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The Healing Enhancement of Second-Degree Skin burn by Hyaluronic Acid Extract and Aloe Vera Gel in Rabbit

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Abstract:

This study was conducted to evaluate the difference between the effect of hyaluronic acid extract from vitreous eye of bovine and fresh aloe vera gel on the healing of induced cutaneous burn in rabbits. 45 adult male New Zealand white rabbits were randomly used. The animals were divided randomly into three equal groups after creation a skin burn on the back of each experimental animal. In first group, the site of skin burn was treated by hyaluronic acid extract while in second group the animals treated with fresh aloe vera gel and the animals of third group were left without treatment as a control group. The healing process was evaluated macroscopically and microscopically on 7,14-, and 21-day post-treatment.

The Hyaluronic acid extracted-treated group showed significantly accelerated wound healing, faster re-epithelialization, reduced inflammation, and minimal scarring compared to both the Aloe Vera extracted -treated and control groups. The Aloe Vera extracted -treated group showed moderate improvement in wound healing but lagged behind the Hyaluronic acid extracted group.

Histological examinations revealed enhanced collagen deposition, fibroblast activity, and tissue regeneration in the Hyaluronic acid extracted-treated wounds, which were significantly better than those observed in the other two groups ($p \leq 0.05$). These findings indicate that The Hyaluronic acid extracted, with its biocompatibility and regenerative properties, holds great promise as a natural, effective treatment for burn injuries, offering a viable alternative to traditional Hyaluronic acid-based treatments.

The conclusions of this study discovered that the healing of hyaluronic acid extracted group was better and faster than the other groups.

Aims:

Study to investigate the effectiveness of hyaluronic acid extract and fresh aloe vera gel on the

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healing of skin burns clinically and histopathologically and compare between them.

Keyword: Hyaluronic acid, Aloe Vera, Burn, skin, rabbit

Introduction

The skin considers the greatest organ in the body and its essential for numerous internal processes, including excretion, vitamin D synthesis, protection from external environments'and regulation. Therefore, serious skin damage may risk life. The regeneration of skin wounds illustrates a remarkable and distinct cellular functional apparatus. The cells growing factors, and cytokines collaborate throughout the healing route to repair the injury (Tottoli et al., 2020 ; Jabbar and Abid,2024). Burns are considered a significant public health threat due to their potential to produce severe injuries that damage organs and tissues. They are directly associated with tissue degeneration, infection, discomfort, and perhaps mortality, occurring when tissue is subjected to physical, chemical, and biological agents (Brassolatti et al., 2018). Burn injuries, particularly second-degree burns, are a common type of skin damage that affects both the epidermis and dermis, resulting in pain, blistering, and inflammation (Jeschke et al., 2020; Haichal, and Towfik. 2025).

Hyaluronic acid (HA) is a high molecular weight biopolymer, identified in 1934 by Karl Meyer and his assistant, John Palmer, in the vitreous humor of bovine eyes. HA is a naturally occurring biopolymer that plays significant biological roles in both bacteria and higher organisms. It is present in the majority of connective tissues especially abundant in synovial fluid, the vitreous humor of the eye, umbilical cords, and chicken combs. It is synthesized by integral membrane proteins known as hyaluronan synthases and degraded by enzymes referred to as hyaluronidases (Bolivar et al., 2020; Hussein et al.,2024). The vitreous humor is that a clear gel-like substance that's located and fill the space between lens and retina of eye. The majority of the vitreous humor is generated during ocular development. It is devoid of blood vessels. The vitreous is composed of 99% water, along with soluble and insoluble proteins, organic salts, lipids, collagen, and hyaluronic acid (Bishop, 2000).

Aloe Vera is a renowned medical plant from the Liliaceae family (Nagare & Shekokar, 2022). The plant has been utilized for therapeutic determinations across various nations and cultures, possesses a wide array of therapeutic claims attributed to its pharmacological properties and used in treatment of various veterinary and human illnesses. (Salem et al., 2022). The foliage of the plant encompasses a variety of minerals, enzymes, amino acids, natural sugars, and other bioactive substances possessing emollient, purgative, antimicrobial, anti-inflammatory, antioxidant, aphrodisiac, anti-helminthic, antifungal, antiseptic, and cosmetic properties beneficial for health care. Aloe Vera acts as metabolic regulation involving Brady kinase, carboxypeptidase, and cyclooxygenase. The plant is an abundant source of various natural health-enhancing compounds,

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including vitamins and minerals such as Vitamin C, A, E, B vitamins, beta-carotene, zinc, calcium, copper, magnesium, manganese, and phosphorus. (Akek et al., 2023). Aloe vera has been used in a number of industrial applications due to its beneficial properties such as drugs, cosmetics and food industries. The current research discusses the medicinal uses of Aloe vera, also its cosmetic and food applications (Sánchez-Machado, 2017; Lanka, 2018). It also known as medicinal plant due to its various useful applications including skin irritation, burns, and skin diseases (Hussien*et al*,2018; Shakib et al., 2019; Svitina et al., 2019; Lee et al., 2021; Mahmood,2024).

Materials and Methods:

Ethical Approval:

The work was agreed upon by the Ethics Committee of the Faculty of the Veterinary Medicine College, University of Al-Qadisiyah. No.4956.

Experimental animals:

forty five adult male white New Zealand rabbits, aged 8–10 weeks and weigh 1 ± 0.3 kg, were used in this study. The rabbits were obtained from a certified supplier and acclimatized to the laboratory environment for 7 days prior to the experiment. They were housed in standard cages under controlled conditions, maintaining a temperature range of 22–24°C, with free access to food and water. Following general anesthesia an intramuscular injection of a combination of Xylazine 2% (3 mg/kg B.w.) and ketamine (30 mg/kg B.w.) (Abdullah et al., 2019) , the back area of all rabbits was trimmed and shaved. Subsequently, thermal injuries were inflicted using a tool of solid aluminum bar with a circular end at (2 cm in diameter), which had been heated in boiling water at 100℃. To create 2nd degree burns, the bar is held in contact with the dorsal proximal region of the animal's skin for 15 second. The pressure applied to the animal skin equated to the mass of a 51g aluminum bar, which resulting severe damage of epidermis and part of dermis layer characterized by blistering, swelling, erythema, crusting, hemorrhage, exudation. The treatments were used topically once daily for seven days (Paula et al., 2011; Tavares Pereira et al., 2012). The animals were randomly divided into three groups of 15 rabbits each. The first group received treatment with Hyaluronic acid extract 0.2% in concentration and 0.5mg on burn area , the second group was treated with fresh aloe vera gel 85% in concentration and 0.5mg on burn area , and the third group served as a control group, receiving no treatment.

Preparation of HA extract

Collection of bovine vitreous humor fluid

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Vitreous humor was collected from the anterior chamber by gentle aspiration into a 3 ml syringe following corneal penetration a 16-gauge needle in cattle. Vitreous humor was collected from the central portion of the vitreous body following insertion of a needle through the sclera and aspiration into a 10 mL syringe (Hanna et al., 1990). 50 ml of bovine vitreous humor fluids were collected post-slaughter from the Al- Diwaniyah slaughterhouse and immediately preserved in an ice box before being transferred to a laboratory refrigerator at 4ºC .

According to (Murado et al., 2012) with modifications. The vitreous humor fluids apply by using Whatman filter papers for precipitate other unwanted molecules and other substances, then use microfilter in size 0.45 micron and then use microfilter in size 0.22 micron for clearing from unwanted substances. The hydroalcoholic preparing by add ethanol 99% to make solution (v/v) at 5ºC for sediment HA and proteins fraction and incubation 3 to 5 hours. The sedimentation uses the proteinase 1/10ml for analyzing proteins and lysozyme as antibacterial agent to the sedimentation was added in test tube and cleared by centrifugation at 6,000 rpm for 15 minutes, remove the sediment (which contained only insoluble protein) and the upper part of tube was the clear HA extract.

Preparation of Aloe Vera gel

Mature Aloe vera (Aloe Barbadensis) leaves were obtained from a private garden. The freshly harvested leaves of Aloe Barbadensis were manually cut in the early morning for research purposes .

According to (Fahimeh et al.,2016) to avoid bio-degradation, the Aloe vera leaf is carefully harvested from the parent plant to prevent damage to the peel and washed with fresh water for 5 min and rinsed with sterile distilled water. Their thick epidermis was removed and they were cut transversely into pieces. Then the colorless solid mucilaginous thick tissue (Aloe vera gel) was scraped out by using a sterile knife. According to (Chandīgarh and Varshney. 2013) with modification, the domestic blender was used to process the fillets into a uniform pulp. The charcoal was additional with natural gel (0.1g/100ml of natural gel) for purifying purposes and then centrifuged at 10,000 rpm for 30 min for mixing with charcoal and to remove the fibers from the gel. Pasteurization the gel by heated at 65c for periods of less than 15 minutes, the biological activity remains essentially intact and help destroy microorganisms and then cooling the pure gel and collected in the sterilization test tubes.

Results

Clinical Evaluation

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All animals throughout the time of experiment (21 days) post wounding (P.W.), clinically were seen energetic, healthy, active, and with good healing processes arranged the site of injury and no mortality were recorded.

Morphometric evaluation of burn healing

All wound locations mostly enlarged by 4 hours post-creation and continued to swell and expand in size over the subsequent 24 hours. P.W. exhibiting strong inflammatory symptoms. The whole wound seemed enlarged, with raised margins., red in color, and from the second day P.W. show a thick scab upon the wound persisting more than the 7th day P.W... The wound gradually decreased in size till the 21th day were become small scar tissue as circular or liner in shape.

Burn dimensions were directly measured on the 7th, 14th, and 21st days post-injury using a progressed millimeter ruler. Initially, the diameter of the circular burn (on days zero and seven) was measured. As the form of the injury altered and ceased to be round (on days fourteen and twenty-one), the outside measurements of the wound length (L, along the longest axis) and width (w, the shorter axis perpendicular to the length) were recorded. The same device was consistently used, and stringent aseptic conditions were maintained to avert infection (Nichols, 2015.)

1- Assessment of wound area (size): alterations in the extent of the burn were observed with direct assessment of wound dimensions on the 7th, 14th, and 21st days post-injury. When the burn is circular, the rounded surface area is calculated as (half the diameter) ^{2} x 3.14 .When the configuration of the burn is altered, the surface area is calculated as length multiplied by breadth.

2 -Measurement of burn contraction: Burn contraction on the 7th, 14th, and 21st days post-injury was quantified as a percentage decrease in the initial burn size using the following formula:

% Burn contraction = (burn area on day 0 - burn area on day n) / (burn area on day 0) x 100 (Patil et al., 2012).

Morphometric data were subjected to statistical analysis using ANOVA one way and Least Significant Difference (LSD) to determine significance among groups at a threshold of $P \leq 0.05$(Yunus, 2010).

Wound Surface Area

The initial wound surface area on first day of experiment was **(2 mm^2)**. Skin burns were measured on days 0,7,14 and 21 post burn injury. The average area of burn on 7th day in G1, G2 and G3and were1.630, 1.688, and 1.864 respectively

There were no significant differences between G1 and G2 while they recorded a significant difference when compared with G3 whereas the noted a substantial disparity in comparison to other categories.

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On day 14 the surface area in G1, G2 and G3 were 1.174 ,1.308 and 1.576 respectively, the difference was significant ($p \leq 0.05$). between G1,G2 and other groups was noticed regarding the wound size between G1, G2 when compared with G3 recorded lesser value of surface area after 14 days post burn injury.

On day 21, the recorded surface areas of G1, G2 and G3 were 0.636, 0.868 and 1.180 respectively. The significant difference between the G1 and the other groups was noted G3 recorded lesser value of surface area after 21 days post burn injury ($p \leq 0.05$).

Table (1): Wound surface area.

Groups/Periods	Weak 1	Weak 2	Weak 3
G 1	1.630 ± 0.013 Ca	1.174 ± 0.010 Cb	0.636 ±0.018 Cc
G 2	1.688 ± 0.010 Ba	1.308 ± 0.005 Bb	0.868 ±0.019 Bc
G 3	1.864 ±0.009 Aa	1.576 ± 0.011 Ab	1.180 ±0.013 Ac
LSD(p<0.05)	0.038		

•.Capital letters denote to the vertical statistical reading

•Small letters denote to the horizontal statistical reading

• Different letters denote to the significant difference at P<0.05

Wound Contraction:

The contraction of a lesion is a metric utilized for evaluating wound healing, characterized by a steady reduction in the lesion area as healing time advances.

The shrinkage of the injury at 7 days for G1, G2, and G3 was observed as 14, 48.1, and 45.1, sequentially. A substantial increase ($p < 0.05$) was observed in G2 and G3 opposed to G1, with G3 also showing a substantial difference when opposed to G1.

On day 14, the percentages of wound shrinkage for G1, G2, and G3 were obtained as 58.12%, 89.35%, and 78.8%, sequentially. G2 and G3 exhibited increases opposed to G1, with G3 showing a substantial difference when opposed to G1.

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On the 21st day, the G1, G2, and G3 values were observed as 78.2, 90.42, and 89.47, significantly. Wound contraction was notably more rapid in G2 and G3, exhibiting a substantial difference when opposed to G1. Additionally, G3 demonstrated a substantial difference relative to G2 (Table 2).

Animals (in G2) treated with hyaluronic acid extract showed signs of full wound healing. The rabbits given hyaluronic acid extract had the quickest rate of lesion contraction and the shortest duration of wound care compared to the other groups on day 21.

Table (2): Wound contraction %.

Groups/Periods	0 day	Weak 1	Weak 2	Weak 3
G 1	0 Aa	14 Ab	58.12 Ac	78.02ABd
G 2	0 Aa	48.1 Bb	89.35 Bc	90.42 Bc
G 3	0 Aa	45.1 Cb	78.8Cc	89.47 Bd
LSD(p<0.05)	4.6			

•Capital letters denote to the vertical statistical reading

•Small letters denote to the horizontal statistical reading

• Different letters denote to the significant difference at

Morphological Appearance

The morphological appearance of the burn wounds in rabbits treated with Hyaluronic acid, Hyaluronic acid extract, Aloe vera , and the control group (no treatment) was observed on 7,14-, and 21-day post treatment . The groups displayed distinct differences in wound healing, as observed macroscopically) figure 1).

In the control group, the wounds showed the slowest healing progress. At first week, the burn wounds remained inflamed with significant erythema, and there was no visible contraction. By second week, the wound edges had only slightly contracted, and the tissue still appeared red and inflamed. By third week, while some wound contraction was observed, the area remained discolored with prominent scarring and poor tissue regeneration. The control group's wounds exhibited the least favorable healing outcomes, with delayed recovery and persistent inflammation

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In the Hyaluronic acid -treated group, the wounds began to show visible signs of healing by the end of the first week, with reduced erythema (redness) and no signs of infection. By the second week, the wound edges contracted significantly, and the tissue appeared more regenerated with minimal redness. By the third week, the burn wound was almost completely healed, with minimal scarring. The skin in this group regained a healthy and s mooth appearance.

In the Aloe vera -treated group, the healing process was noticeably slower than group treated with Hyaluronic acid. At first week, the wounds showed moderate erythema, inflammation, and no significant contraction. By second week, the wound edges contracted noticeable, but the healing process was accompanied by less visible redness and some scarring. By week3 ,although the wounds had contracted.

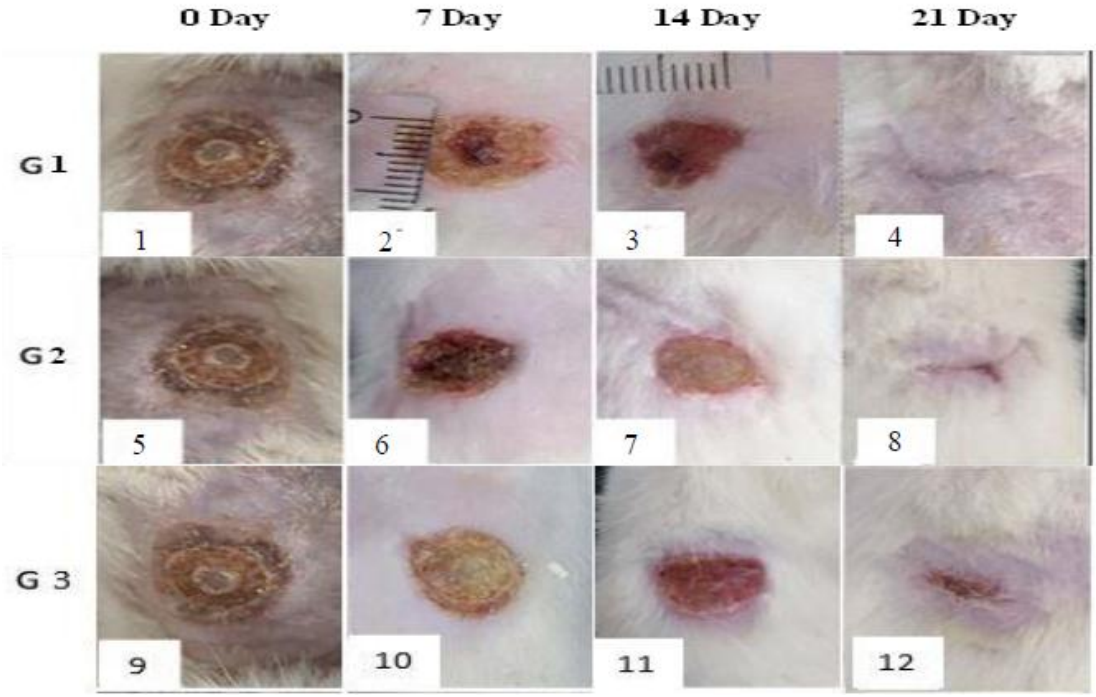

Figure1: Morphological characteristics of burns in groups at various time intervals (post treatment).

Histopathological Assessment of the Burn Healing:

G1. W1. Histological alterations subsequent to burn damage shown profuse purulent exudate and thick crust above the dermis Complete sloughing of the epidermis. Necrosis and denaturation of collagen fibers and dermal adnexa like hair follicles, sweat glands (Figure 2).

G1. W2. Histological alterations subsequent to burn damage shown thick crust and pus formation above the dermis with complete sloughing of the & epidermis. High infiltration of inflammatory cell with granulation tissue formation of New small blood vessels and fibrosis with thin and irregular Collagen fibers with marked denaturation of hair follicles (Figure3).

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G1. W3: Histological alterations subsequent to burn damage shown profuse granulation tissue and high infiltration of inflammatory cells with thick Collagen fiber and in the top of the section, there is hyperplastic epidermis (Figure 4).

G2. W1. Histological alterations subsequent to burn damage shown higher magnification of previous section. Note high infiltration of neutrophils and macrophages in the dermis. Also there is pus and tissue debris above The dermis (Figure 5).

G2. W2. Histological alterations subsequent to burn damage shown thick crust above the dermis with hyperplasia of stratum basal of the epidermis. Coarse and irregular network of collagen fibers with high infiltration of inflammatory calls and marked hemorrhage in the dermis (Figure 6).

G2.W3. Histological alterations subsequent to burn damage shown disintegration and separation of the crust above the skin with marked hyperplasia of the epidermal layers . Numerous new congested blood vessels and fibrosis in the dermis with scattered inflammatory cells and coarse collagen fibers network (Figure 7).

G3. W1. Histological alterations subsequent to burn damage shown higher magnification of the previous section, There is mild infiltration at inflammatory cells mainly neutrophils and eosinophils with mild hyperplasia of the epidermis and thin collagen fibers (Figure 8).

G3. W2. Histological alterations subsequent to burn damage shown marked granulation tissue and infiltration of inflammatory cells mainly macrophages with Few neutrophils and eosinophil's (Figure 9).

G3. W3. Histological alterations subsequent to burn damage shown mild hyperplasia of the epidermal layers toward the Site of burn. Destructed and separated crust above the dermis. Regular and thick Collagen network, and scattered inflammatory cells (Figure 10).

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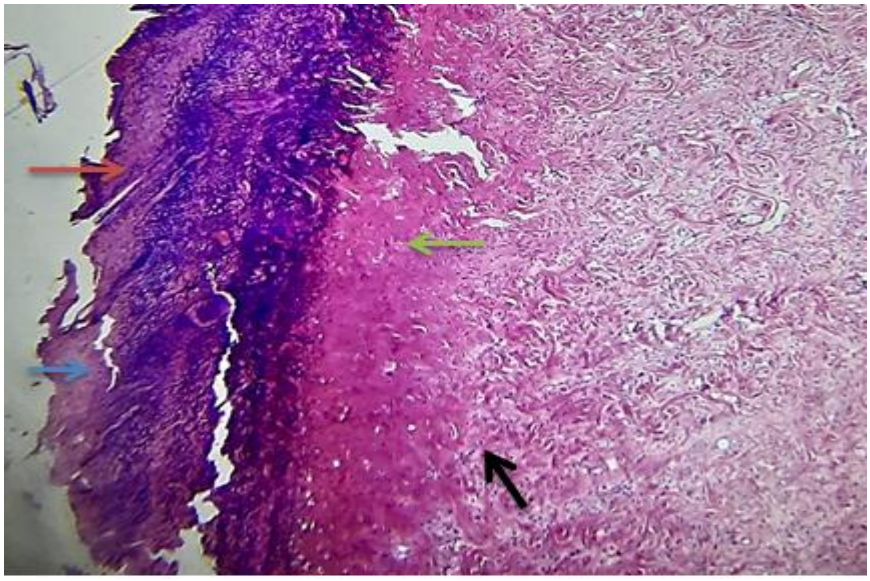

Figure 2:(G1w1) Histopathological section show profuse purulent exudate (blue arrow) and thick crust (brown arrow) above the dermis complete sloughing of the epidermis. Necrosis (green arrow) and denaturation of collagen fibers and dermal adnexa like hair follicles, sweat glands. (black arrow) (10x H&E).

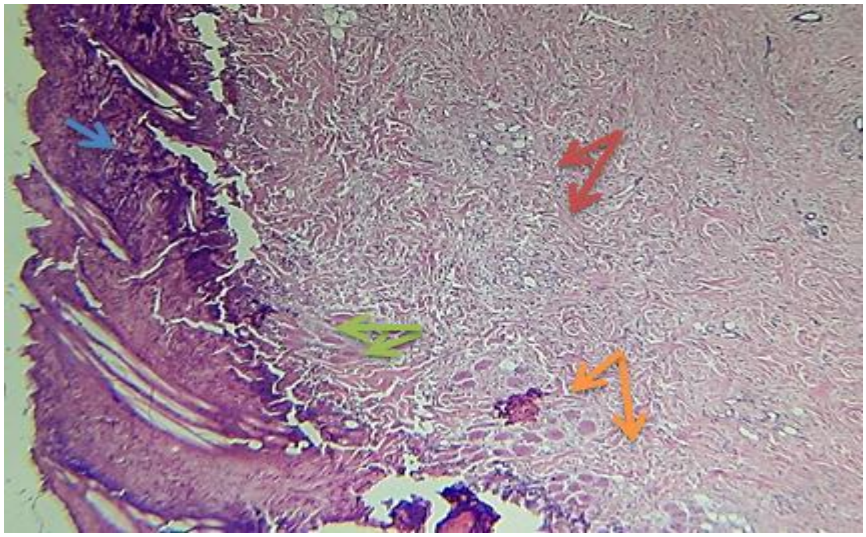

Figure 3:(G1w2) Thick crust (blue arrow) and pus formation above the dermis with complete sloughing of the & epidermis. High infiltration of inflammatory cell (green arrow) with granulation tissue formation of New small blood vessels and fibrosis with thin and irregular collagen fibers (red arrow) with marked denaturation of hair follicles (brown arrow) . (4X H&E).

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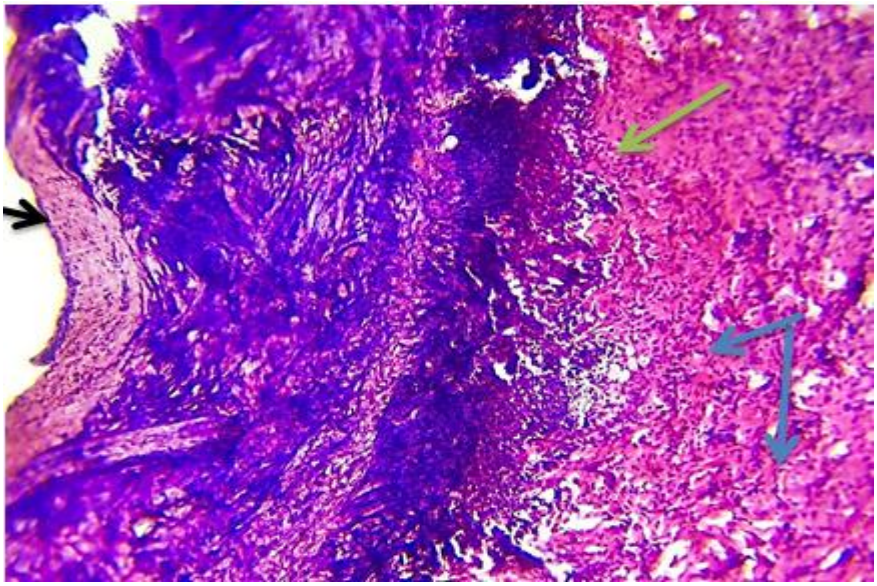

Figure 4:(G1w3) Histopathological section show profuse granulation tissue and high infiltration of inflammatory cells (green arrow) with thick collagen fibers (blue arrow) .In the top of the section, there is hyperplastic epidermis (black arrow). (10X H&E).

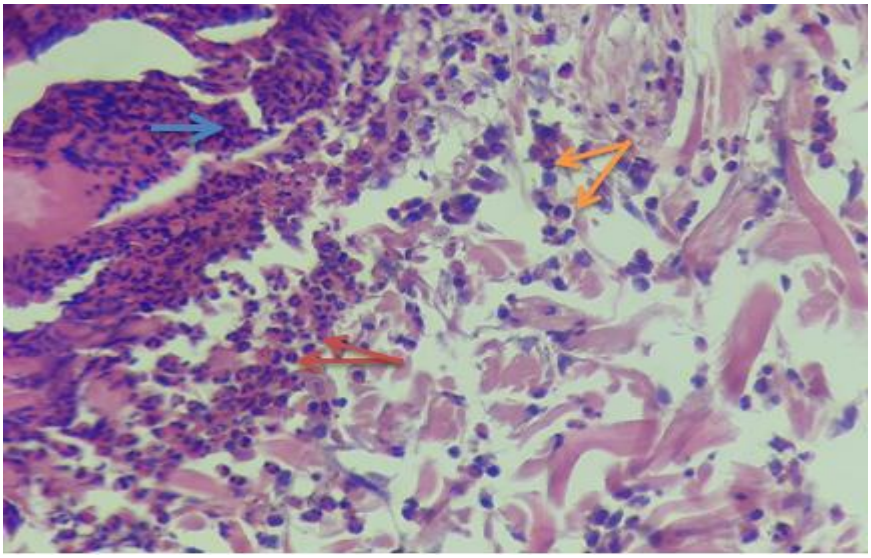

Figure 5 :(G2w1) Histopathological section show higher magnification of previous section. Note high infiltration of neutrophils (red arrow) and macrophages (brown arrow) in the dermis. Also there is pus and tissue debris above (blue arrow) the dermis .(40X H&E).

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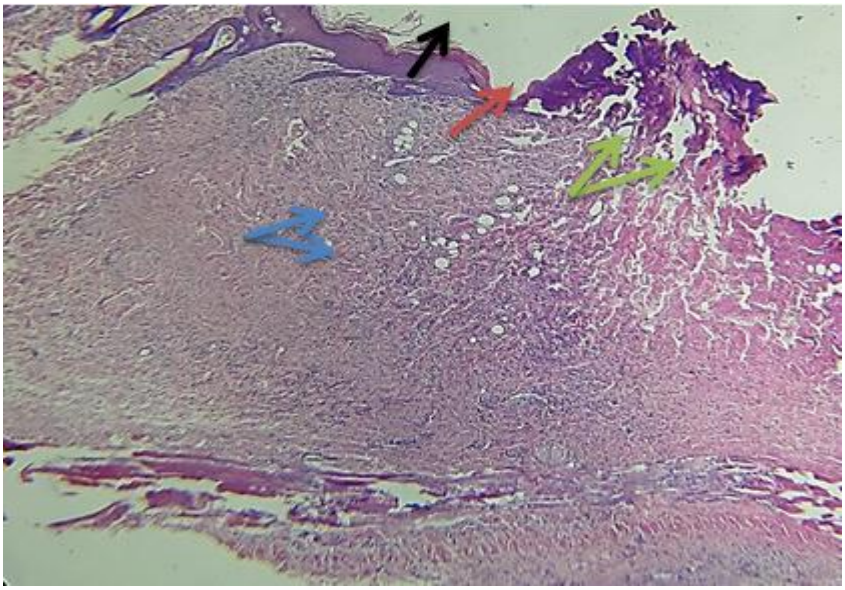

Figure 6 :(G2w2)Thick crust above the dermis with hyperplasia (black arrow) of stratum basal of the epidermis. Coarse and irregular network of collagen fibers (blue arrow) with high infiltration of inflammatory cells (red arrow) and marked hemorrhage (green arrow) in the dermis. (10x H&E).

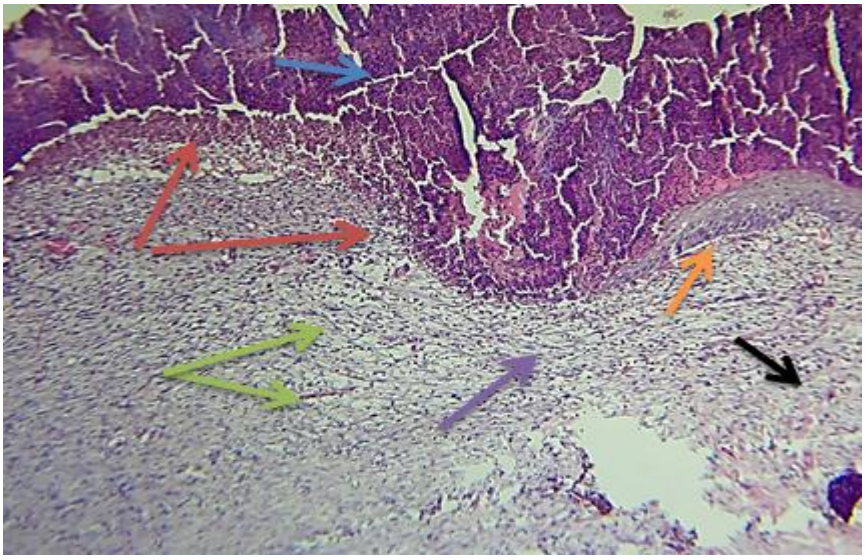

Figure7:(G2w3) Disintegration and separation of the crust (blue arrow) above the skin with marked hyperplasia (brown arrow) of the epidermal layers . Numerous new congested blood vessels (green arrow) and fibrosis (purple arrow) in the dermis with scattered inflammatory cells (red arrow) and coarse collagen fibers network (black arrow) .(10X H&E).

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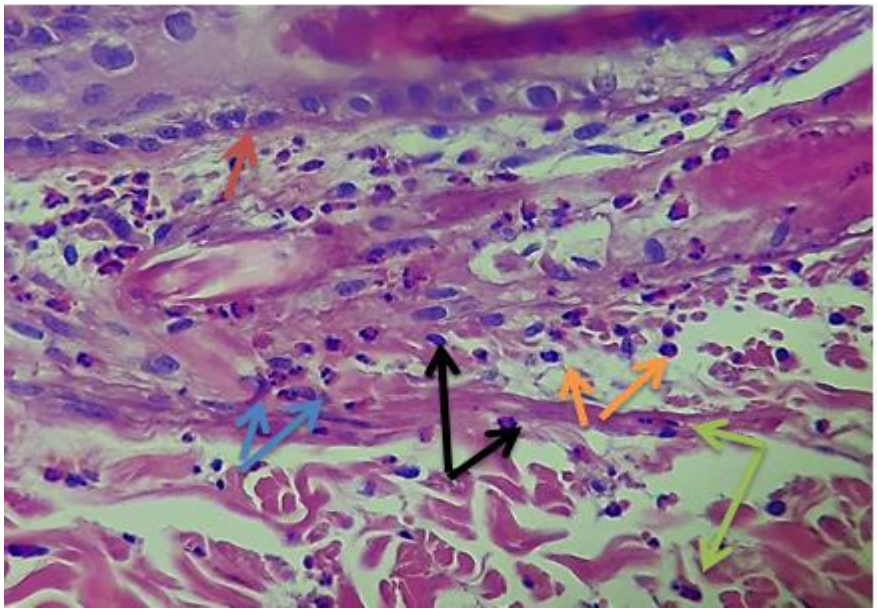

Figure 8:(G3w1)Higher magnification of the previous section, There is mild infiltration at inflammatory cells mainly neutrophils (green arrow) and eosinophils (black arrow) and macrophages (blue arrow) with mild hyperplasia (brown arrow) of the epidermis and thin collagen fibers (green arrow) .(40X H&E).

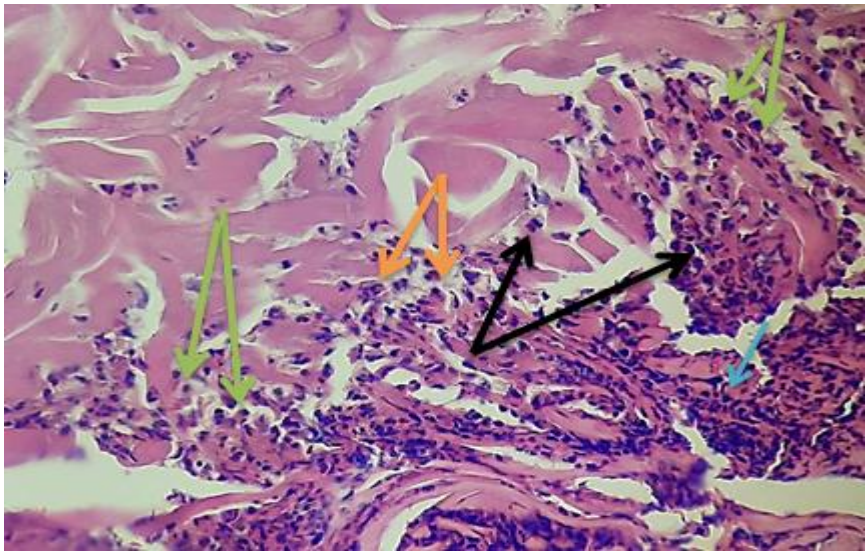

Figure 9: (G3w2) Marked granulation tissue (blue arrow) and infiltration of inflammatory cells mainly macrophages (blue arrow) with Few neutrophils (black arrow) and eosinophil's (brown arrow) . (40X H&E).

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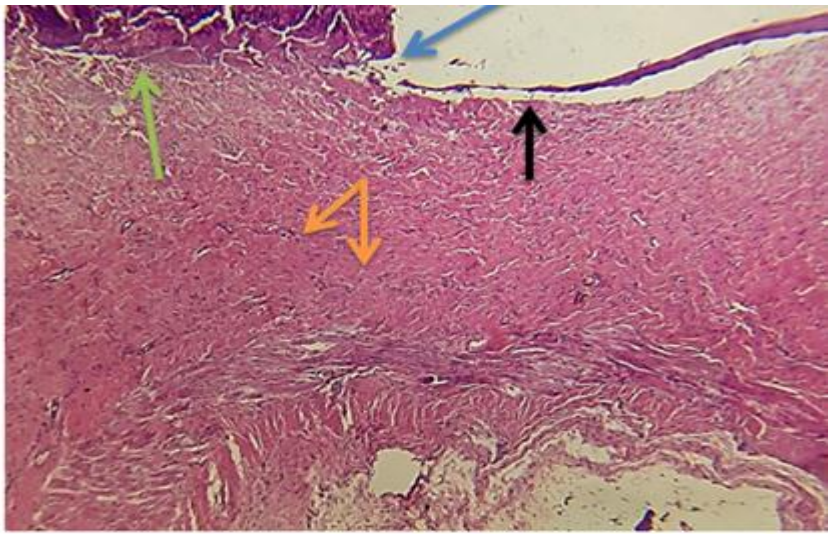

Figure 10: (G3w3) Histopathological section show Mild hyperplasia (black arrow) of the epidermal layers toward the Site of burn. Destructed and separated crust (blue arrow) above the dermis (green arrow). Regular and thick collagen network (brown arrow). (4X H&E).

Discussion:

Clinical practice uses topical medications and dressings to create and sustain a moist and sterilized environment, which is optimal for the process of wound healing. Nonetheless, they are often expensive, inefficient, and may elicit adverse reactions, underscoring the necessity for innovative alternative therapies. (Duque et al.2016).

The morphometric data in this study showed a significant reduction in wound surface area in the HA group contrast of gross and histopathological findings compared to the Aloe vera gel group. By the third week, the HA treated wounds achieved near-complete closure, a finding consistent with (Linlin et al,.2024). the HA functions the augment the natural high molecular weight hyaluronic acid in the epidermis, enhancing hydration. Hyaluronic acid in the dermis reduces the synthesis of inflammatory substances interleukins, which generate free radicals that may damage skin cell components and the extracellular matrix(ECM) homeostasis and that increase stimulation of fibroblast production . Hyaluronic acid is a naturally occurring humectant (including polyethylene glycol and glycerol-landethylene glycol and propylene, and sorbitol) is its insensitivity to relative humidity. when compared with G3 and G1

In contrast, the control group demonstrated slower healing, with noticeable scarring and less organized collagen deposition (Albozachri,2022) . While Aloe vera gel has been widely acknowledged for its effectiveness in reducing hypertrophic scars, its performance in promoting

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early-stage wound healing appears limited. These findings are in agreement with (Zago,2021), who highlighted that traditional treatments with Aloe vera gel are often less effective than advanced therapies in addressing complex wounds ,the effect of the Aloe vera extract also might contain Water (99%), as well as other solid substances (1.0%), such vitamins, enzymes, inorganic compounds and coatings containing hydroxyl anthracene, chromes, etc., are present in gel that reservation the moistness of the burn which help in healing method and also Aloe vera demonstrates several properties, including antibacterial, antiviral, anticancer, antioxidant, anti-allergic, anti-inflammatory, anti-ulcer, anti-diabetic, anti-aging, and healing effects for wounds, burns, and other skin diseases which found that Aloe vera The extract served as an exceptional scaffold in tissue engineering due to its ability to enhance fibroblast proliferation..

In this study we demonstrate that HA extracted group from vitreous humuor significantly enhances the healing of second-degree burns compared to Aloe vera gel group. The superior results of HA treatment align with previous researchers highlighting the advantages in wound healing due to their unique physicochemical properties, histological alterations of the HA extracted group subsequent to burn injury demonstrated full restoration of all skin layers, including the epidermis, papillary dermis, reticular dermis, and hypodermis, along with hair follicles, sweat glands, and sebaceous glands. New formation of blood vessels and fibrosis with regular and thick collagen fibers and scattered inflammatory cells (Siamak et al,.2024). The effectiveness of the HA utilized for G2 was evident in accelerating angiogenesis and collagen fiber formation. as mention by (Jianye et al,.2021; Leite and Frade,2021) when they said the HA functions the augment the natural high molecular weight hyaluronic acid in the epidermis, enhancing hydration. Hyaluronic acid in the dermis reduces the synthesis of inflammatory substances interleukins, which generate free radicals that may damage skin cell components and the extracellular matrix(ECM) homeostasis and that increase stimulation of fibroblast production . Hyaluronic acid is a naturally occurring humectant (including polyethylene glycol and glycerol-land ethylene glycol and propylene, and sorbitol) is its insensitivity to relative humidity

Conclusions:

The HA extract accelerates wound healing through enhanced tissue regeneration and reduced inflammation. The HA derived from vitreous humor of bovine eyes shows particular promise as a biocompatible and eco-friendly alternative for burn therapy. Future studies should focus on clinical trials and explore the broader therapeutic applications of this study in regenerative medicine.

Recommendations:

Using combinations between Hyaluronic acid with Aloe vera on treatment burn 2nd injury and studying the therapeutic effect of Hyaluronic acid nanoparticle to improve healing in burn 2nd injury and studying the therapeutic effect of Aloe vera nanoparticle to improve healing in burn 2nd injury.

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Conflict of interest:

The authors declare that there is no conflict of interest of this paper.

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This research was conducted entirely by the authors, who were responsible for study design, data collection, data analysis, and writing of the final manuscript.

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