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Modification of 3D Printed Denture Base Material by Hyaluronic Acid to Improve Healing

Immunohistological Effect on MMP2 and VEGF

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Abstract

Objectives: To evaluate the effect of topical release of different concentrations of hyaluronic acid from 3D printed denture bases on the healing of skin wounds. Materials and Methods: Fifteen healthy adult male rabbits from New Zealand were randomly split into three groups based on how long they would be kept: 3 days, 7 days, and 14 days. We shaved the skin on the back of each rabbit and then made five cuts in it. The wounds were sutured to allow for healing. The animals were split into three groups based on their treatment type. The first group had their wounds treated with just an incision (control negative), the second group had their incisions treated with a 3D printed specimen under the skin incision without hyaluronic acid (control positive). We added 0.25% hyaluronic acid and a 3D printed denture base specimen to the third incision, and we added 0.5% hyaluronic acid and a 3D printed denture base to the fourth incision. The fifth cut was treated with 1% HA acid and a 3D printed denture base specimen. After that, the biopsies were sent for immunohistochemistry evaluation. Results: The data from the treated group showed that hyaluronic acid (HA) speeds up healing. Conclusion: HA-treated groups, particularly those administered 0.5% and 1% concentrations, demonstrated markedly accelerated and more comprehensive epithelial regeneration.

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Introduction

Hyaluronic acid (HA) is a naturally occurring polymer made up of a linear polysaccharide structure that can degrade spontaneously under certain conditions. It plays a crucial role as a primary component of the extracellular matrix (ECM) [1]. This biopolymer is both biocompatible and biodegradable, and it can be found in various biological fluids and tissues [2]. The beneficial characteristics of HA have made it an important biopolymer in the biomedical field [3]. HA is an important biopolymer in biomedicine due to its numerous advantages. It maintains well-preserved structural properties and interacts with various ECM proteins and collagen fibers, facilitating cell adhesion, movement, migration, and growth [4]. Numerous biological roles in wound healing, including angiogenesis and re-epithelialization, have been observed both in vitro and in vivo through the topical application of HA [5]. It has been used in the healing of the socket after tooth extraction [6].

Tissue regeneration and wound healing are complex biological events that rely on the coordinated interaction of growth factors, extracellular matrix (ECM) remodeling enzymes, and cellular responses [7]. Among the most important mediators involved in these processes are vascular endothelial growth factor (VEGF) and matrix metalloproteinase 2 (MMP2), both of which play essential roles in angiogenesis, ECM turnover, and cell migration [8,9].

VEGF is a potent pro-angiogenic cytokine that stimulates endothelial cell proliferation,

migration, and the formation of new blood vessels. Adequate vascularization is fundamental for oxygen and nutrient supply to the regenerating tissue, thereby supporting successful repair. Upregulation of VEGF expression has been strongly correlated with accelerated healing, whereas impaired VEGF signaling is often linked to delayed tissue repair and chronic wounds [10]. MMP2, a member of the gelatinase subgroup of the MMP family, contributes to ECM remodeling by degrading type IV collagen and other basement membrane components. MMP2 enables cellular migration, angiogenesis, and proper tissue remodeling through this activity. Nevertheless, excessive or dysregulated MMP2 expression can lead to pathological outcomes such as chronic inflammation, impaired healing, or cancer progression [8].

Material and Methods

Fifteen Zealand adult male rabbits were used, 5-7 months in age, weighing 1.25-1.5 kg. These rabbits stayed in the Animal House. The house was prepared for the experimental studies in the College of Dentistry at standard-setting with temperature maintained at 25 ± 2 °C. The feeding of these rabbits were fed three times daily with a normal diet (lettuce and grass). All rabbits had good health throughout the period of the study. All procedures were carried out per the rules established by the Research Ethics Committee of the College of Dentistry at the University of Mosul in Iraq, using the code (UOM.Dent. 25/1006).

We used fifteen adult male rabbits from New Zealand that were 5 to 7 months old and weighed between 1.25 and 1.5 kg. The Animal House was set up for the experimental studies at the College of Dentistry, where the rabbits stayed at a temperature of 25 ± 2 °C. They were fed three times a day with a normal diet of lettuce and grass.

Three groups of three rabbits were randomly chosen from a group of animals. There were five experimental groups of incisions in the dorsal skin of each rabbit, based on the type of dressing material used (Figure 1). The groups were:

Group 1: N=5, negative control. Skin incisions did not receive any treatment.

Group 2: N=5, positive control. Skin incisions treated with a sample of 3D printed denture base material only.

Group 3: N=5, treated with hyaluronic acid 1%. Skin incisions treated with the topical part of 3d printed denture base material combined with hyaluronic acid 1%

Group 4: N=5, treated with hyaluronic acid 0.25%. Skin incisions treated with the topical part of a 3d printed denture base material combined with hyaluronic acid 0.25%

Group 5: N=5, treated with hyaluronic acid 0.5%. Skin incisions treated with the topical part of a 3d printed denture base material combined with hyaluronic acid 0.5%.

Biopsies were collected and subjected to immuohistopathological examination according to specified time intervals. The animals in each group were randomly split into five smaller groups, each with three rabbits. These groups were:

G1: The animals were put to sleep three days after surgery.

G2: The animals were put to death seven days after the surgery.

G3: The animals were put to death two weeks after their surgery.

Overdose anesthesia killed all the animals. The samples from skin and buccal defects were preserved in 10 percent formaldehyde for 48 hours, subsequently treated with ethanol alcohol and xylene, embedded and labeled in paraffin wax blocks, frozen for 24 hours, and then sectioned coronally into 4-micron thick slices using a microtome. A strip of cut tissue with wax at the incision level was then put in a 60 °C water bath, where the tissues were put on a glass slide that had been marked. After that, the slides were de-waxed, stained with hematoxylin and eosin, mounted with DPX, and examined with a light microscope.

Results

Table 1 shows the median scores of granulation tissue (GT) formation in five experimental groups across three-time intervals (Day 3, Day 7, and Day 14), with five rabbits per group (N=5). The Kruskal-Wallis test was used to assess statistically significant Differences among groups and time points. The scores are expressed as median and interquartile Range (IQR).

On Day 3, there was a statistically significant difference among the groups (p=0.05). The HA 1% group (G5) exhibited the highest granulation tissue formation, while the negative control group (G1) had no granulation tissue. Capital letters (A, B, AB) reflect these differences: G5 was significantly higher (A), G1 was lower (B), and other groups were intermediate (AB).

On Day 7, intergroup differences remained significant (p = 0.044). G5 (HA 1%) and G3 (HA 0.25%) showed higher granulation tissue scores compared to G1 and G2. This suggests an early stimulatory effect of HA on granulation tissue formation, especially at higher concentrations.

On Day 14, the differences between groups were still statistically significant (p=0.048). G3 and G4 (HA 0.25% and 0.5%) recorded the highest scores (3), indicating enhanced granulation tissue development. G1 and G2 showed lower scores, suggesting that HA accelerated the healing process.

For G1 (negative control), there was a statistically significant increase in granulation tissue formation over time (p=0.05), progressing from no granulation on Day 3 to moderate levels by Day 14.

In G2 (positive control), granulation tissue also increased significantly over the three time points (p=0.05), but the levels remained relatively low compared to HA-treated groups.

G3 (HA 0.25%) and G4 (HA 0.5%) showed clear time-dependent increases in granulation tissue, with statistically significant changes (p=0.042 and p=0.048, respectively). By Day 14, both groups reached peak granulation scores (score 3), indicating strong tissue regeneration.

Interestingly, G5 (HA 1%) showed high granulation early (Day 3 and 7), but slightly decreased by Day 14, possibly due to transition from granulation to tissue remodeling (p=0.05).

The most prominent effects were observed in groups treated with 0.25% and 0.5% HA, especially by Day 14. The HA 1% group showed a rapid early response, but granulation plateaued or declined slightly, likely reflecting advanced healing. The differences were statistically significant between groups and within each group over time.

Data expressed as median and IQR (Inter-Quartile-Range) (N=3 rabbits) (Kruskal-Wallis test). The difference in capital letters means there are significant differences between groups at $p \leq 0.05$. The difference in small letters means there are significant differences between periods at $p \leq 0.05$.

Table 2 presents the median histopathological scores of angiogenesis (new blood vessel formation) in five experimental groups across three-time intervals (Day 3, Day 7, and Day 14). Each group included five rabbits (N=5), and the Kruskal-Wallis test was used to evaluate statistically significant differences across groups and over time. Data are expressed as medians and interquartile ranges (IQR).

On Day 3, no statistically significant differences were observed between the groups (p=0.078). All groups showed low angiogenesis activity, with medians ranging from 1 to 2. This suggests minimal early vascular response to treatment at that time point.

On Day 7, the Kruskal-Wallis test indicated a significant difference among groups (p=0.05). The HA-treated groups (G3–G5) showed markedly increased angiogenesis (median=4), while the control groups (G1 and G2) had lower scores (medians=2–3). Capital letters show that these differences are statistically significant between groups,

indicating the pro-angiogenic effect of HA at this stage of healing.

By Day 14, the differences remained significant (p=0.048). The HA 0.25% and 0.5% groups (G3 and G4) maintained the highest angiogenesis scores (median=4), while the negative control group (G1) exhibited lower values. G5 (HA 1%) showed a slight reduction compared to Day 7, possibly indicating a transition from active angiogenesis to vascular stabilization or tissue remodeling.

In G1 (negative control), angiogenesis gradually increased over time, with significant differences observed between days (p=0.048). However, the increase was moderate compared to the HA-treated groups.

G2 (positive control) also showed a significant rise in angiogenesis from Day 3 to Day 14 (p=0.034), suggesting a delayed but noticeable natural angiogenic response.

G3 (HA 0.25%) and G4 (HA 0.5%) both demonstrated a rapid and sustained increase in angiogenesis, with statistically significant differences over time (p=0.028 for both). These groups had consistently high scores from Day 7 onward, highlighting the effectiveness of these HA concentrations in promoting vascularization.

G5 (HA 1%) also showed early enhancement of angiogenesis (Day 3 to Day 7), followed by a slight decrease by Day 14 (p=0.05). This might reflect earlier maturation or stabilization of newly formed vessels. The findings demonstrate that hyaluronic acid (HA) significantly enhances angiogenesis in rabbit skin wounds, particularly at 0.25% and 0.5% concentrations. Although all groups exhibited a natural increase in angiogenesis over time, HA-treated groups achieved faster and higher vascular growth, especially by Day 7 and 14. The differences were statistically significant across groups and within each group over time, emphasizing the therapeutic role of HA in promoting wound healing through enhanced vascularization.

The histological evaluation of rabbit skin wound sections across all experimental groups at various time intervals (Days 3, 7, and 14) are shown in Figures 1 to 6.

Discussion

Additive manufacturing, especially three-dimensional (3D) printing, has become a new and better way to make prosthetics instead of using heat-polymerized polymethyl methacrylate (PMMA) [11]. 3D printed denture bases have several benefits, such as the ability to integrate digital workflows, shorten lab time, improve reproducibility, and allow for patient-specific customization [12]. The layered printing method is important because it lets you control how bioactive agents are added to the polymer matrix. This is not easy to do with traditional processing methods [13]. This creates new chances to turn denture bases from passive prosthetic devices into biofunctional systems that can help keep oral tissues healthy [14]. Adding bioactive substances like hyaluronic acid or bioactive glass speeds up the healing of soft tissue and makes it less painful. This helps patients adjust better [15]. Modification of denture base materials by different materials to improve physical and biological effect [16-18].

The rabbit was chosen for the skin wound model due to its comparatively extensive skin surface area, white skin, and structural resemblance to human skin, which facilitated the simultaneous creation of multiple wounds [19]. Histologically, rabbits' buccal mucosa is like humans' oral mucosa. In our study, after day three and day seven, the HA 1% group exhibited the highest granulation tissue formation, while the negative control group had no granulation tissue. Also, the most prominent effects were observed in groups treated with 0.25% and 0.5% HA, especially by Day 14. The HA 1% group showed a rapid early response, but granulation plateaued or declined slightly, likely reflecting advanced healing [20]. The wound area and contraction ratio of the groups treated with HA revealed a significant wound healing acceleration effect [21]. Previous studies have also shown that the topical application of HA can speed up the wound healing process [22]. HA can speed up the wound healing process in oral ulcer [23]. PDGF can promote the expression of CD44 to enhance cell migration. CD44 serves as the primary receptor for HA. The association and interaction between HA and CD44 regulate numerous intracellular signaling pathways that govern cellular biological processes. These encompass angiogenesis, cellular migration, proliferation, adherence to ECM constituents, and the internalization and degradation of HA [24]. In our study, the level of PDGF in the different groups reveals intense positive expression to improve the healing process in days 3, 7, and 14 [25]. On the other hand, MMP2 showed intense positive expression in days 3 and 7, and moderate positive expression in day 14, as previous work [26].

Conclusions

We concluded that hyaluronic acid release from 3d printed denture base with different concentrations (0.25%, 0.5%, and 1%), especially 1% HA that had a highly positive effect as immunohistochemical changes in wound healing.

Acknowledgements

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Conflict of Interest

The authors have no conflicts of interest to declare.

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A B C

Figure 1. (A) Surgical procedure for skin; defect created by scalpel blade no.15 on the dorsal skin of a rabbit. (B) 3D printed denture sample. (C) Sutured skin.

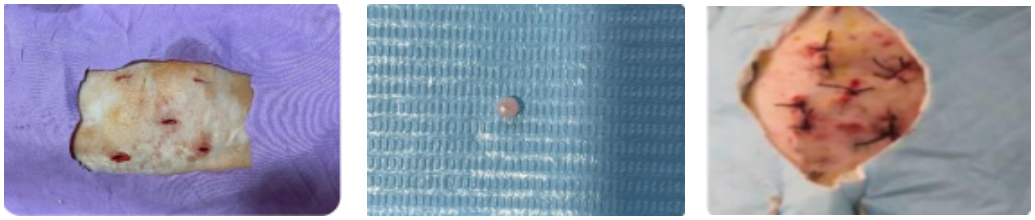

Table 1. Histopathological scores of the granulation tissue GT among study groups in the rabbit skin.

Intervals Groups	Day 3 (N=5) Median	Day 7 (N=5) Median	Day 14 (N=5) Median	*P*-value
G1 Negative control group (wound only)	0 (0) B b	1 (0) B ab	2 (0) B a	0.05
G2 Positive control group (wound + acrylic)	1 (1) AB b	1 (1) B b	2 (0) B a	0.05
G3 HA 0.25% group (wound + acrylic+HA)	1 (1) AB b	2 (1) B ab	3 (1) A a	0.042
G4 HA 0.5% group (wound + acrylic+HA)	1 (0) AB b	2 (2) AB b	3 (1) A a	0.048
G5 HA 1% group (wound + acrylic+HA)	2 (2) A a	3 (1) A a	2 (1) AB b	0.05
P-value	0.05	0.044	0.048	

Table 2. Histopathological scores of angiogenesis (newly formed blood vessels) among study groups in the rabbit skin.

Intervals Groups	Day 3 (N=5) Median	Day 7 (N=5) Median	Day 14 (N=5) Median	*P*-value
G1 Negative control group (wound only)	1 (0) A b	2 (1) B ab	3 (1) B a	0.048
G2 Positive control group (wound + acrylic)	1 (1) A b	3 (1) B a	4 (2) A a	0.034
G3 HA 0.25% group (wound + acrylic+HA)	1 (1) A b	4 (1) A a	4 (1) A a	0.028
G4 HA 0.5 %group (wound + acrylic+HA)	1 (1) A b	4 (2) A a	4 (0) A a	0.028
G5 HA 1 group (wound + acrylic+HA)	2 (1) A b	4 (1) A a	3 (1) B a	0.05
P-value	0.078	0.05	0.048	

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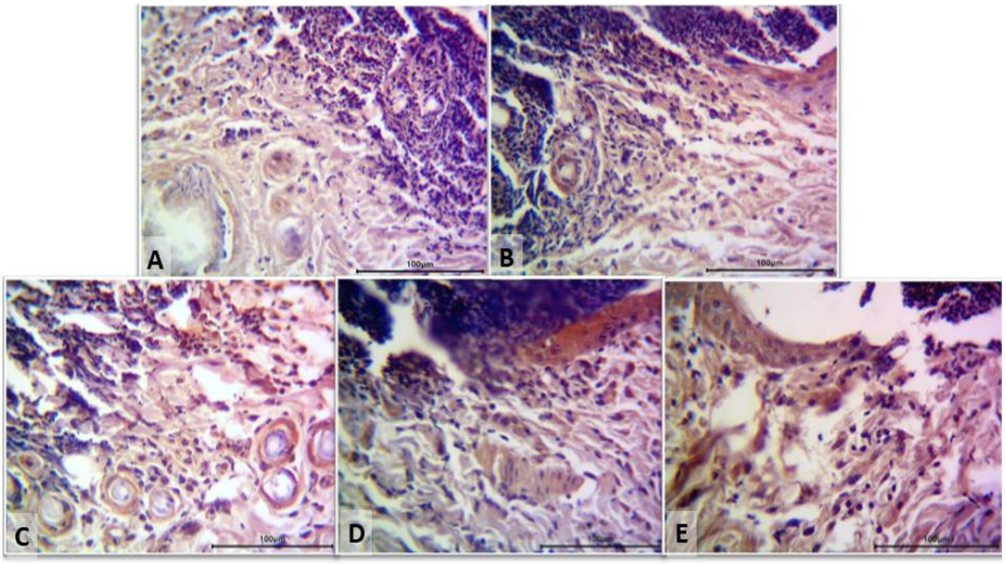
Figure 1. Immunohistochemistry sections of VEGF from rabbit skin at day 3 period. [A]: Negative control (wound only) group reveals slight positive expression. [B]: Positive control (wound +acrylic) group reveals weak positive expression. [C]: hyaluronic acid 0.25% (wound+acrylic+HA 0.25%) group reveals moderate positive expression. [D]: hyaluronic acid 0.5 % (wound+acrylic+HA 0.5%) group reveals moderate positive expression. [E]: hyaluronic acid 1% (wound+acrylic+HA 1%) group reveals intense positive expression 400X, scale-bar=100µm.



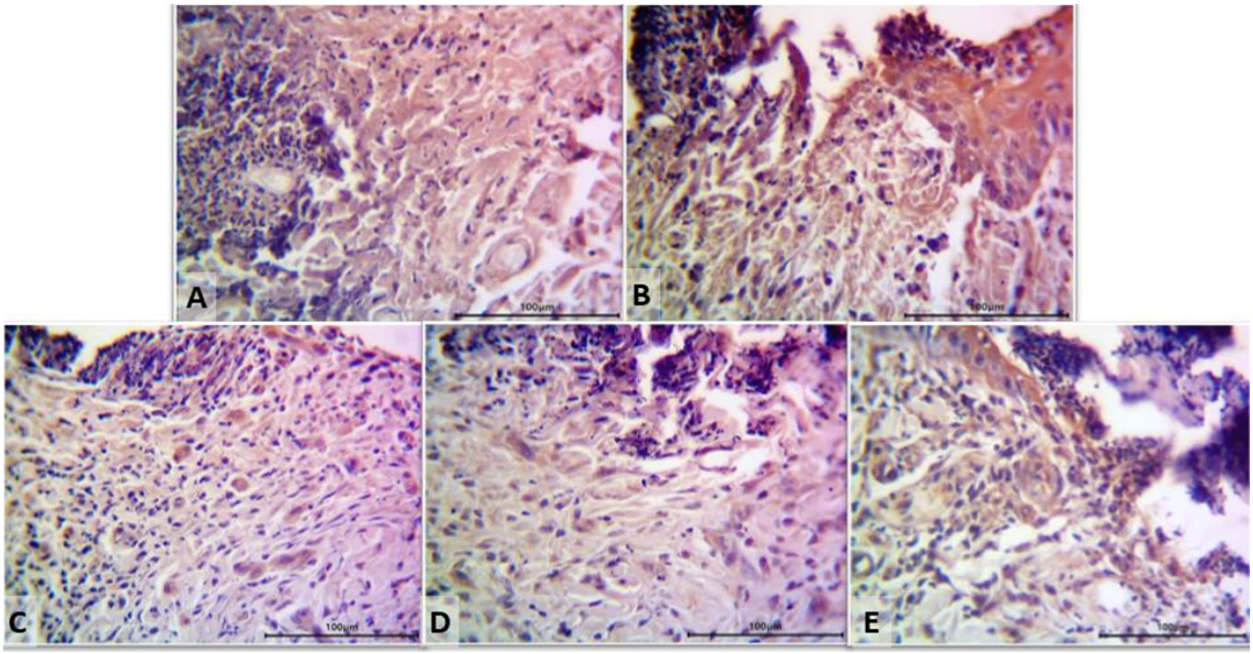


Figure 2. Immunohistochemistry sections of VEGF from rabbit skin at day 7 period. [A]: Negative control (wound only) group reveals weak positive expression. [B]: Positive control (wound +acrylic) group reveals moderate positive expression. [C]: hyaluronic acid 0.25% (wound+acrylic+HA 0.25%) group reveals moderate positive expression. [D]: hyaluronic acid 0.5% (wound+acrylic+HA 0.5%) group reveals moderate positive expression. [E]: hyaluronic acid 1% (wound+acrylic+HA 1%) group reveals intense positive expression 400X, scale-bar=100µm.

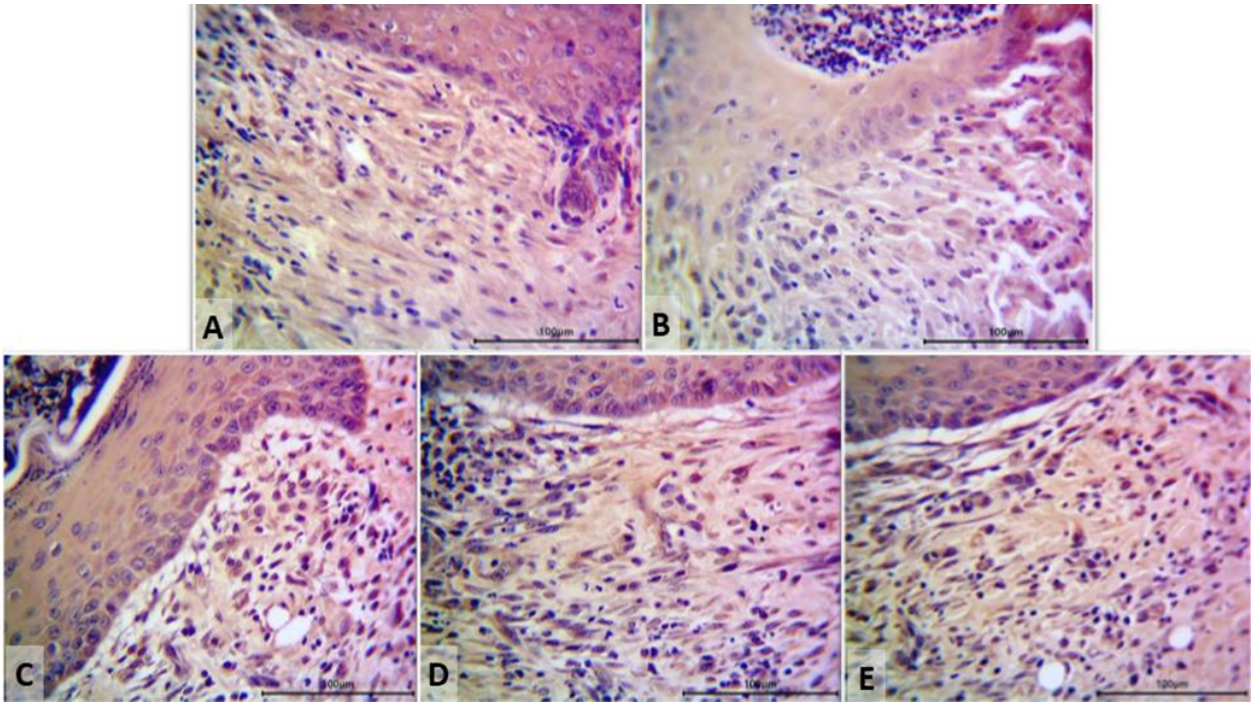


Figure 3. Immunohistochemistry sections of VEGF from rabbit skin at day 14 period. [A]: Negative control (wound only) group reveals weak positive expression. [B]: Positive control (wound +acrylic) group reveals moderate positive expression. [C]: hyaluronic acid 0.25% (wound+acrylic+HA 0.25%) group reveals intense positive expression. [D]: hyaluronic acid 0.5 (wound+acrylic+HA 0.5%) group reveals intense positive expression. [E]: hyaluronic acid 1% (wound+acrylic+HA 1%) group reveals intense positive expression 400X, scale-bar=100µm.

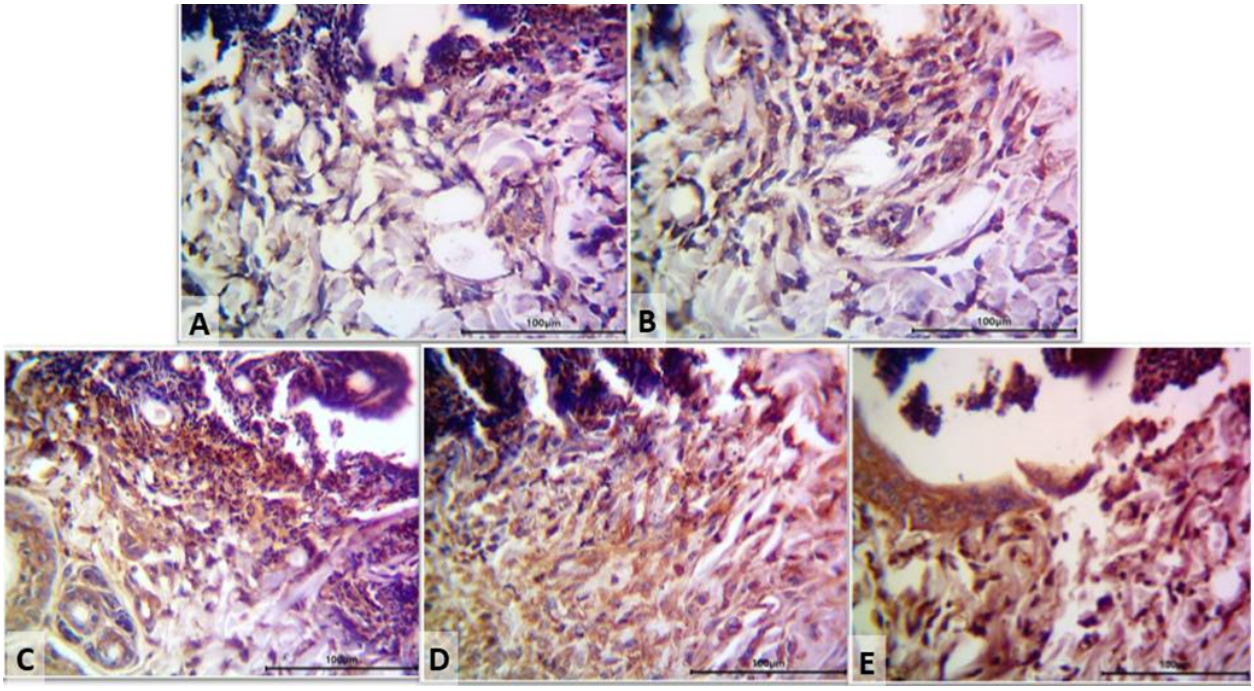


Figure 4. Immunohistochemistry sections of MMP2 from rabbit skin at day 3 period. [A]: Negative control (wound only) group reveals weak positive expression. [B]: Positive control (wound +acrylic) group reveals moderate positive expression. [C]: hyaluronic acid 0.25% (wound+acrylic+HA 0.25%) group reveals moderate positive expression. [D]: hyaluronic acid 0.5% (wound+acrylic+HA 0.5%) group reveals moderate positive expression. [E]: hyaluronic acid 1% (wound+acrylic+HA 1%) group reveals intense positive expression 400X, scale-bar=100µm.

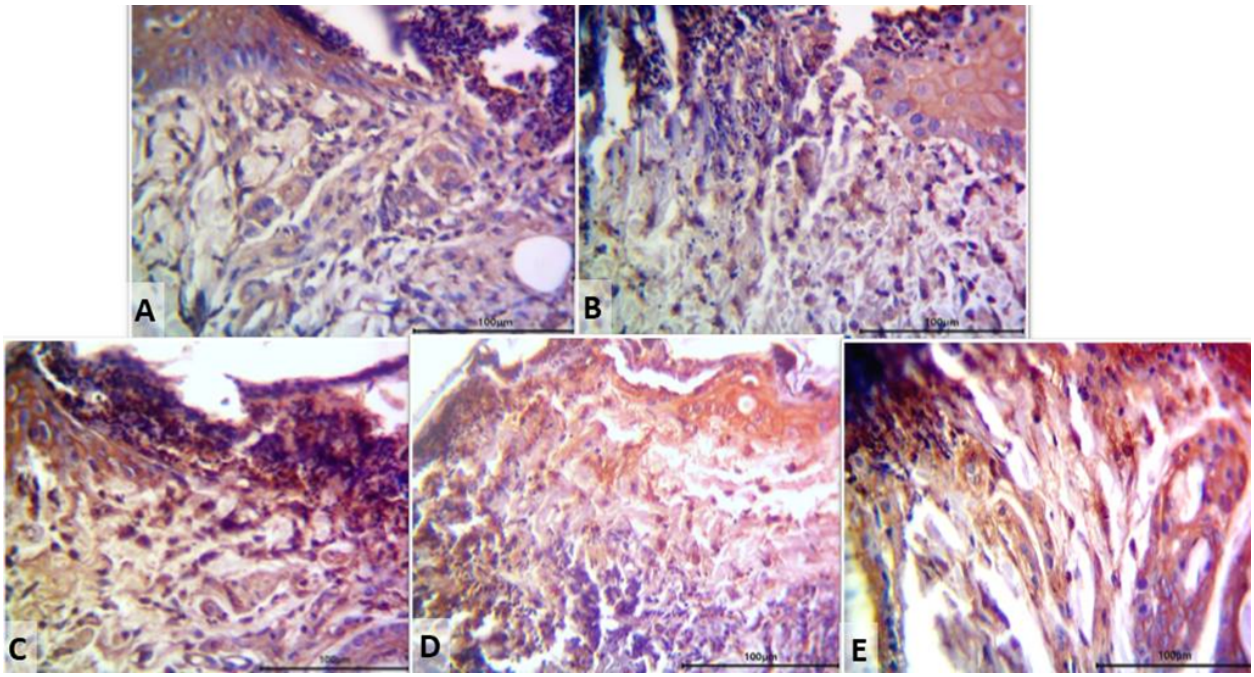


Figure 5. Immunohistochemistry sections of MMP2 from rabbit skin at day 7 period. [A]: Negative control (wound only) group reveals weak positive expression. [B]: Positive control (wound +acrylic) group reveals moderate positive expression. [C]: hyaluronic acid 0.25% (wound+acrylic+HA 0.25%) group reveals intense positive expression. [D]: hyaluronic acid 0.5% (wound+acrylic+HA 0.5%) group reveals intense positive expression. [E]: hyaluronic acid 1% (wound+acrylic+HA 1%) group reveals intense positive expression 400X, scale-bar=100µm.

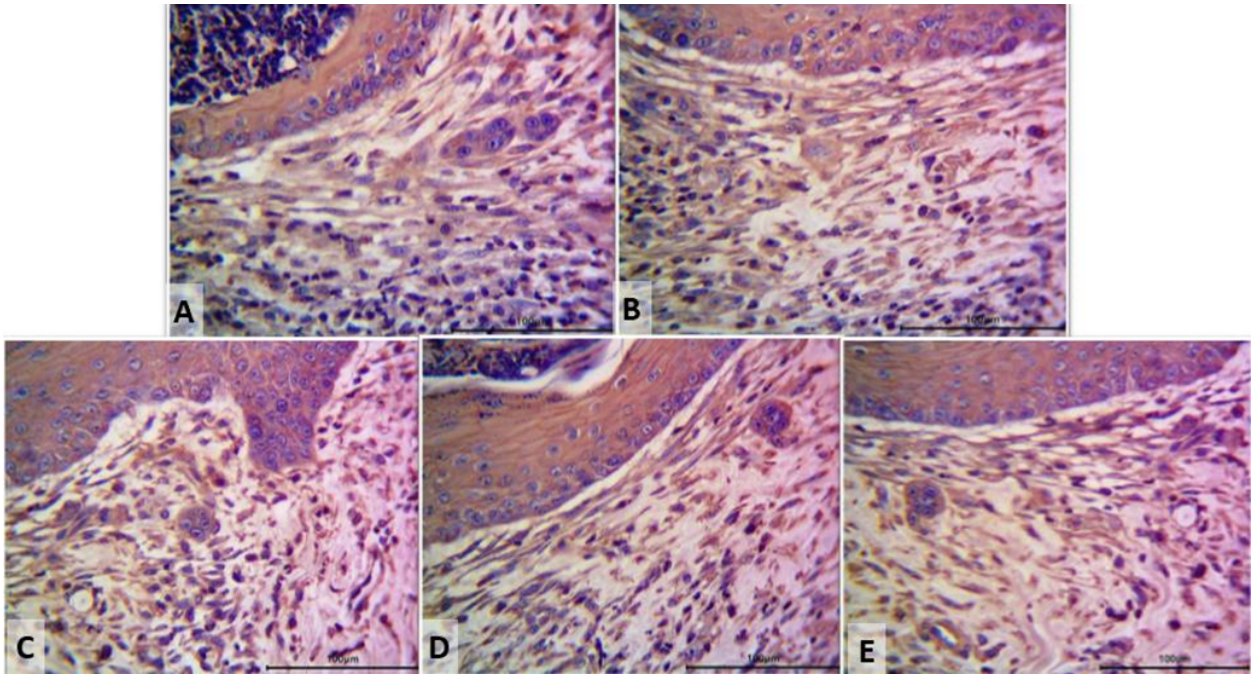


Figure 6. Immunohistochemistry sections of MMP2 from rabbit skin at day 7 period. [A]: Negative control (wound only) group reveals moderate positive expression. [B]: Positive control (wound +acrylic) group reveals moderate positive expression. [C]: hyaluronic acid 0.25% (wound+acrylic+HA 0.25%) group reveals intense positive expression. [D]: hyaluronic acid 0.5% (wound+acrylic+HA 0.5%) group reveals intense positive expression. [E]: hyaluronic acid 1% (wound+acrylic+HA 1%) group reveals moderate positive expression 400X, scale-bar=100µm.