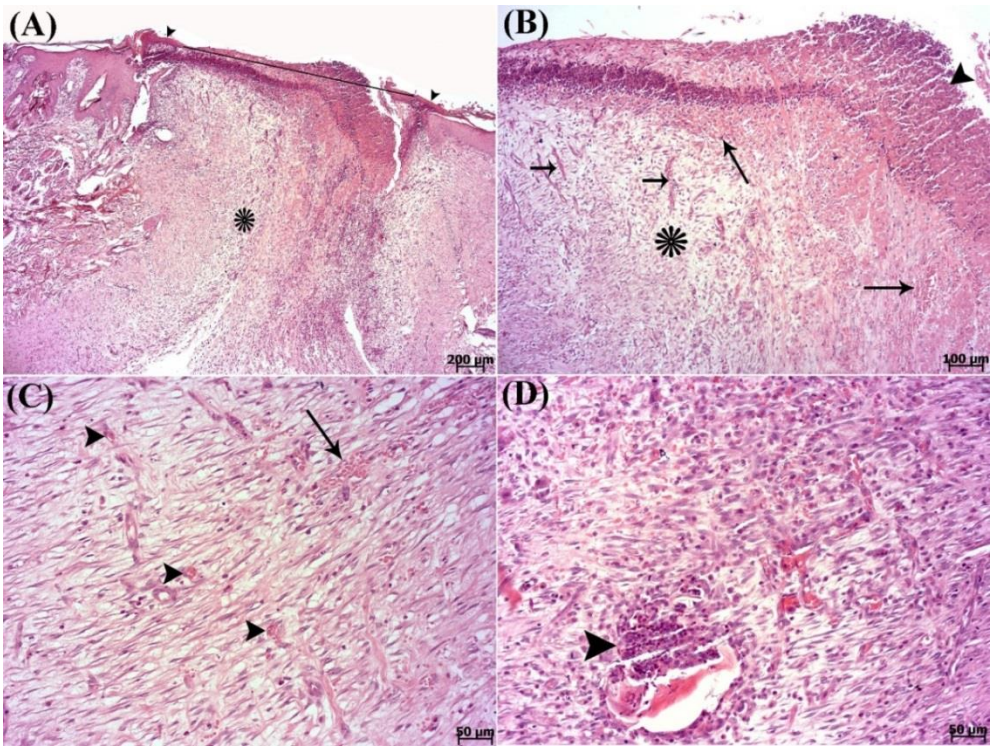

Figure 1(A-D): Histological evaluation of wound healing in the rabbit control skin sample 7 days after injury induction. (A): Newly formed epidermis (arrowheads) only at the two edges of the wound (black line), large granulation tissue (*). (B): Crust (arrowhead), focal hemorrhages (long arrows), edema (*), and blood vessels perpendicular to the wound surface (short arrows) in the granulation tissue. (C): Angiogenesis (arrowheads) with focal hemorrhage (arrow). (D): Microabscess (arrowhead), H&E.

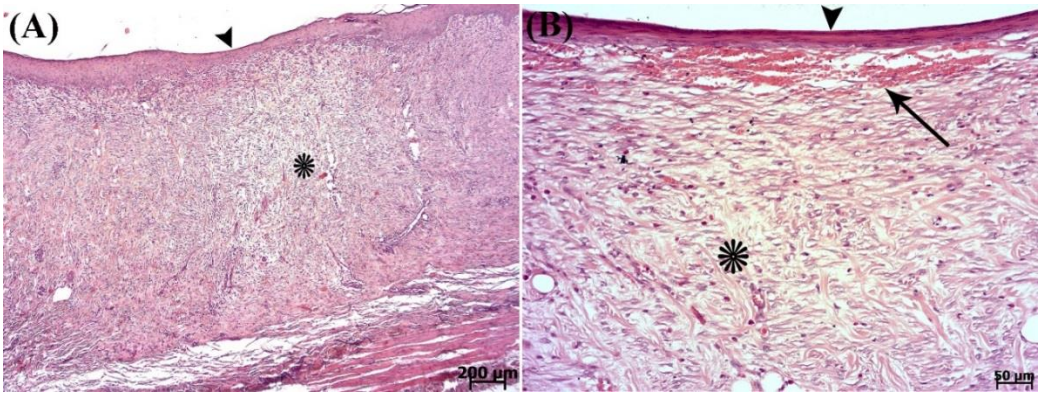

Figure 2(A-B): Histological evaluation of wound healing in the treatment rabbit skin sample 7 days after injury induction. (A): Newly formed epidermis (arrowhead) with very little thickness without stratum corneum and granulation tissue (*). (B): Higher magnification of figure A Newly formed epidermis (arrowhead), sub-epidermal hemorrhage (arrow), and granulation tissue (*), H&E.

Microscopic examination of control skin tissue samples, 14 days post-injury induction, was similar to that of treatment skin samples at 7 days post-injury. Specifically, the newly formed epidermis was immature, although it covered the entire wound surface, characterized by disorganized cellular arrangement, minimal thickness without stratum corneum. In the granulation tissue, moderate edema and significant angiogenesis was observed. There were fibrocytes, fibroblasts, and collagen fibers arranged in a disorganized manner. At higher magnification, there was noticeable lymphoplasmacytic cell infiltration with a few neutrophils.

Focal and moderate hemorrhages were also observed in the granulation tissue (Fig. 3A-b). Microscopically, treatment skin tissue samples at 14 days post-injury revealed a well-formed epidermis with an organized cellular arrangement, increased thickness with stratum corneum. The granulation tissue was smaller and more organized, tiny and sparsely distributed blood vessels associated with fibrocytes, fibroblasts, and collagen fibers oriented parallel to the wound surface. In higher magnification, minimal inflammatory cell infiltration was observed in the granulation tissue (Figs. 3C-D and 4).

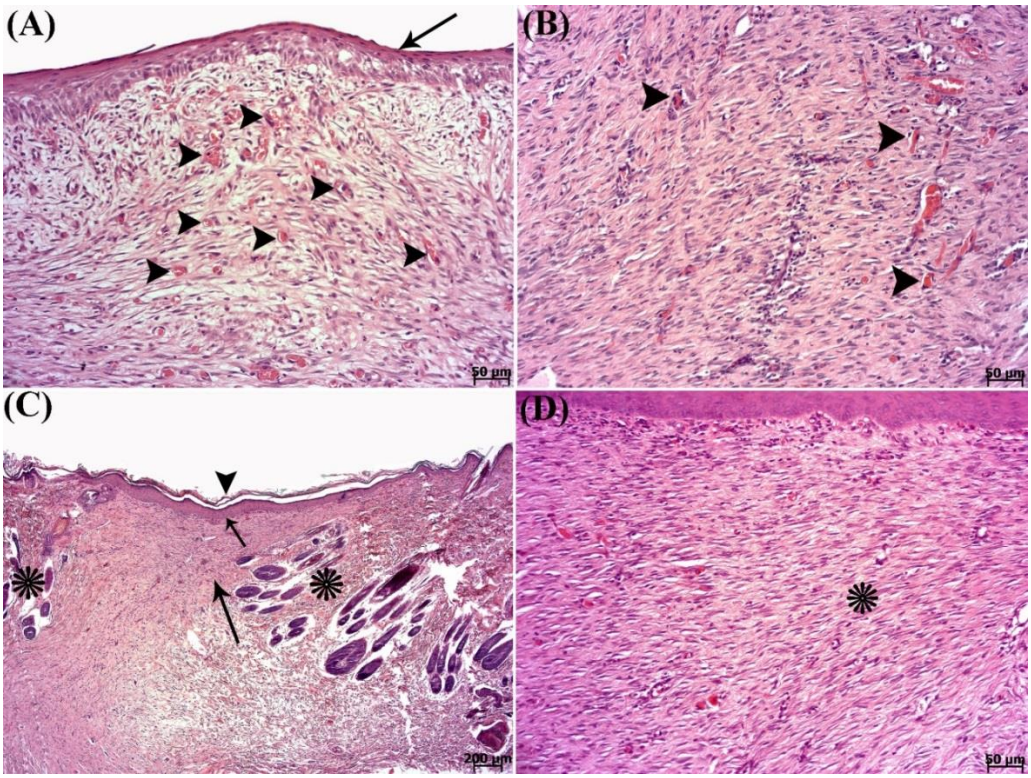

Figure 3 (A-D): Histopathological findings of the rabbit control and treatment skin sample 14 days after injury induction. (A-B): The control skin sample, newly formed epidermis (arrow) without stratum corneum and new blood vessels (arrowheads) in the granulation tissue. (C): The treatment skin sample, well-formed epidermis with greater thickness (short arrow) with stratum corneum (arrowhead), small and organized granulation tissue (long arrow), normal skin tissue (*). (D): The treatment skin sample, few blood vessels with fibrocytes, fibroblasts, and collagen fibers (*) parallel to the wound surface, H&E.

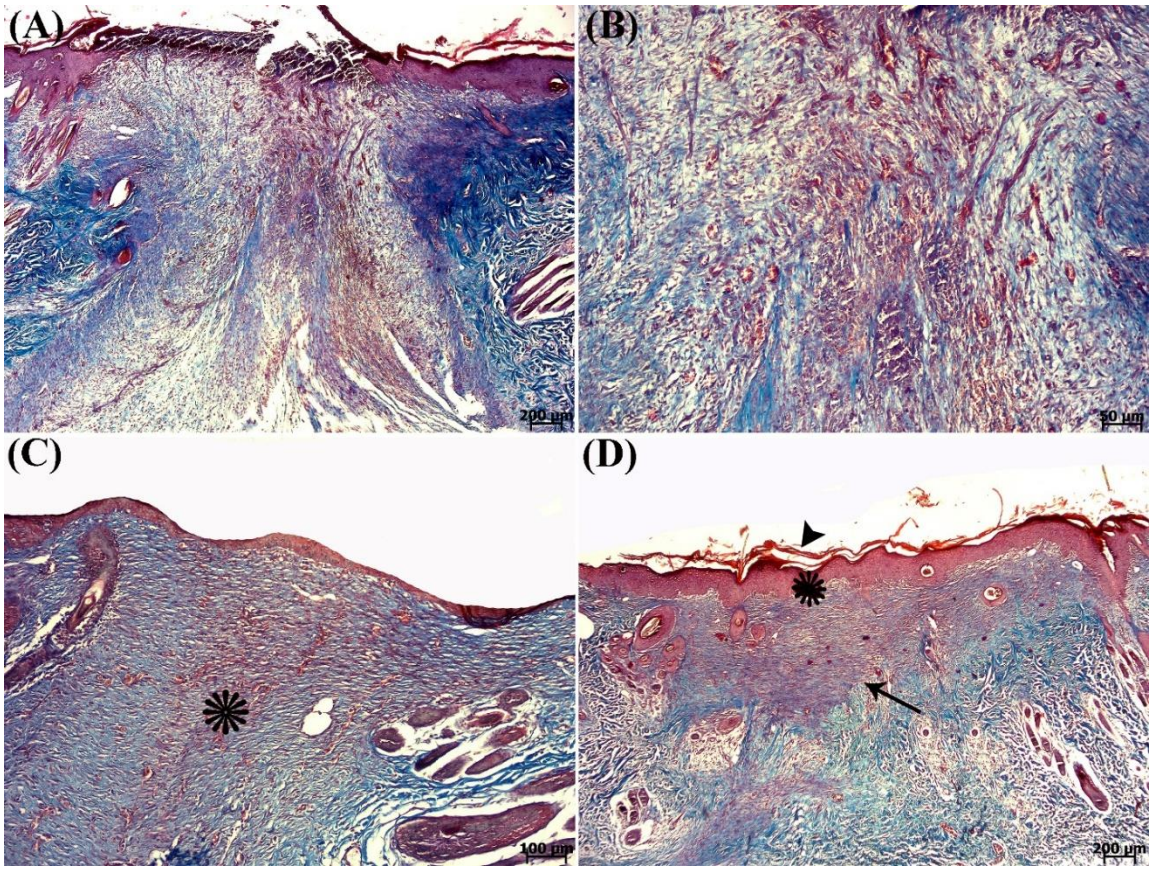

Figure 4 (A-D): Collagen assessment using Masson trichrome staining in rabbit skin wounds. (A): Large and disorganized granulation tissue beneath the defect in the control skin sample, 7 days after injury induction. (B): Granulation tissue with fibrocytes, fibroblasts, and collagen fibers somewhat parallel to the wound surface in the treatment skin sample, 7 days after injury induction. (C): Small and organized granulation tissue (*) in the treatment skin sample, 14 days after injury induction. D: organized granulation tissue (arrow), epidermal layer (*) and stratum corneum in the treatment skin sample, 14 days after injury induction.

Comparative analysis of control and treatment groups at day 7 and 14

In summary, the microscopic examination of skin tissue sections from the treatment group on day 14 demonstrated complete coverage of the wound surface by the epidermis, characterized by an organized and mature cellular arrangement, as well as the presence of a stratum corneum. In contrast, the control group at day 14 exhibited epithelialization like that observed in the treatment group at 7 days post-injury, with a newly formed epidermis that was immature, disorganized, minimal in thickness without stratum corneum, thus failing to completely cover the wound surface. The control group on day 7 post-injury, the newly formed epidermis, was immature and observed only at the wound edges, without full coverage of the wound surface. At 7 days post-injury in the control group, blood vessels oriented perpendicularly to the wound surface associated with edema, inflammation, and microabscesses in two rabbits were seen. In contrast, the

treatment group at 7 days post-injury displayed normal-appearing blood vessels with a reduced severity of injuries. By day 14, the granulation tissue in the treatment group had become smaller and more organized, with blood vessels, fibrocytes, fibroblasts, and collagen fibers arranged parallel to the wound surface. At higher magnification, minimal inflammatory cell infiltration was noted within the granulation tissue. However, in the control group at 14 days post-injury, significant angiogenesis and large, disorganized granulation tissue persisted.

Discussion

The present study provides compelling evidence that the combined topical application of hyaluronic acid (HA) and azelaic acid (AzA) significantly enhances the wound healing process through multiple synergistic mechanisms. Histopathological findings demonstrate clear advantages of this combination therapy over untreated controls, with notable improvements observed at both the macroscopic and microscopic levels throughout the healing timeline. At the 7-day post-injury evaluation, control wounds exhibited characteristic features of delayed healing, including incomplete epithelial coverage, persistent inflammatory infiltrates, and the formation of microabscesses. These findings are consistent with previous reports indicating that untreated wounds often remain in the prolonged inflammatory phase, which can impair subsequent healing stages (Gillitzer and Goebeler, 2001). In stark contrast, wounds treated with the HA-AzA combination showed complete epithelial bridging despite some residual inflammation. This accelerated re-epithelialization can be attributed to HA's well-documented ability to stimulate keratinocyte migration and proliferation (Kawano *et al.,* 2021), while AzA's anti-inflammatory properties likely helped modulate the local tissue response (Li *et al.,* 2022). The differences between treatment and control groups became even more pronounced at the 14-day evaluation point. Control samples continued to display hallmarks of impaired healing, including a thin, disorganized epidermal layer and poorly structured granulation tissue with excessive angiogenesis. These findings suggest a failure to properly transition from the proliferative to the remodeling phase of healing. In contrast, treated wounds exhibited complete epidermal regeneration with proper stratification, well-organized collagen deposition, and significantly reduced inflammatory infiltrates. The presence of mature stratum corneum in treated wounds further confirms the advanced stage of healing achieved with the combination therapy. Hyaluronic acid extracts are considered safe and effective for skin repair (Neuman *et al.,* 2015). The superior healing outcomes observed with the HA-AzA combination can be explained through several complementary mechanisms. HA, as a major component of the extracellular matrix, plays multiple roles in wound healing. Its hygroscopic properties

maintain optimal wound hydration, while its interaction with cell surface receptors (particularly CD44) activates signaling pathways that promote cell migration and proliferation (Graça *et al.,* 2020). In individuals with chronic periodontitis, HA-containing gels applied during early wound healing after scaling and root planting led to a significantly higher reduction in probing depth and fewer pockets with probing depth ≥5 mm, compared to scaling and root planting alone (Eick *et al.,* 2013). Furthermore, HA of varying molecular weights has been shown to differentially regulate the expression of key healing mediators such as IL-1β, VEGF, and MMPs (Kawano *et al.,* 2021). Studies using full-thickness surgical wound models have shown that HA facilitates re-epithelialization, promotes soft tissue formation with good elasticity, and increases microvascular density (Zhao *et al.,* 2013; Shimizu *et al.,* 2014). Azelaic acid contributes to the healing process through its multifaceted pharmacological actions. It demonstrated antibacterial activity against both aerobic and anaerobic bacteria (Li *et al.,* 2022) help prevent wound infection, a common complication that can significantly delay healing. Additionally, AzA's ability to normalize keratinization processes (Yu and Van Scott, 2004) likely supports proper epidermal differentiation during re-epithelialization. The anti-inflammatory effects of AzA may be particularly valuable in preventing excessive or prolonged inflammation, which is known to contribute to poor healing outcomes and excessive scar formation. The observed reduction in inflammatory cell infiltration in treated wounds at day 14 suggests that combined therapy may help resolve inflammation more efficiently than natural healing processes. This is particularly important as prolonged inflammation has been associated with chronic wound development and impaired healing (Gillitzer and Goebeler, 2001). The more organized appearance of granulation tissue and collagen fibers in treated wounds further supports the notion that the HA-AzA combination promotes a more structured and efficient healing response. Notably, the treatment group showed evidence of enhanced angiogenesis without the excessive, disorganized vascular proliferation seen in controls. This balanced angiogenic response is crucial for proper wound healing, as both insufficient and excessive angiogenesis can impair healing outcomes. HA's known ability to modulate angiogenesis (King *et al.,* 1991) may work in concert with AzA's effects on tissue remodeling to create an optimal environment for blood vessel formation and maturation.

This study demonstrates the therapeutic potential of a combined hyaluronic acid (HA) and azelaic acid (AzA) formulation for wound healing. HA’s extracellular matrix modulation, hydration, and cellular migration stimulation, synergistically combined with AzA’s antibacterial, anti-inflammatory, and keratinization-

normalizing effects, accelerate wound closure, improve tissue organization, and reduce inflammation compared to controls. This HA-AzA combination shows promise for treating acute and chronic wounds. Future research should optimize the formulation, explore efficacy in diverse wound models and clinical settings, and investigate the underlying molecular mechanisms and cost-effectiveness for broader clinical application.

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