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Efficiency of Low Alpha Dose Therapy for Achieving Complete Skin Tissue Regeneration

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ABSTRACT

Introduction: The process of wound healing represents a dynamic and multifaceted phenomenon characterized by intricate cellular and molecular mechanisms aimed at the restoration of tissue integrity. The present study examined the impact of low-dose ionizing radiation, particularly alpha particles released by americium-241, on the process of wound healing in murine experimental models.

Material and Methods: Twenty-four male mice were randomly divided into three groups: a control group (CG) and two experimental groups exposed to radiation for 5 minutes (IG-5) and 15 minutes (IG-15), respectively (n = 8 per group). Each mouse received two 8 mm circular full-thickness skin excisions on the dorsum. Wound healing was evaluated over 10 days using photographic analysis (quantified via ImageJ software) and histological assessment.

Results: Results indicated significantly enhanced wound closure in both irradiated groups, particularly IG-15, compared to the CG. Biochemical analyses revealed elevated levels of growth factors in irradiated tissues. Histological findings showed increased collagen deposition, greater fibroblast proliferation, and reduced inflammatory cell infiltration in the experimental groups.

Conclusion: These findings suggest that controlled low-dose alpha radiation, particularly in the IG-15 protocol, may beneficially modulate the wound healing process and hold potential for novel therapeutic applications.

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Introduction

Wounds are often referred to as the "silent epidemic" because they impair the patient's quality of life [1]. The cellular and anatomical continuity of living tissue is disrupted by physical, chemical, electrical, or microbial insults, leading to tissue damage. Wound healing is an effective dynamic process involving substitutes [2] and regeneration of missing or damaged tissues [3] and cellular structures after an injury [4]. This is achieved through four complex phases; the initial stage of this process involves hemostasis, followed by inflammation and proliferation, which are later concluded by remodeling and wound contraction [5]. For the functional integrity of the injured tissue, all four phases and their biophysiological functions must progress sequentially at specific times with optimal intensity [6]. Quick wound healing is an essential factor for effective healthcare [7]. In addition to the biological elements that affect wound healing, several biophysical interventions, [8] such as ultraviolet light, [9] pulsed radio-frequency radiation, [10] and pulsed laser therapy, can also influence the healing process of wounds [11]. Radiation refers to the release of energy from a source, whether it occurs naturally or is induced. This study primarily focuses on ionizing radiation, which involves the emission of high-energy particles capable of causing ionization in a material [12]. Americium (Am-241) is the most significant man-made radioisotope of americium in terms of its presence in the environment [13]. It is an actinide with a half-life of 432 years [14], emitting mainly alpha particles with a very low level of gamma-ray emission (3%) [15]. The emitted alpha particles have a short range and high linear energy transfer, allowing them to selectively target tissues while minimizing damage to surrounding non-targeted tissues [16]. This characteristic offers promising prospects for therapeutic applications [17]. Platelet-derived growth factor (PDGF) is among the initial growth factors discharged at the site of injury as a result of platelet degranulation [18]. PDGF is later released by monocyte-derived cells, fibroblasts, and endothelial cells in the advanced phases of wound healing [19]. PDGF assumes a pivotal function in different phases of wound healing, particularly in facilitating the development of granulation tissue within the wound through the activation of fibroblast proliferation, the attraction of mesenchymal stem cells, and the

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improvement of extracellular matrix synthesis [20]. The involvement of vascular endothelial growth factor (VEGF) is of great significance in the promotion of the formation of new blood vessels in wound sites by initiating the process of angiogenesis, which plays a crucial role in delivering oxygen, nutrients, and essential molecules to the site of injury [21]. At the cellular level, the interaction between VEGF and monocyte-derived cells, as well as endothelial cells, occurs via the VEGF receptor, facilitating the stimulation of blood vessel growth within granulation tissue [22]. PDGF is collected and released at different stages of the wound healing process by various cells such as platelets, fibroblasts, erythrocytes, and monocyte-derived cells [23, 24]. Studies have demonstrated that low-dose radiation can accelerate wound healing by influencing the number of fibroblasts, macrophages, blood vessel sections, and neutrophils in the early stages of wound repair [24]. A recent hypothesis suggests that ionizing radiation can disrupt the healing of wounds by interfering with normal cellular and molecular processes, leading to prolonged recovery times and negative effects on tissue regeneration [25]. Candice Diaz et al. demonstrate that ionizing radiation affects wound healing by causing moderate to severe damage, delayed closure, altered functionality, increased proliferation in the epidermis, hypovascular dermis, and prolonged healing time [26]. Additionally, radiotherapy, a form of ionizing radiation, has been widely used in cancer treatment [27]. To the best of our knowledge, no studies have been conducted to evaluate wound healing with varying doses of ionizing radiation therapy utilizing alpha radiation. The present study aims to investigate the potential beneficial impacts of different doses of alpha radiation emitted from an americium-241 (Am-241) radiation source on the wound healing process in murine models.

Materials and Methods

Ethical Approval

The authors confirm that ethics approval for this study was obtained from the Research Ethics Committee at the Mustansiriyah University, College of Science (Approval No. BCSMU/1123/0001Ph) on November 1, 2023.

Preparation of Animals

Twenty-five male BALB/c mice, aged 12 weeks and exhibiting a weight range of 25–28 g, were employed for the purpose of in vivo analysis. The selection of the mice was conducted through randomization, and wounds were deliberately induced in a randomized subset of this specific population. Subsequently, the animals were stratified into three distinct experimental groups: Group 1 (IG-5) was subjected to a 5-minute exposure, Group 2 (IG-15) received a 15-minute exposure, while Group 3 functioned as the control group (CG) without any exposure. All mice were maintained in a controlled animal facility under standardized environmental conditions: temperature was regulated at 25 ± 2°C, relative humidity was sustained at 50 ± 5%, and a 12-hour light/dark cycle was implemented. They were provided with standard rodent chow and unrestricted access to water, complemented by wood shaving bedding. Measures involving environmental enrichment shavings were instituted to alleviate potential stressors. The experimental procedures involving the animals adhered to the ARRIVE guidelines and received approval from the Research and Ethics Committee of the College of Science at Mustansiriyah University (Approval No. BCSMU/1123/0001Ph).

Excisional wound model

Skin wound formation was carried out under anesthesia, induced by an intraperitoneal injection of a mixture containing 80 mg/kg ketamine (10%) and 10 mg/kg xylazine [28]. The dorsal fur of each mouse was shaved using an electric clipper, followed by a razor blade to fully expose the skin. Two full-thickness circular excisional wounds (8 mm in diameter) were created on the dorsal surface using a sterile biopsy punch (Kai Medical, Chiyoda, Japan). Following the procedure, mice were housed under standard laboratory conditions at room temperature for ten days. The wound healing process was monitored regularly throughout this period. All animals received equal post-operative care and were maintained under identical environmental conditions to ensure consistency.

Euthanasia and blood collection

On the tenth day of the study, blood specimens were obtained from profoundly anesthetized murine subjects through cardiac puncture utilizing a microsyringe apparatus. The collected blood was subsequently transferred into Gel and Clot Activator tubes for further processing. A minimum volume of 0.4 mL of whole blood was subjected to analysis employing a hematology analyzer (Element HT5; Heska, Loveland, CO, USA) according to the manufacturer's instructions. For serum preparation, samples were allowed to clot at room temperature for at least 30 minutes, then centrifuged at 3000×g for 10 minutes. The resulting serum was immediately stored at −80 °C for future analyses. Following blood collection, euthanasia was completed via cervical dislocation, and the skin tissue from the wound area was harvested for subsequent analysis.

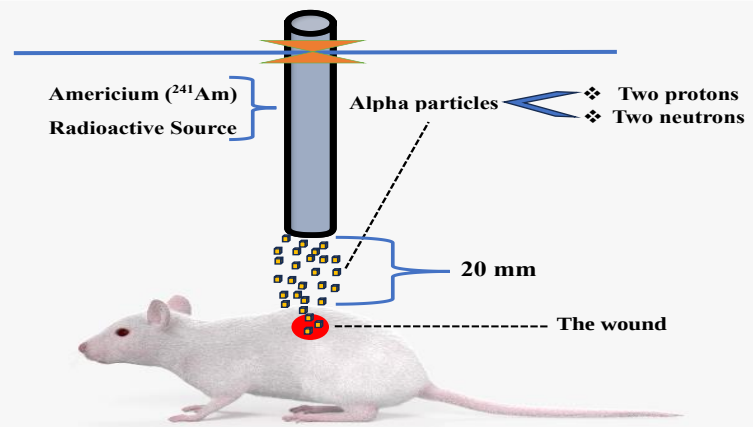

Figure 1. Schematic representation of the experimental methodology

Experimental Design Treatment and Irradiation Protocol

Male mice were irradiated using a ^{241}Am radiation source (RADIO and AKTIV Amersham Buchler Am-241, Braunschweig, Germany). The sealed source was housed in a lead-shielded casing with a circular active window measuring 7.21 mm in diameter. The activity of the source was previously determined to be 370 ± 10 kBq. To ensure minimal movement while maintaining ventilation, mice were placed in a custom-designed box during exposure. The radioactive source was positioned approximately 20 mm above the two dorsal wounds, as shown in Figure 1. Irradiation was performed on four separate occasions, spaced every other day. Wound progression was monitored and documented on days 0, 2, 4, 6, 8, and 10 post-surgeries. At each time point, a measurement scale was placed adjacent to the wounds, and standardized photographs were taken perpendicularly using the same digital camera to ensure consistency. Following each exposure, mice were placed in a warm environment to aid in recovery.

Histological Analysis

Regenerative tissue specimens from all animal cohorts were procured on day 10 for subsequent histological analysis. The specimens were preserved in 10% buffered formalin solution, meticulously processed, and subsequently embedded in paraffin at a temperature range of 40–60 °C. The paraffin-embedded specimens were meticulously sectioned to a thickness of 5 µm utilizing a microtome, followed by staining with hematoxylin and eosin (H&E) for the purpose of morphological evaluation. The stained sections were scrutinized under a light microscope to discern histological alterations [29]. Comparative analysis was performed across all experimental groups and evaluated against the CG to assess differences in tissue regeneration.

Measurement of wound contraction, reduction, and epithelialization

The reduction in wound size was assessed by measuring it with a ruler. The wound area was quantified through planimetric measurements every other day until complete healing occurred. The contraction was calculated using a specific formula [30].

$$\text{Wound contraction} = \frac{\text{Wound area on day 0} - \text{Wound area on day n}}{\text{Wound area on day 0}} \times 100\%$$

pithelialization time was determined by counting the days it took for dead tissue remnants to fall off completely, leaving no raw wound behind. This was calculated using a specific formula [31].

$$\text{Wound reduction} = \text{Wound area on day} - \text{Wound area on day n}$$

$$\text{Wound epithelialisation} = \text{Wound area of reduction} - \text{Wound area of contraction}$$

Statistical analysis

The mean ± standard deviation (SD) was used to express the quantitative data, and statistical comparisons were conducted using Microsoft Excel 2019. Significant differences were identified with a P-value of less than 0.05, and a one-way ANOVA was employed

Results

Macroscopic Evaluation of Wounds

Wound repair is a complex biological process requiring coordinated cellular and molecular responses. Although ionizing radiation has traditionally been associated with tissue damage, this study investigated whether controlled, low-dose exposure to alpha radiation from americium-241 (^{241}Am) could positively influence wound healing.

Alpha radiation was applied at defined exposure times (5 minutes for IG-5 and 15 minutes for IG-15), and its effects on healing were compared to a non-irradiated CG. Wound progression was monitored macroscopically through sequential photographs taken on days 0, 2, 4, 6, 8, and 10 (Figure 2), representing key healing stages: induction, inflammation, tissue formation, and epithelialization. Initial wound sizes were comparable

across groups: CG: 98.58 ± 2.13 mm², IG-5: 100.79 ± 1.05 mm², and IG-15: 98.72 ± 1.45 mm².

Throughout the study, no visible complications, infections, or radiation-induced damage were observed in any group. Despite the relatively large wound size (~100 mm²) in proportion to the mice's body surface area, healing proceeded efficiently, particularly in the irradiated groups. Histological and hematological evaluations confirmed the absence of significant systemic or local adverse effects, indicating that the alpha radiation doses were safe and well-tolerated.

Wound contraction and epithelialization were quantified using ImageJ software, with results summarized in Table 1. By day 10, complete epithelialization was achieved in both irradiated groups, while the CG showed delayed healing and only partial wound closure.

Wound contraction by day 10 was CG: 37.49%, IG-5: 67.25% and IG-15: 95.34%. These results confirm a dose-dependent acceleration of wound healing, with the 15-minute exposure (IG-15) demonstrating the most pronounced improvement (Figure 3). The first measurable differences in wound size were observed as early as day 2 in the irradiated groups.

On day 1, no significant differences were evident among groups, and no signs of infection were noted. A slight reduction in wound area appeared in IG-5, while IG-15 showed more substantial contraction and early scab formation. By day 6, CG remained in a prolonged inflammatory phase with minimal healing. IG-5 showed moderate improvement, whereas IG-15 exhibited rapid contraction and early scar development—indicative of progression to later healing stages.

By day 10, inflammation had resolved in CG, but wound closure remained incomplete. In contrast, both IG-5 and IG-15 had achieved near or complete re-epithelialization. Notably, although the CG showed a marginally faster initial rate of contraction, the irradiated groups quickly surpassed this trend in later stages.

These findings suggest that topical exposure to alpha radiation, particularly from ^{241}Am at the 15-minute dose, may significantly enhance wound repair by accelerating epithelialization and contraction. The simplicity, and cost-effectiveness of the procedure-requiring only localized exposure and no complex equipment highlight its therapeutic potential.

Table 1. Displays the wound area in square millimeters (mm^2) that is statistically significant ($p < 0.05$).

Group	Day 0	Day 2	Day 4	Day 6	Day 8	Day 10
CG	98.583 ±2.13	89.95±3.96	82.96±4.03	78.70±3.40	77.61±3.37	60.87±2.74
IG-5	100.79±1.05	87.93±4.41	73.43±4.09	63.85±3.44	49.69±3.96	33.58±2.40
IG-15	98.72±1.45	59.73±2.36	57.52±2.39	39.50±4.04	19.11±3.18	5.70±0.26

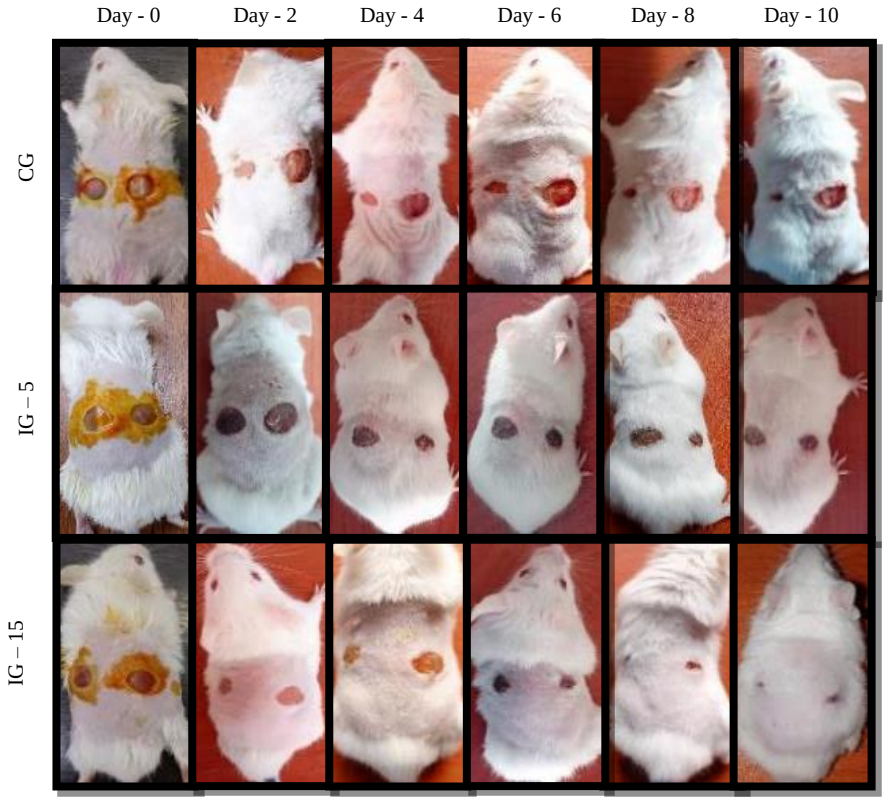

Figure 2. Sequential photographic documentation of dorsal skin wounds in mice from day 0 to day 10 post-injury.

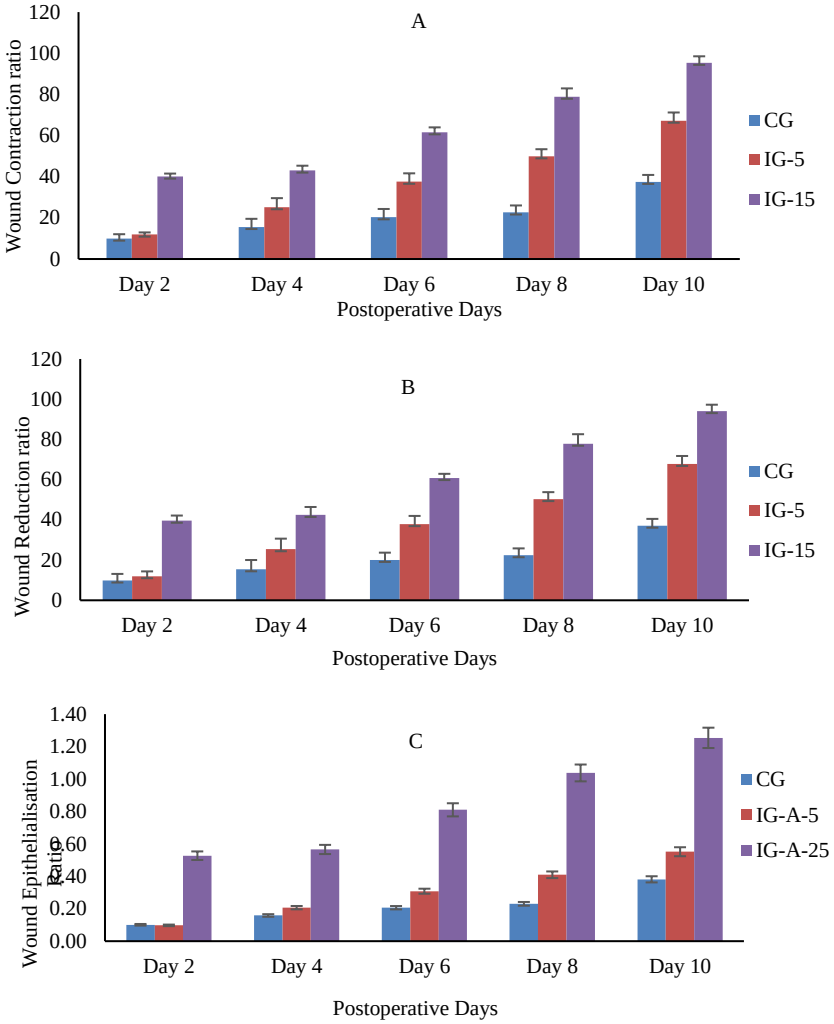

Figure 3. A percentage-based statistical analysis was performed on wound area in both treatment and control groups at days 0, 2, 4, 6, 8, and 10. (A): Wound contraction and healing time were evaluated across the experimental groups. (B): Ratios of wound area reduction were compared among groups. (C): Ratios of wound epithelialization were assessed to evaluate re-epithelialization during healing. Data are presented as mean ± standard deviation, and statistical significance was defined as $p < 0.05$.

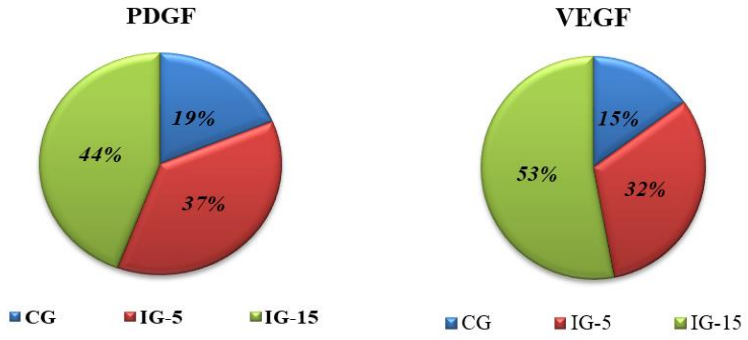

Figure 4. Synergistic effects of upregulated PDGF and VEGF signaling pathways on skin wound healing in mice.

Histological analysis

Histological examination of skin sections from the positive control group (normal mice) across all experimental groups, up to the tenth day, reveals intact skin layers and normal skin appendages. Figure 5 illustrates the positive control group, highlighting the organized layers of normal skin tissue, which include the epidermis and dermis, as well as the presence of hair follicles and sebaceous glands.

Figure 6A depicts the CG, showcasing visible sebaceous glands and an irregular skin surface, accompanied by a disorganized dermal layer. In

contrast, Figure 6B presents irregular collagen bundles and a high density of fibroblasts within the dermal layer, along with the infiltration of inflammatory cells.

The treatment groups began with IG-A-5, which demonstrates incomplete regeneration of skin cells, characterized by numerous sebaceous glands and increased collagen deposition (Figure 7). However, the dermis remains somewhat disorganized, and regeneration appears partial.

IG-A-15 shows hyperplasia of the epidermal cells, with a high density of hair follicles and further collagen deposition, as depicted in Figure 8. This suggests an ongoing, although still incomplete, regeneration process.

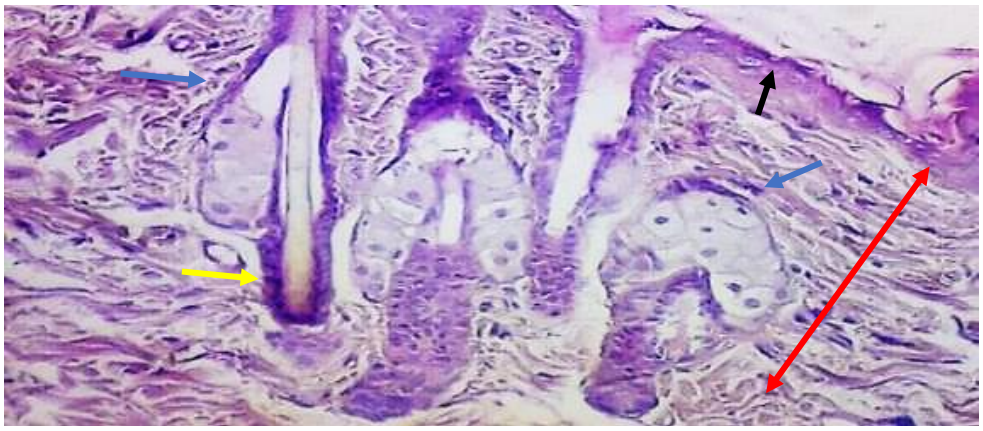

Figure 5. A longitudinal section of healthy, uninjured dorsal skin. The epidermis displays a regular, intact surface (black arrow), while the dermis exhibits normal architecture with organized connective tissue (double red arrow). Visible skin appendages include hair follicles (yellow arrow) and associated sebaceous glands (blue arrows), indicating unaltered skin morphology and serving as a baseline for comparison with irradiated and wounded tissues. (Hematoxylin and Eosin staining, 10X).

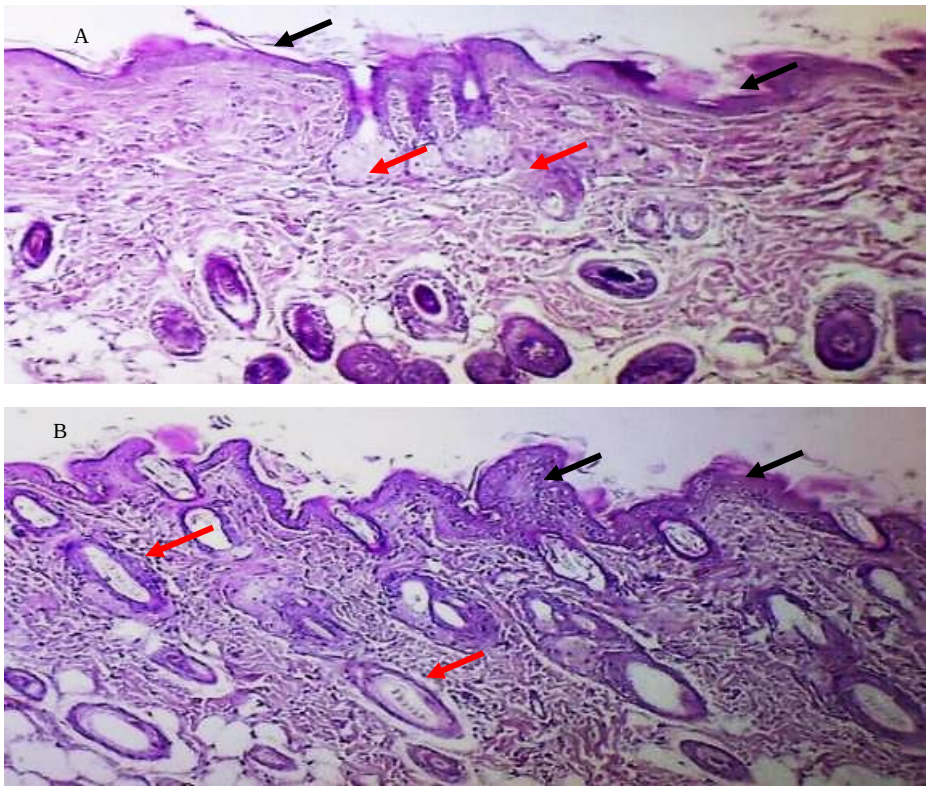

Figure 6. Longitudinal histological section of healed skin from the CG on day 10 post-wounding. (A): The epidermal surface appears irregular (black arrows), indicating incomplete or disorganized re-epithelialization. The dermal layer shows structural disarray (red arrow), with partial regeneration of sebaceous glands also observed (red arrow). These features reflect delayed and suboptimal tissue remodeling in the absence of alpha radiation treatment. (B): The dermal layer exhibits disorganized collagen bundles and numerous fibroblasts (black arrows), indicative of ongoing tissue remodeling. Infiltration of inflammatory cells is also evident (red arrows), suggesting incomplete resolution of the inflammatory phase and a delayed transition to tissue maturation in the CG (Hematoxylin and Eosin staining, X4).

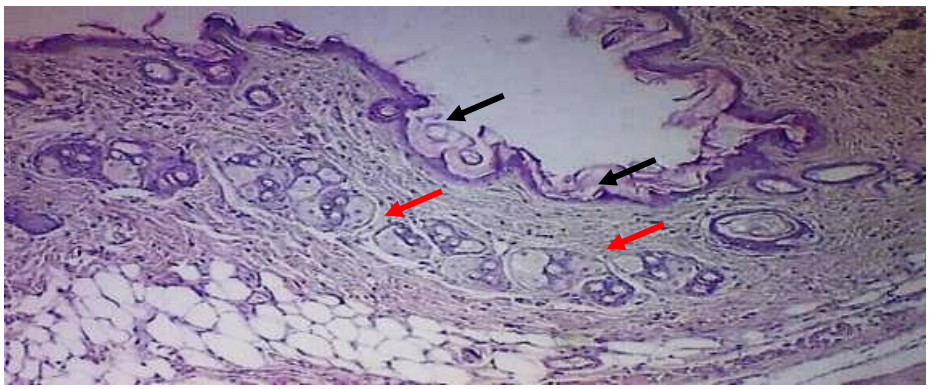

Figure 7. Longitudinal histological section of healed skin from the IG-5 group on day 10 post-wounding. Epidermal regeneration appears incomplete, with irregular or disrupted epidermal continuity (black arrows). Numerous sebaceous glands are observed within the dermis (red arrows), indicating partial restoration of skin appendages. Enhanced collagen deposition is evident, reflecting active extracellular matrix remodeling and progression toward tissue repair (Hematoxylin and Eosin staining, X4).

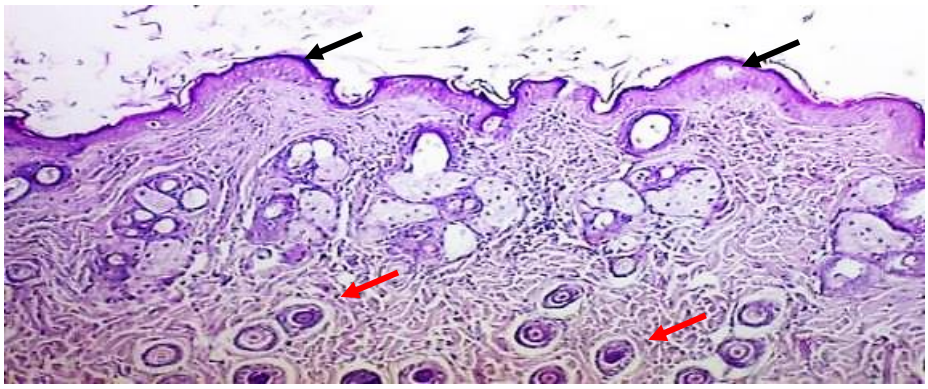

Figure 8. Longitudinal histological section of healed skin from the IG-15 group on day 10 post-wounding. Marked epidermal hyperplasia is observed (black arrows), indicating active cellular proliferation and re-epithelialization. Numerous hair follicles are present within the dermis (red arrows), suggesting advanced tissue regeneration and restoration of skin appendages. Collagen deposition is significantly increased, reflecting robust extracellular matrix formation and accelerated wound remodeling (Hematoxylin and Eosin staining, X4).

Discussion

Wound healing and the enhancement of ideal tissue restoration remain pivotal focuses in clinical applications [32]. This complex process progresses through distinct stages: hemostasis, inflammation, proliferation, and remodeling [33], involving key signaling molecules such as PDGF and VEGF. [34]. Successful progression through each phase is critical, as disruptions may prolong healing or cause chronic wounds [35]. Therefore, assessment and treatment of wounds require careful consideration of these intricate, sequential events [36].

A multitude of clinical, biochemical [37], and histological-parameters [38] are utilized to assess the advancement of wound healing. The histological assessment incorporates variables such as angiogenesis, inflammation, wound contraction, epithelialization, and differentiation. Histological parameters comprise components, including angiogenesis, inflammation, wound contraction, epithelialization, and differentiation [39]. Taking these into account, this study investigated the potential impact of alpha radiation on wound-healing, focusing especially on the inflammatory phase. Using an in vivo experimental model, we found that inflammation decreased after 10 days of irradiation in all treated groups compared to controls. Angiogenesis was delayed in the control group, whereas collagen fiber accumulation and deposition were apparent in all treated specimens. Staining demonstrated higher organized collagen fiber accumulation in the irradiated groups.

Researchers have long aimed to minimize complications in healing, such as severe scarring, infection, and collagen abnormalities [40]. To achieve this, diverse strategies have been explored, including pharmaceutical drugs [41], homeopathic remedies [42] and physical interventions such as laser therapy [43] alongside conventional methods [44]. However, a limited understanding of the molecular pathways involved in wound healing, combined with a scarcity of animal model studies, has slowed progress in developing effective, timely therapies. Unattended wounds risk localized infections and may even lead to cancer development [45]. Recognizing these challenges, there is an ongoing effort to develop novel treatments with minimal side effects [46].

Alpha radiation, emitted by the americium-241 (^{241}Am) [47] is a form of direct ionizing radiation composed of two protons and two neutrons [48]. Application of alpha radiation at wound sites initiates a range of biological responses that may improve healing.

One critical effect is the activation of angiogenesis—the formation of new blood vessels essential for supplying oxygen and nutrients to damaged tissue. Controlled exposure to alpha radiation also helps regulate inflammation, reducing excessive inflammatory responses that can impede healing. Additionally, alpha radiation promotes cellular proliferation, enhancing the replication of key cells like fibroblasts and keratinocytes involved in tissue repair. Collagen deposition is also increased, contributing to the organization of the extracellular matrix necessary for tissue regeneration.

Our research extensively evaluated the safety and efficacy of alpha particle radiation in wound treatment. Notably, the combined action of VEGF and PDGF exhibits a strong, synergistic effect in promoting cutaneous repair in mouse models [49]. These growth factors coordinate angiogenesis [50], cell proliferation, extracellular matrix synthesis, and overall tissue regeneration, accelerating and improving wound healing efficiency [51,52]. The combined effect of VEGF and PDGF surpasses that of either factor alone, significantly contributing to effective tissue repair [53]. Analysis revealed enhanced PDGF and VEGF function in treated mice, indicating a direct link between their expression and wound healing physiology [54].

It is hypothesized that low doses of alpha radiation may stimulate the generation and release of PDGF and VEGF, thereby promoting cellular proliferation, migration, and angiogenesis. Compared to other radiation therapies used for wound care, alpha particle radiation has unique advantages. Its penetration depth is limited to a few tens of micrometers in biological tissue [55], making it ideal for superficial wound treatment without affecting deeper layers. In contrast, gamma rays or high-energy electrons penetrate more deeply, risking damage to healthy surrounding tissues [56]. This limited penetration is advantageous for targeted treatment of superficial wounds because it can restrict radiation exposure to the desired area without affecting deeper tissues. On the other hand, alternative types of ionizing radiation, like gamma rays or high-energy electrons, exhibit a superior level of penetration [57]. This could potentially lead to adverse effects on surrounding healthy tissues. Alpha radiation possesses a high Linear Energy Transfer (LET) [58], resulting in the deposition of a significant amount of energy per unit distance traveled in the tissue. This high LET can lead to more efficient cell and tissue damage, particularly by inducing DNA double-strand breaks and triggering apoptosis (programmed cell death) in target cells [59]. This high LET offers the potential to selectively eliminate damaged or undesirable cells, which could be beneficial in certain wound healing contexts.

Research indicates alpha particles promote angiogenesis, modulate inflammatory responses, and enhance the growth and differentiation of crucial cells like fibroblasts and keratinocytes. These distinct biological effects may underlie the therapeutic benefits observed with alpha radiation in wound healing. Overall, alpha particle radiation represents a unique and promising approach that leverages its specific physical and biological properties.

Building on current findings and previous molecular and tissue studies, radiation therapy may hold potential in wound management. While most wound care innovations focus on topical medications requiring expensive clinical trials, alpha radiation offers a cost-effective, accessible, and easy-to-use alternative. Our results demonstrate the technical efficacy of alpha radiation treatment and support further investigation into its clinical application.

Conclusion

The use of alpha radiation as a therapeutic modality for wound healing presents a novel, promising approach, supported by dose-dependent histological evidence. This method is simple, cost-effective, safe, and effective in accelerating tissue repair. However, therapeutic efficacy varies with exposure time: lower-dose treatment (IG-5) resulted in incomplete skin regeneration, as indicated by the irregular formation of collagen and sebaceous glands. In contrast, the higher-dose treatment (IG-15) led to more robust skin restoration, including the development of a well-defined keratinized layer, organized collagen fibers, functional sebaceous glands, and the emergence of specialized hair follicles, along with reduced inflammatory infiltration. These findings highlight the importance of optimizing dosage to maximize regenerative outcomes while minimizing adverse effects. Specifically, IG-15 demonstrated superior potential in promoting comprehensive skin tissue regeneration. As such, controlled application of alpha radiation may represent a viable and accessible technique for enhancing wound healing. Further preclinical studies and rigorously designed clinical trials are needed to validate its safety, elucidate underlying mechanisms, and confirm therapeutic efficacy in human subjects.

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