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# Polyvinyl Alcohol/ Gelatin/ Silver Nanocomposites Treatment for Rats Skin Wound Irradiated by γ-rays

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CUTANEOUS wound healing is a complex process for the repair of damaged/ injured tissues; it is vital to find an effective method to boost skin healing. The aim of the present work is to investigate the role of polyvinyl alcohol (PVA)/ gelatin/ silver nanocomposites, in wound healing. Thirty rats were equally divided into 5 groups as follows: 1) Normal intact skin (NS), 2) Topical garamycin (G), 3) γ-irradiated (8 Gy), 4) Poly Vinyl Alcohol (PVA), 5) Poly Vinyl Alcohol+ γ-rays (PVA + γ-rays). Rats in groups 2,3,4,5 were subjected to a surgical wound. Rats from each group were sacrificed on the 5$^{th}$ and 21$^{st}$ day from the surgical procedure. Histopathological and biochemical investigations (tumor necrosis factor alpha (TNF-α), interleukin-1β (IL-1*β*) and interleukin-8 (IL-8)) were evaluated in the wound region of the skin. The current results revealed that γ-irradiation delayed the healing process of rat's skin wound with less reepitheliazation , prominent fatty tissues and higher levels of inflammatory markers. PVA gelatin/ silver nanocomposites treatment enhanced the healing process, as presented by both pathological and biochemical results. In Conclusion: PVA/ gelatin/ silver nanocomposites treatment may enhance skin healing.

**Keywords:** PVA, Rats, Skin, Wound, γ-rays.

## Introduction

Wound healing enhancement has been a goal for several decades. The regulation of skin wound healing is a complex process, which is dependent on many cell types and mediators interacting in a highly sophisticated temporal sequence (Oliveira et al., 2023).

During normal skin healing, different selections of chemokines were started; they correlated spatially and temporally with the phase-specific recruitment and trafficking of neutrophils, macrophages, and lymphocytes (Mohammed et al., 2022).

The TNF-α is an imperative mediator in the pathogenesis of trauma, sepsis, and inflammation. It has important roles in accelerating wound epithelialization and neovascularization in-vivo. TNF-α is capable to compensate the negative effect of macrophage reduction and seems to have a direct effect on the wound-healing process (Zhang et al., 2023). In 2017, Takada and his colleagues reported that the sequential function of endogenous IL-8 in all phases of human wound healing is detected (Takada et al., 2017). Moreover, in 2017, Law and his coworkers indicated that interleukin-1 induced overexpression of interleukin-8 and growth-related oncogene-α in human keratinocytes. These changes are correlated with characteristic functional alterations of the epidermis observed in psoriasis and wound healing (Law et al., 2017).

Epigenetic regulation in wound healing refers to genome-wide molecular events, including DNA methylation, histone modification, and non-coding RNA regulation, represented by microRNA (miRNA), long noncoding RNA (lncRNA), and circular RNA (circRNA) (Yu et al., 2022). Epigenetics not only has a positive effect

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on wounds, but also may produce synergistic amplification effects when combined with traditional or existing treatment methods such as physical therapy, negative pressure suction, and drug treatment.

The development of nanogels is the result of successful application of nanotechnology in the field of gel technology to improve validity. Nanogels are hydrogel polymeric network dispersions with particle size in the nanometer range. The term Nanogel (NanoGel) was announced for the first time by Alexander & Serguei (2008) to describe cross-linked bifunctional systems of a nonionic polymer and a polyion for transport of polynucleotides (Oh et al., 2021). Nanogels are basically a carrier system for delivering drugs or they can be chemically modified to incorporate various ligands for targeted drug delivery and triggered drug release (Wang et al., 2023). Due to their exclusive construction, nanogel polymer networks possess dual properties of cross-linked polymer gels and dispersed colloidal particles. They also enhance cellular accumulation significantly, without causing observable cytotoxic processes. They are also categorized as hydrogel nanoparticles. However, with respect to the classic nanoparticles, they have an elevated degree of encapsulation which offers an ideal tridimensional microenvironment for many macromolecules (Shehzad et al., 2024). Moreover, nanogels also display abundant quicker response as compared to the conventional hydrogels.

Nanogels can be produced via high-energy irradiation of polymer aqueous solutions in the presence of small amounts of functionalizing polymers or monomers, so that polymer crosslinking, monomer grafting to the network and product sterilization can be obtained in a single step. Irradiation-based methods are gaining a lot of interest as a way to synthesize non-toxic nanogels. This method is based on the use of ionizing radiation and, in some cases, on physical self-assembly techniques which do not require polymerization initiators or crosslinking agents. Essentially the only substrates needed are polymer and water, which greatly eliminates toxicity concerns. Another noteworthy advantage of this method of synthesis is that sterilization occurs simultaneously with the synthesis of the nanogel (Srikhao et al., 2023).

Polyvinyl alcohol (PVA) is a biocompatible polymer which has been generally utilized in progressive biomedical bids, such as wound bandages (Iqbal et al., 2020). This polymer has certain properties, including non-toxicity, great hydrophilicity, excellent processability, chemical conflict and high mechanical asset (Chi et al., 2022). PVA has OH-hydrophilicity with unique properties including water solubility, multiple OH-groups for further decoration, and its biocompatibility and low toxicity are FDA-approved. The use of PVA as a biomaterial gained a great attention in biomedical applications such as protein/ enzyme immobilization, cell encapsulation in the form of micro/hydrogel scaffolds (Cheng et al., 2023). The modification of OH-groups on PVA is largely considered to introduce more convenient sites for conjugation and chain extension using ester, carbamate, ether and acetyl linkages (Alves et al., 2011). It should be mentioned that core–shell PVA based micro-gels shielded with hyaluronic acid (HA) were prepared by "click" chemistry and inverse emulsion techniques for targeted local delivery of doxorubicin to adenocarcinoma colon cells (HT-29) (Kupal et al., 2012). The aim of this work is to investigate the role of a nanogel formed by a combination of polyvinyl alcohol (PVA), gelatin, silver nanoparticles, ascorbic, glycerol, and tween 20 which is biocompatible in wound dressing and healing.

## Materials and Methods

*Experimental animals*

Thirty adult male Wister rats were used (weighting 220-240g, aged 12-13 months). Rats were obtained from the animal house that belongs to the NCRRT, Cairo, Egypt. Animals were reserved under normal ventilation condition and had free access to water and normal concentrated pellet, and were adapted in standard planned cage 6 rats per cage in a 12/12-h light-dark cycle and under normal pressure and temperature conditions. This experiment was carried out according to the international guidelines of animal handling and care and approved by the Research Ethics Committee for animal experimental studies at the NCRRT, Cairo, Egypt.

*Experimental design*

Thirty male rats were divided into five equal groups (n-6) as follows:

1) Normal intact skin group (NS); animals were shaved only (no wound).

2) Control group (C); only topical garamycin cream applied to the wounds for 7 successive days.

3) γ-rays group; an hour after wound was made, rats were irradiated with a single dose of γ-rays (8 Gy) and then topical garamycin cream applied to the wounds for 7 successive days.

4) PVA group; an hour after wound was made, topical garamycin cream and PVA were applied to the wound for 7 days.

5) PVA+ γ-rays group; rats were irradiated with a single dose level of (8 Gy) then topical garamycin + PVA applied to the wound every day for 7 days.

*Chemical reagents*

*P*olyvinyl alcohol (PVA)its molecular weight is 1, 15,000, (-C2H4O)n by loba chemie, India. Gelatin, was obtained from El-Gomhouria co., Egypt. Ascorbic acid (C6H8O6), m.w. 176.13,was obtain from alpha chemika. Tween -20 (polyoxyethylene (20)/ sorbittan monolaurate), m.w. 1227.72, was obtained from loba chemie, India. Glycerin was obtained from El Gomhouria Co., Egypt.

*Preparation*

An accurately weighed amount of PVA equivalent to 8% and 0.5% of gelatin were added to distilled water at the ratio of (90:10) respectively during stirring and temperature at 80°C. After the complete dissolution of PVA and gelatin, 0.1% of Ascorbic acid was added. Then, 5% of Glycerin and Tween -20 were added to the solution during the continuous stirring. Finally, 1% of silver nitrate was added. The prepared solution was irradiated via γ-rays with dose of 2.5 kGy.

*Characterizations*

The surface topography and structural features of the produced nanostructure films were examined using Scanning Electron Microscopy (SEM) (ZEISS-EVO 15-UK). EDX was utilized to identify and investigate the elemental composition. EDX was attached to scanning electron microscopy (SEM) (ZEISS-EVO 15-UK). To display composite particle size distribution and geometry, a high-resolution transmission electron microscope (HRTEM) model (JEOL/JME-2100, Japan) was employed.

*Radiation facility*

It was applied using gamma cell-40 ($^{137}Cs$) located at NCRRT, Cairo, Egypt. Rats were irradiated with a single dose (8 Gy) delivered at a dose rate of 0.37 Gy/ min at the time of experimentation.

*Experimental surgical procedures*

The animals were anesthetized before surgical procedures with ketamine hydrochloride (10%, 0.005 mL/kg) intramuscularly after weighing. Next, a 6-cm2 area on the abdominal side of the animal was hairless via an electric clipper, and local antisepsis was done using 0.5% topical chlorhexidine alcohol. The wounds were ready on all groups except group (NS), a 3 cm in diameter full thickness biopsy were made by a standardized fashion with the assistance of a circular metal tool with a metal blade (nº 4). Immediately after surgical excision, the lesions of the animals in all groups received garamycin cream locally on wounds for seven successive days, after completing the surgical processes, the rats in all groups except group NS were kept in individual cages.

*Sample collection and preparation*

Three animals from each group were sacrificed on the 5th day from the beginning of the experiment and the rest after 3 weeks from the beginning of the experiment.

Skin samples were collected from wounds skin or healing skin tissues and divided into two parts. The first part, the tissues were washed and a homogenate (10% weight/volume w/v) was prepared in phosphate-buffered saline (0.02 M sodium phosphate buffer with 0.15 M sodium chloride, pH7.4) using Teflon-glass homogenizer (Glass-Col, Terre Haute, Ind., USA) and centrifuged at 1000xg for 15 min in a cooling refrigerated centrifuge (K3 Centurion Scientific Ltd, London, UK). The supernatant was obtained for the further biochemical analysis. The second part, skin was put in 10% buffered formalin for the histopathological studies.

Assessment of inflammatory markers TNF-α, IL-1$\beta$ and IL-8 was performed using ELISA method (Bio Source International, Camarillo, CA, USA) in accordance to the manufacturer's instructions. All tasters examine was recurrent more than one time (Thermo Scientific Multiskan MK3, USA).

*Histopathological study*

Skin samples were fixed in 10% neutral formalin solution. After one weak, skin was dehydrated over a series of classified alcohol, inserted in paraffin, and cut into 4-micron sections, then stained with hematoxylin and eosin (H&E) according to Bancroft et al. (1996).

*Statistical analysis*

Data was presented as means+ SE. Statistical analysis of the results was performed using ANOVA-test followed by LSD as Post Hoc-test. Acceptable significance was logged when the P-values were less than 0.05.

## Results

High-resolution Transmission Electron Microscope (HRTEM) was employed to assess and inspect the morphology of the materials, and to determine the magnitude of molecular spots at the nanoscale. Fig. 1 (A) illustrates irradiated PVA/ Gelatin nanogel embedded silver nanoparticles. Fig. 1 (B) illustrates a full porous structure for PVA/ Gelatin surface morphology. In addition, Fig. 1 (A & B), shows the formation of nanotubes from PVA/ Gelatin copolymer in the presence of ascorbic acid and glycerol (Sapalidis et al., 2018). They display the cross-section mode images for PVA/ Gelatin nanogel containing silver after irradiation.

*Histopathological findings*

There are three principal layers of normal intact skin (NS): the epidermis, the dermis, and subcutaneous fascia. Skin appendages such as sweat glands, hair follicles, and sebaceous glands are reviewed in-depth in a different place (Fig. 2). Skin wound (polyvinyl group) after 5 days, has low necrotic tissues and little edema, while in skin wound (control group) after 5 days, necrotic debris, persistence necrotic tissues in the middle of the wound encircled by edematous granulation tissues were found (Fig. 3 A). However, in case of γ-rays group, wound contained extra-vascular hemorrhage and little fibrous tissues containing massive leukocytes in the wound gap (Fig. 3 B). The wound gap in PVA + γ-rays group showed the wound defected devoid from blood with proliferation capillaries sprouts, and permanent mature granulation tissues and little crust on the surfaces (Fig. 3 C). On the contrary, after 3 weeks, skin wound in control group showed reepitheliazation of wound with whole filling of the wound by fibrous tissues and fat (Fig. 4 A). While, irradiated skin wound with γ- rays revealed maturation of fibrous tissues, less reepitheliazation with prominent fatty tissues (Fig. 4 B). Skin wound healing in case PVA + γ-rays group showed that wound gap did not completely cover by epidermis, but contained collagen fibrous and fat tissues (Fig. 4 C), while rat skin wound of PVA group, the wound gap contained collagen deposits and was partially covered by epidermis and fat in vicinity of the wound (Fig. 4 D).

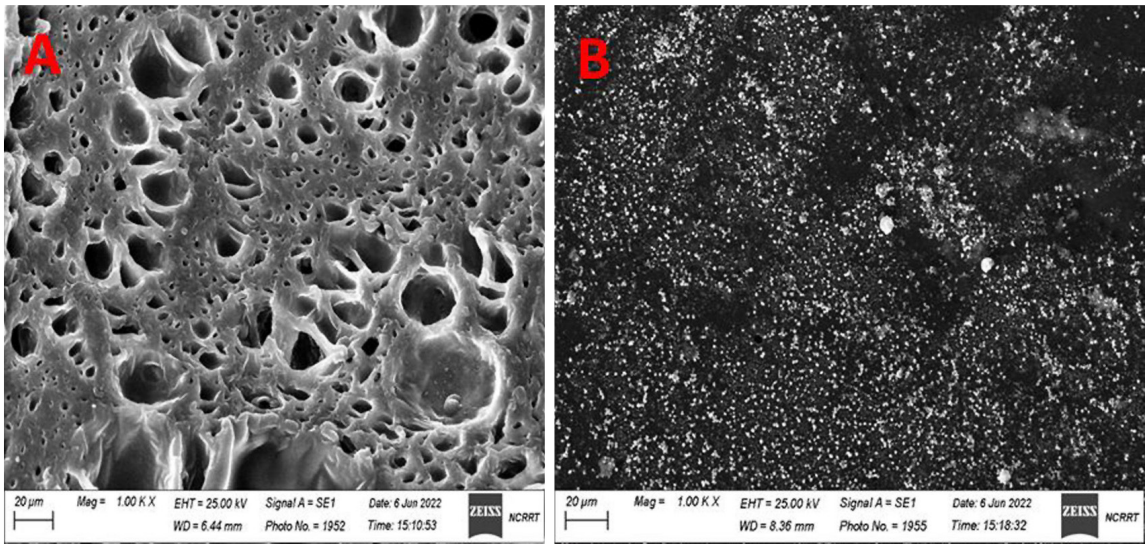


**Fig. 1. Photomicrograph of HRTEM measurement, A) Cross section image for cross linked and porous PVA/ Gelatin containing silver nanoparticles after gamma irradiation process at 2.5 kGy, B) Surface mode image for the same sample**

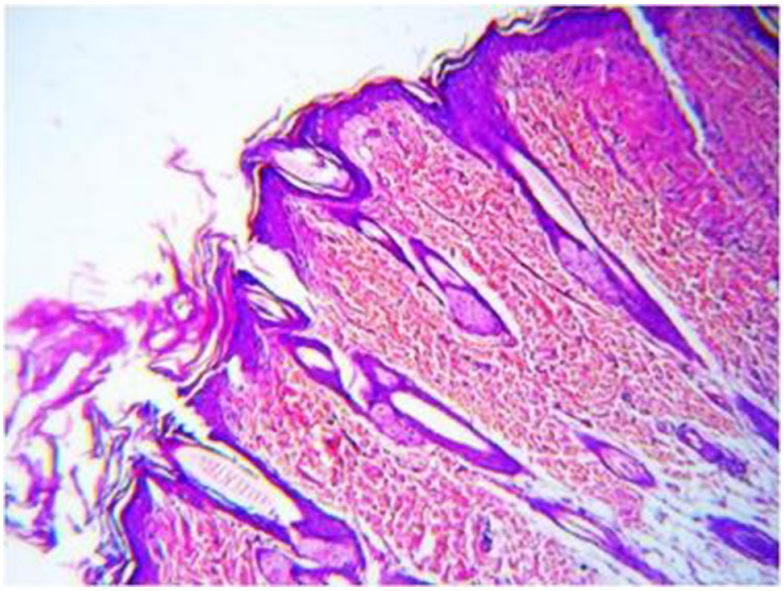

**Fig. 2. Photomicrograph of normal intact rat skin showing normal epidermis, dermis and skin adnexa (H&E 100x)**

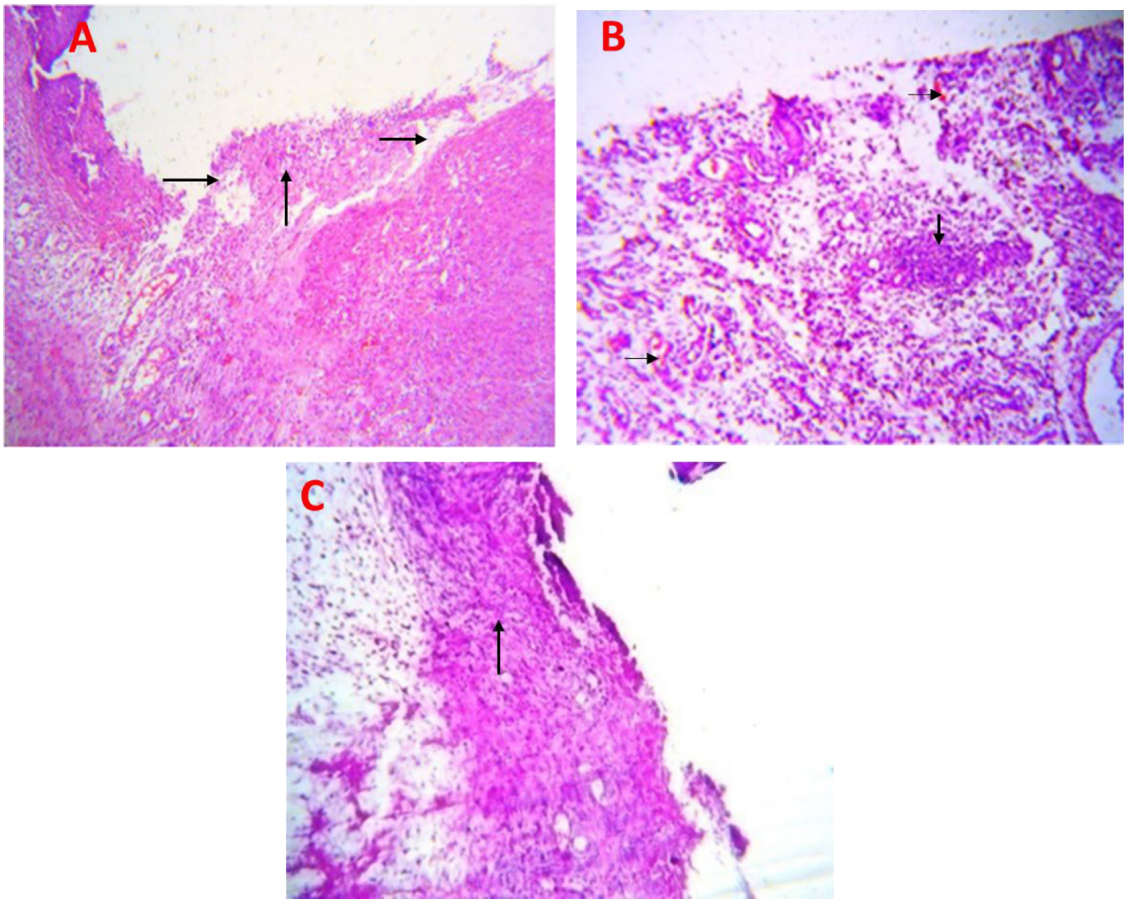


**Fig. 3. Photomicrograph of rat skin dermis at the 5th day (H&E 100x), A) control rat showing necrotic tissues in the center of the wound (↑) encircled by edematous granulation tissues (→), B) γ- rays rat showing granulation tissues containing numerous capillaries (→) within immature fibrous tissues (↓), C) PVA + γ- rays rat showing permanent mature granulation tissues (↑) and little crust on the surface**

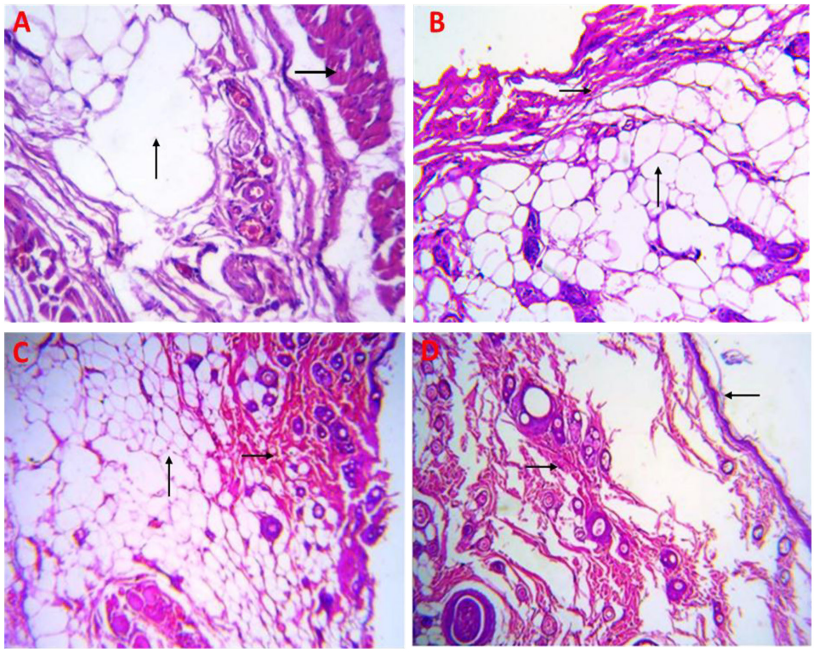


**Fig. 4. Photomicrograph of rat skin both epidermis and dermis at the 21st day (H&E 100x), A) Control rat lees reepitheliazation of wound with complete filling of the wound by fibrous tissues (→) and fat (↑), B) γ- rays rat showing maturation of fibrous tissues (→), less reepitheliazation with prominent fatty tissues (↑), C) PVA +γ- rays rat showing wound gap contain collagen deposits (→) and partially covered by epidermis and fat (↑) in vicinity of the wound, D) PVA rat showing wound gap completely cover by epidermis (←) and contain collagen fibrous (→)and less fat tissues**

*Inflammatory markers*

When TNF-α, IL-1β and IL-8 levels were examined in normal skin and after garamycin application; there was no significant difference in both groups after 5 days or 3 weeks.

The level of skin TNF-α, IL-1*β* and IL-8 levels in **γ-** Irradiated Skin wound is significantly increased ($P > 0.05$) compared to the control after 5th day and 3rd week. It was also noticed that PVA application raised most of inflammatory markers after 5 days in a significant manner; and after 3 weeks their levels decreased though still higher than the control levels. On the other hand, when the authors compared between the application of PVA in **γ-** irradiated skin wound group and **γ-** irradiated skin wound group without PVA, it was found that PVA decreased the level of inflammatory markers (TNF-α, IL-1*β* and IL-8 levels) significantly ($P> 0.05$) after 3 weeks as shown in Table 1.

## Discussion

The potential need of natural flexible multifunctional hydrogel with high-strength, wear-resistant, antibacterial and conductive for tissue repair is in demand nowadays (Liu et al., 2022). However, the difference between rodent and human skin with abundance of hair follicles in rats' skin than in humans can promote wound healing more in rodents (Grada et al., 2018).

Ionizing radiation is known to impair skin healing process which requires a fine balance between promoting and inhibiting factors. Early inflammatory reaction to radiation is primarily caused by pro-inflammatory cytokines (IL-1, IL-3, IL-5, IL-6, and TNF-α) chemokine's (eotaxin and IL-8), receptor tyrosine kinase, and adhesions molecules (intercellular adhesion molecule 1 [ICAM-1], E-selectin, and vascular cell adhesion protein). These factors can produce a local inflammatory response of eosinophils & neutrophils, leading to self-perpetuating tissue damage and loss of protective barriers (Peter, 2015). Moreover, Schäffer and his colleagues confirmed that exposure to electron beam using a single dose of 12 or 24 Gy electron radiation at the dorsal rat skin up-regulated skin healing factors (TNF-α and IFN-γ) in the skin wound after exposure to radiation (Schäffer et al., 2002).

**TABLE 1. TNF-α, IL-1β and IL-8 levels in the skin tissue of different animal groups**

| Groups | Days post irradiation | TNF-α (pg/ g tissue) | IL-1$\beta$ (pg/ g tissue) | IL-8 (pg/ g tissue) |
|---|---|---|---|---|
| N S | 5th day | 11.4± 0.7 | 15.6± 1.2 | 10.1± 1.3 |
| | 3 weeks | 11.4± 0.8 | 15.6± 1.1 | 10.1± 1.3[3] |
| Control | 5th day | 34.4± 1.5 [a3] | 35.1± 2.8 [a3] | 26.5± 2.1 [a3] |
| | 3 weeks | 29.1± 2.0 [a3] | 27 ± 1.9 [a3] | 17.8± 2. [a3] |
| γ-rays | 5th day | 37.4± 2.0 [a3b1] | 41.3± 3.2 [a3b2] | 28.6± 2.1[a3b] |
| | 3 weeks | 34.1± 1.4 [a3b1] | 32.2± 2.8 [a3b1] | 25.1± 2.3 [a3b2] |
| PVA | 5th day | 33.2± 3.0 [a3b] | 36.2± 1.8 [a3b] | 24.6± 2.2 [a3b] |
| | 3 weeks | 14.4± 2.3 [a1b3] | 15.2± 1.7 [ab3] | 12.9± 1.1 [a1b1] |
| PVA + γ-rays | 5th day | 38.2± 1.4[a3b1c] | 40.3± 2.2[a3b1c] | 23.4± 2.9[a3bc1] |
| | 3 weeks | 19.5± 2.1[a2b2c3] | 21.0± 2.4[a2b1c3] | 16.2± 1.9[a1bc3] |

- Values are expressed as means ± S.E (n = 6). a, Significance vs NS group (normal intact skin). b, Significance vs control group (control). c, Significance vs γ-rays group (γ-rays).
- Differences between means were considered significant (a1b1c1) at P ≤ .05, highly significant (a2b2c2) at P ≤ .01 and very highly significant (a3b3c3) at P ≤ .001, a,b,c non-significant at P > 0.05.

Yang et al. (2020) reported that in short-lived, radiation induce skin injury which is an extra common radiation therapy problem. This type of skin shield and repair is of a great meaning. Usually accepted guidelines for necrotic tissues, infection prevention and treatment, wound ooze management, and re-assessment of treatment plans based on observation of wound advancement should be conducted to treat full-thickness wounds resulting from late radiation injury. Patient instruction should consist of regular skin and wound care organization and topical medicines. More cost-effective protective actions applying fewer side belongings should be advanced to effectively protect the benefits of patients, confirming smooth chemotherapy, as well as increasing the value of life of patients.

It was found in the current study that the skin wound exposed to γ irradiation; TNF-α (37.4± 2.0 after 5 days and 34.1± 1.4 after 21 days), IL-1β (41.3±3.2 after 5 days and 32.2±2.8 after 21 days) and IL-8 levels (28.6 ± 2.66 after 5 days and 25.1± 2.34 after 21 days) significantly increased (P<0.05) compared to the control.

Moreover, in the present study, PVA was incorporated with silver nanoparticles; the use of PVA after γ- exposure decreased significantly (P > <0.05) the level of tissue cytokines after 21 days TNF-α (19.5± 2.1), IL-1β (21.0±2.4) and IL-8 levels (16.2 ± 1.59) in the different rat groups compared to the 5th day with tendency towards normal level.

It should be mentioned that PVA alone or after γ- exposure produced nearly similar results after 5 days in the levels of skin tissues TNF-α, IL1β, IL8 respectively. However, after 21 days, these cytokines where down-regulated with PVA alone more than with γ- exposure.

Regarding the histopathological results, PVA seems to improve reepitheliazation after γ irradiation with more collagen deposits in order to refill wound gap.

Fasola et al. (2023) recorded the treatment of delayed wound healing following radiation therapy. Impairments after radiation treatment take place in about 60% of surgical cases. Medical outcome includes skin atrophy, soft tissue fibrosis, desquamation, epithelial ulceration, fistula formation and main vessel break. Diminished pre and postoperative wound healing and the problems related with it can be observed commonly and may need extensive reconstructive efforts (Luze et al., 2022). Current treatment is limited, and more studies are needed to develop best-practice recommendations. Investigatory treatment options targeting specific mechanisms of injury may offer potential solutions to this significant clinical and surgical problem.

It is well known that PVA revealed suitable biocompatibility, especially PVA at pharmaceutical grade, it is a macromolecular organic substance that has no side effects on the human body, it has been used in various biomedical applications, including artificial joints (Cui et al., 2021), contact lenses (Wu et al., 2021), cardiovascular devices (Pereira et al., 2019) and wound dressing (Tang et al., 2019). Because of the linear structure of PVA, it can be cross-linked by strategies such as irradiation and chemical agents. PVA seems to have an important role in wound healing as a synthetic polymer by accelerating skin angiogenesis and collagen deposition; especially when incorporated with gelatin silver nanoparticles. Thus, it is essential to select a suitable polymer and bioactive compound which has a significant effect on accelerating wound repair. Silver nanoparticles have an antibacterial activity and also they enhance the effect on cell migration and proliferation quality through changing the amount of m-RNA in the wound environment and modulation of cytokines which can stimulate fibroblasts (Júnior et al., 2021**)**.

## Conclusion

PVA incorporated with silver nanoparticles seems to play an important role in skin wound healing in the near future.

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