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EVALUATION OF THE ENHANCEMENT EFFECTS OF COD-LIVER OIL ON THE HEALING OF LARGE-SIZED METACARPAL WOUNDS IN EQUINES

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ABSTRACT

Equine distal limb wounds are frequent and healed after a long time, with the development of excessive granulation tissue and poor wound contraction and epithelialization. This study intended to investigate the effect of the local application of cod-liver oil on the healing of large-sized metacarpal wounds in equine. Three adult donkeys were generally anesthetized. A large-sized metacarpal full-thickness skin wound (5x10 cm) was inflected on the lateral aspect of the right forelimb. Cod liver oil was applied locally, followed by a protective bandage. Follow-up of wound healing was evaluated at week intervals until healing was complete. Evaluation of healing was carried out by gross examination, photographing and image analysis by ImageJ software, and histopathology. Results revealed that granulation tissues filled the gap of the wound without signs of infection. Epithelialization was grossly observed by day 35. Reduction in wound size was significant by day 56 (60% reduction of the original size) and stayed significant until the end of the study. Histopathology revealed new blood vessels and epithelial hyperplasia, scar tissue heavily infiltrated with inflammatory cells at the surface of the wound area, and a moderate amount of collagen fiber. In conclusion, cod-liver oil was beneficial in the healing of surgically-induced large-sized wounds by the acceleration of epithelialization and enhancement of healthy scar formation. Therefore, it is recommended to use cod-liver oil for dressing recent surgical wounds.

Key words: distal limb, wound healing, enhancement, equine

INTRODUCTION

Equine distal limb injuries are common and represent more than 60% of all injuries. These injuries are more challenging than others elsewhere in the body due to their high liability to contamination, poor healing nature, and high tendency to form exuberant granulation tissue (Schumacher and Stashak, 2016). These wounds form excessive granulation tissue and heal after a long time, because they have an extended preparatory phase of healing, inordinate retraction of the margins, and slower rates of

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wound contraction and epithelialization compared with other wounds in the body (Jacobs *et al.*, 1984).

A number of topical therapeutic agents have been used in wound management, including yeast cell derivatives (Crowe *et al.*, 1999), honey (Iftikar *et al.*, 2010), and phenytoin (Qunaibi *et al.*, 2009) with variable results. Cod liver oil originates from the fresh liver of cod (Gadus morrhua) and other species of Gadus (Terkelsen *et al.*, 2000). Cod liver oil has been gradually used as a naturally occurring product and biological treatment in clinical practice. Most authors attribute the curative effect of cod liver oil to its high levels of vitamins A and D (Terkelsen *et al.*, 2000). Others attribute that effect to fatty acids (Addisu, 2018) and found that fatty acids have a bactericidal action on gram-positive bacteria.

The aim of the current study is to evaluate the effects of local application of cod-liver oil on the healing of experimentally-induced large-sized metacarpal full-thickness skin wounds in donkeys.

MATERIALS AND METHODS

Ethical approval

The study received approval from Assiut Veterinary Medicine Research Ethics Committee No. 06/2022/0021 in accordance with Egypt's regulations and OIE standards on animal welfare for the care and use of animals in research and education.

Animals

The study was carried out on 3 adult (age=6.5, 7, and 8 years) donkeys (*Equus asinus*) in good clinical health of both sexes (2 males and one female), received from House of Experimental Animals, Veterinary Teaching Hospital, Faculty of Veterinary Medicine, Assiut University, Assiut, Egypt. The animals were kept in standard stables, delivered with a balanced ration and provided with ad libitum water.

Induction of the Metacarpal Wound:

Food and water were withheld for 12 and 6 hours (h), respectively, before surgical operations. The right forelimbs were operated. Animals were anesthetized by intravenous (IV) administration of 1.1 mg/kg xylazine HCl 2% (Xyla-Ject, ADWIA Co., SAE, Egypt), followed 10 min later by rapid intravenous injection of thiopental sodium (Thiopental sodium 1gm vial, EPICO, Egypt) at a dose of 35 mg/kg.

A metacarpal wound was induced at the lateral aspect of the middle third of the metacarpus of both forelimbs. A rectangular-shape (5*10cm) skin excision was induced.

Management of the Wound:

The wound was irrigated with Cod-liver oil (EL Hawag, El Hawag company - Badr City - Cairo) at one week intervals. A non-adherent dressing was applied on the wound after local application of cod-liver oil, followed by a supportive bandage of absorbent cotton and gauze rollers.

Evaluation Criteria

Gross Examination

Wounds were examined grossly at one-week intervals until complete healing for the presence of swelling, inflammatory exudate, granulation tissue formation, scar formation, epithelialization, and time of wound healing. The wounds were photographed by a digital camera (Sony IMX582 Exmor RS of 48 megapixels and aperture f/1.75) to follow up the process of wound healing. A ruler (standardized) has been included in each photo to enable digital calibration. The distance from the camera was not less than thirty centimeters from the wound, and the shape of the wound was visible in the center of the photo. The photo was taken following the focus on the shape of the wound. Photos were analyzed by software (Image J 4.48v software, National Institutes of Health, USA).

Histopathological Examination

At the end of the study, animals were anesthetized by intravenous (IV) administration of 1.1 mg/kg Xylazine HCl

2% (Xyla-Ject, ADWIA Co., SAE, Egypt) and 2.2 mg/kg ketamine HCl 5% (Ketamine, Sigma-tec Pharmaceutical Industries, SAE, Egypt). Full thickness biopsy specimens were obtained from the margins of wounds on 28, 56, and 105 days post-wound creation and under the influence of the previously mentioned anesthetic protocol. The collected specimens were placed in neutral buffered formalin solution (10%) for fixation, dehydrated in ascending ethyl alcohol series, cleared with xylene, and then embedded in paraffin forming tissue blocks. Tissue sections of 5-µm thickness were cut and stained with Hematoxylin and eosin (H&E) staining for histopathological evaluation (Marques *et al*., 2004). In addition, Gomori's trichrome stain was carried out to evaluate the collagen content according to (George, 1950). All stained sections were examined under light microscopy (Olympus CX31, Japan) and photographed by a Digital Camera (Olympus Camera C -5060, Japan) adapted into the microscope.

Statistical Analysis

Data were obtainable as mean ± standard error of the mean (SEM). Data were reconnoitered for normality using Kolmogorov-Smirnov and Shapiro-Wilk tests and revealed non-parametric (not normal) distribution. Mann Whitney was used to relate between two studied groups in non-related samples. Friedman test was used to compare between more than two periods in related samples with Bonferroni test for multi-comparison between each two periods. The level of significance was set at $P < 0.05$. Statistical analysis was made with IBM® SPSS® Statistics Version 26 for Windows.

RESULTS

Gross finding of the wounds (Figure 1 and 2):

By the 7th day post-treatment, wound edges were regular, without swelling or exudates on the wound surface. Healthy granulation tissue with irregular surface grew on wound surface. No signs of epithelialization were noticed at the periphery. There were no signs of wound infection. By the 14th day post-treatment, healthy granulation tissue with irregular surface filled the wound gap to the level of the skin. Epithelialization starts to grow from the periphery of the wound. By day 21, slightly smooth-surfaced healthy granulation tissue was noticed at the wound surface.

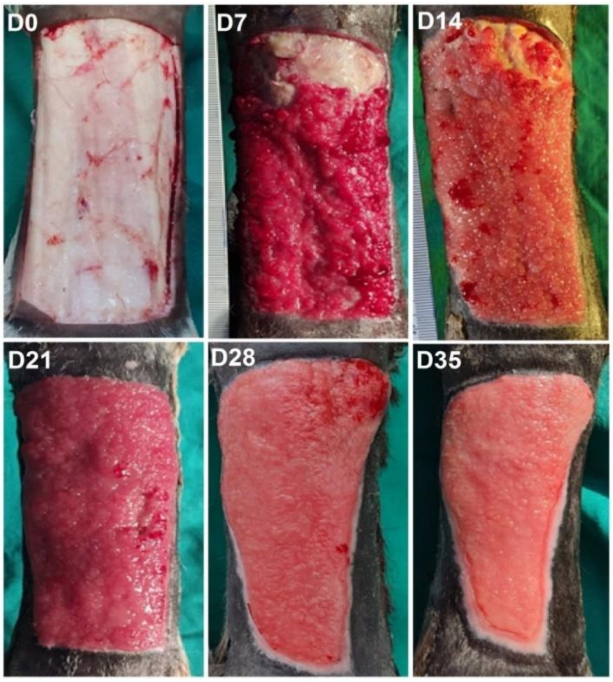

Figure 1: Gross findings of serial pictures of the metacarpal wounds in donkeys (*n*=3) treated by cod-liver oil from Day 0 to Day 35.

These granulation tissues grew over the level of the skin. Wound contraction and epithelialization were noticed at the bottom edge of the wound. On day 28, smooth-surfaced granulation tissues were presented at the wound surface. The granulation tissues were found at the skin level in the majority of the wound surface. Wound contraction and epithelialization were observed at the bottom and vertical sides of the wound. The wound surface was clean without signs of wound infection. On day 35, smooth clean granulation tissues filled the wound gap. These granulation tissues were noticed over the level of the skin at the proximal wound edges. More epithelialization and contraction was noticed. By the 42nd day post-treatment, wound healing was similar to day 35, except for the remarkable wound contraction and epithelialization. By the 49th day, wound surface was smooth. Epithelialization was noticed at the four sides of the wound and was more rapid at the distal side and vertical sides of the wound. The length of the distal side of the wound was approximately one third of the proximal side. On the 56th to 63th day post-treatment, wound size was markedly reduced by the effect of contraction and epithelialization. By the 70th day post-treatment, pigmentation started to appear at the epithelialized distal part of the wound. From the 77th to 84th day post-treatment, the wound took the shape of a triangle with its base proximate and its apex distal. From the 91st to 98th day post-treatment, the wound was epithelialized except a small spot at the proximal third of the wound. Pigmentation was noticed at the margin of the wound. By the 105th day post-treatment, healing of the wound was complete by a small amount of smooth-surfaced scar tissue at the center of the proximal third of the wound. The rest of the wound surface was covered by pigmented epithelial tissue.

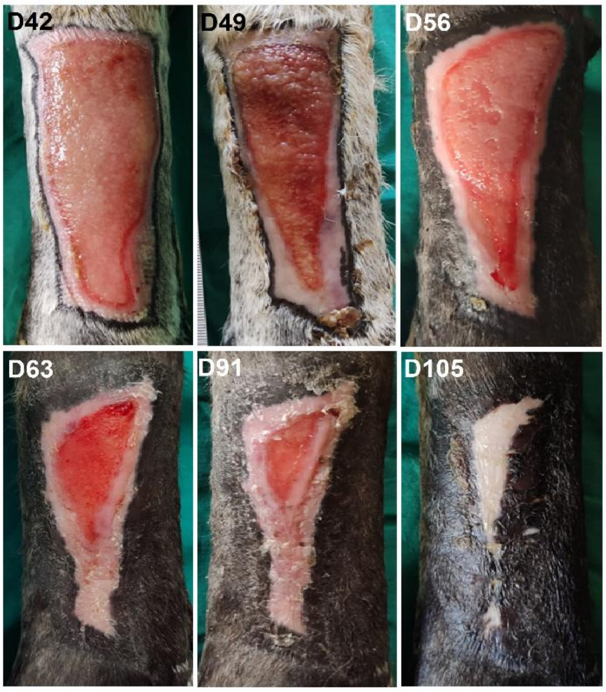

Figure 2: Gross findings of serial pictures of the metacarpal wounds in donkeys (*n*=3) treated by cod-liver oil from Day 42 to Day 105.

Image J analysis of the wound healing:

There was a significant (*P*=0.028) decline in the mean surface area (19.97±0.66 cm^2) of the metacarpal wound starting at day 56 of wound management compared to day 0. By this day (Day 56), the percentage of reduction in the wound size reached 60% of the original wound size. This significant reduction in the mean surface area of the wounds continued until complete wound healing by day 105 (Table 1).

Table 1: Mean (±SE) values of surface areas (cm^2) of the metacarpal wounds of donkeys (*n*=3) treated by cod-liver oil during the study period.

	Surface area (cm^2)				±SE	P value	% of reduction from day 0
Time	**Animal 1**	**Animal 2**	**Animal 3**	**Mean**			
Day 0	48.96	49.27	50.7	49.64	0.54		
Day 7	44.51	43.98	44.52	44.34	0.18	0.784	10.68
Day 14	42.2	41.36	43.17	42.24	0.52	0.584	14.91
Day 21	39.32	38.03	40.7	39.35	0.77	0.411	20.73
Day 28	38.17	37.66	40.3	38.71	0.81	0.273	22.02
Day 35	37.91	36.9	38.04	37.62	0.36	0.171	24.21
Day 42	32.04	33.52	34.19	33.25	0.64	0.100	33.02
Day 49	25.96	26.32	27.14	26.47	0.35	0.055	46.68
Day 56	19.74	18.96	21.2	19.97	0.66	0.028*	59.77
Day 63	16.98	16.87	17.4	17.08	0.16	0.014*	65.59
Day 70	13.73	13.36	12.86	13.32	0.25	0.006**	73.17
Day 77	8.25	9.48	9.365	9.03	0.39	0.003**	81.81
Day 84	6.98	7.01	7.926	7.31	0.31	0.001**	85.27
Day 91	3.84	3.61	3.334	3.59	0.15	<0.001**	92.77
Day 98	2.03	2.44	2.214	2.23	0.12	<0.001**	95.51
Day 105	0	0	0	0	0	<0.001**	100.00

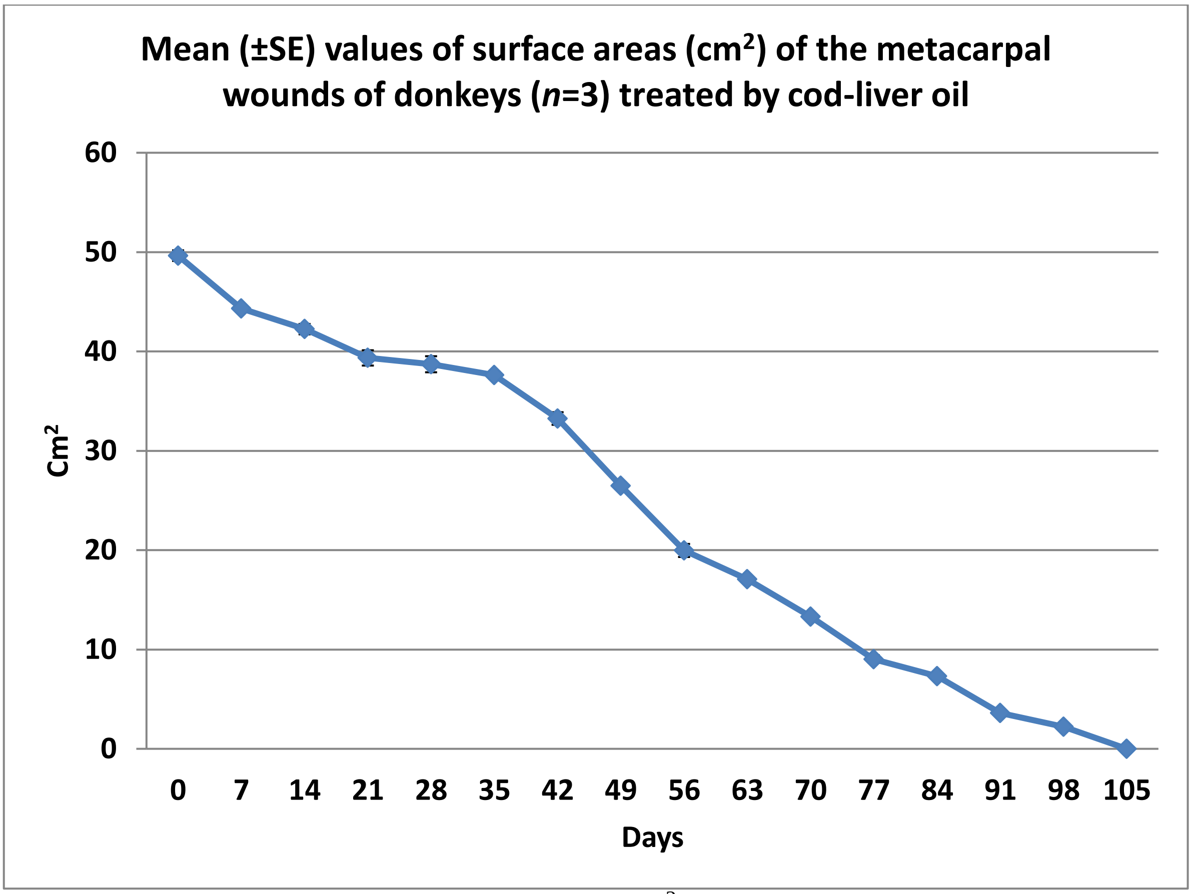

Figure 3: Mean (±SE) values of surface areas (cm^2) of the metacarpal wounds of donkeys (*n*=3) treated by cod-liver oil during the study period.

Histopathological examination:
Careful microscopic examination of tissue sections taken on day 28 of wound creation displayed no notable change in the wound healing rate and epidermal epithelialization. There were no features of epithelial

hyperplasia at the wound edges, evidenced by no obvious decrease in the epithelial gap. Examination of the dermis revealed extensive hemorrhage and abundance of inflammatory cells, including neutrophils and macrophages, infiltrating the wound area. In addition, moderate numbers of hyperemic new blood vessels were noticed. Small amounts of collagen fibers deposited in the wound site were also detected. Such deposited collagen was demonstrated by Gomori's trichrome stain (Figure 4).

On day 56 post-wound creation, re-epithelialization at the wound edges was noticed with slight epidermal hyperplasia toward the center of the wound and reduction of the epithelial gap. Dermal layer showed increased number of new blood vessels and was heavily infiltrated with inflammatory cells. In addition, a moderate amount of collagen fiber was detected in the dermis and highlighted by Gomori's trichrome stain (Figure 5).

Wound sections obtained on day 105 after wound induction revealed epithelial hyperplasia at the edges of the wound. The wounds were not entirely closed, and a small epithelial gap was still observed and roofed with scar tissue heavily infiltrated with inflammatory cells. In the dermis, inflammatory cells infiltration is still detected beside a reduced number of new blood vessels. Moderate amount of collagen was also noticed and confirmed by Gomori's trichrome stain (Figure 6).

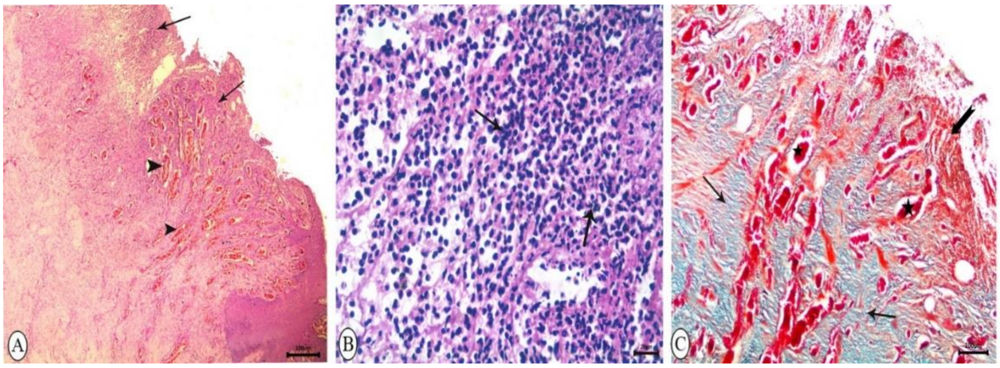

Figure 4: Histopathological evaluation of wound specimens on day 28 post-wound creation. (A) Showing infiltration of the wound site with a heavy number of inflammatory cells (arrow) associated with hyperemic new blood vessels (arrowhead) (H&E, bar=100). (B) Showing extensive dermal infiltration with neutrophils and macrophages (arrow) (H&E, bar=20). (C) Showing small amounts of deposited collagen (arrow), hemorrhage (notched arrow), and hyperemic new blood vessel (star) (Gomori's trichrome, bar=100).

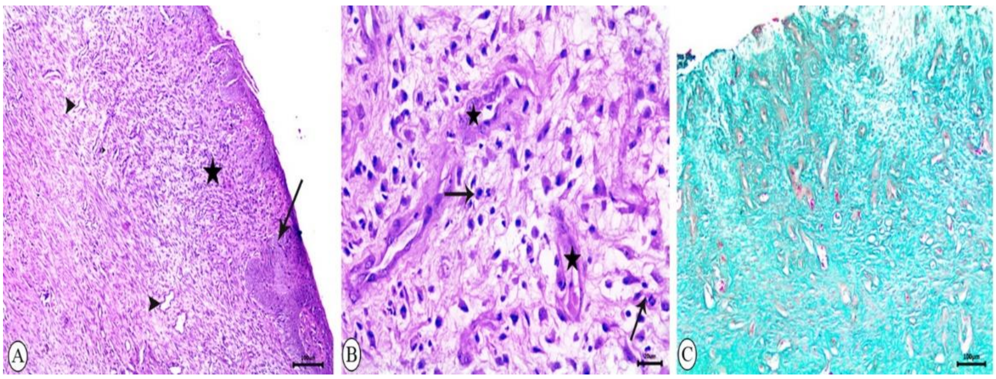

Figure 5: Histopathological evaluation of wound specimens on day 56 post-wound creation. (A) Showing slight epidermal hyperplasia at the wound edges (arrow), infiltration of the dermis with abundant inflammatory cells (star), and new blood vessels (arrow head) (H&E, bar=100). (B) Showing dermal new blood vessels (star) and marked inflammatory cells infiltration (arrow) (H&E, bar=20). (C) Showing moderate amount of deposited collagen at the wound area (Gomori's trichrome, bar=100).

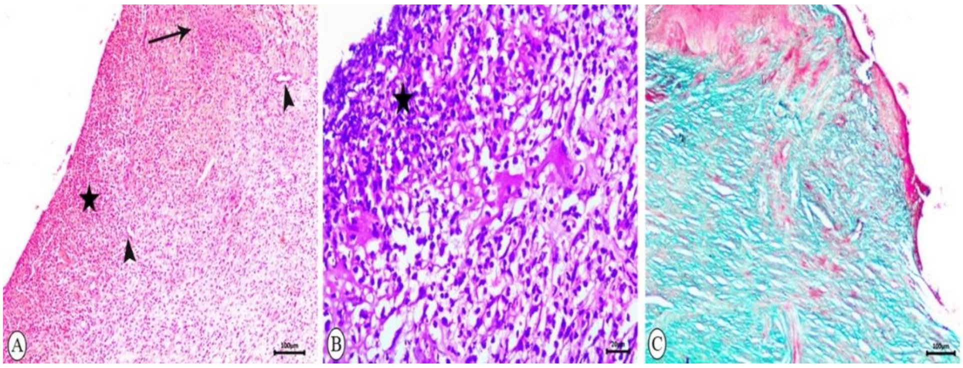

Figure 6: Histopathological evaluation of wound specimens on day 105 post-wound creation. (A) Showing inflammatory cells infiltration (star), new blood vessels (arrow head), and epithelial hyperplasia (arrow) (H&E, bar=100). (B) Showing scar tissue heavily infiltrated with inflammatory cells at the surface of the wound area (star) (H&E, bar=20). (C) Showing moderate amounts of collagen fiber (Gomori's trichrome, bar=100).

DISCUSSION

During the treatment of equine wounds, the main objective is to obtain quick healing of the wounds with a functional and aesthetically satisfying result. Equine animals are known to be prone to injury, likely because of their curious nature, large size, and containment in areas that have potential barriers, such as metal or wire, which leads to their known difficulties with healing (Schumacher and Stashak, 2016). Currently used animals were adult healthy donkeys. It has been reported that wound healing is influenced by animal age. Elderly animals have relatively low rates of wound healing compared to young and growing animals (Schumacher and Stashak, 2016). In the current controlled experimental study, it was observed that frequent application of cod liver oil at one-week intervals prevented wound infection and pus formation at the wound surface. In a clinical study (Ali and Radad, 2011), it was found that treating equine distal limb infected wounds with a combination of honey and cod liver oil resulted in no contamination, clearness, and healthy surface, and a pronounced decrease in the wound surface. In addition, cod-liver oil promoted the formation of healthy granulation tissues that filled the wound gap in the donkeys of the present study. In another study, after 2 - 3 weeks of treatment with a combination of honey and cod-liver oil, the wound surface seemed bright red in color, moist, and not raised above the wound edges (Ali and Radad, 2011). Although formed granulation tissues exceeded the skin level at the proximal part of the wound by day 35, it did not prevent wound epithelialization and contraction. Moreover, cod-liver oil enhanced both wound epithelialization and neovascularization in large- sized full thickness dermal wounds in animals of the current study. Cod-liver oil has been cited to be advantageous in wound healing as it enhances epithelialization and neovascularization (Terkelsen *et al.*, 2000). Various clinical studies have shown that burns, leg ulcers (Steel, 1935), and diabetic wounds (Brandaleone, 1938) have healed faster.

Cod liver oil is made up of various lipophilic vitamins and polyunsaturated fatty acids, which, in theory, can all have an impact on wound healing. Frequent application of cod-liver oil in the present study might achieve sustained release of its active ingredients to the wound surface, which enhanced wound healing. The influence of dietary intake of cod-liver oil on the microcirculation distal to an injury to a blood vessel has been found to improve capillary perfusion significantly (Barker *et al.*, 1993). Moreover, cod-liver oil in overall or one of the active constituents of cod-liver oil, for instance, polyunsaturated fatty acids has been cited to have a dilating effect on the microcirculation, which in theory may activate wound healing (Barker *et al.*, 1993). In the current study, cod-liver oil was applied locally, leaving a relatively high concentration of the active substance in direct contact with the injured tissue. It has been described that vitamin A has a significant role in accelerating the wound-healing process (Terkelsen *et al.*, 2000).

Moreover, fatty acids in cod-liver oil, particularly omega-3, have been reported to increase wound healing through increasing pro-inflammatory cytokines production at wound sites (McDaniel *et al.*, 2008). All wounds in the present study were covered with protective bandages after the application of cod-liver oil, which was beneficial in controlling bleeding, reducing the tendency to formation of granulation tissues, absorbing exudates, and keeping wounds moist, which helps epithelialization, protecting the wound from contamination, dust and flies and better maintain the topical cod liver oil in contact with the wound surface. Bandages are used to improve and support the healing process by reducing contamination, edema, or exudation, protesting against movement and other trauma, and optimization of moisture, temperature, pH, and gas exchange at the wound site (Addisu, 2018). Concerning cod-liver oil, it was reported that topical application of cod-liver oil ointment to surgically-induced large full-thickness cutaneous wounds on the ears of mice resulted in faster epithelialization than those treated with vaseline vehicle (Terkelsen *et al.*, 2000). This is caused by vitamins A and D in cod liver oil. In consistency, it has been described that vitamin A and cholecalciferol promoted epithelialization in excision wounds in rats (Raju and Kulkarni, 1986 and Ramesh *et al.*, 1993). Currently, cod-liver oil produced good results in surgically induced wounds, which was supported by the results of another study (Ali and Radad, 2011). However, the healing time in the present study was longer than that of another study due to the variation in the wound size. The current wound size was much more (5x10 cm) than that of the other study (a circle with a radius of 4 cm) (Ali and Radad, 2011). The enhancement of wound healing currently might be due to proper epithelialization and formation of a healthy scar that revealed a higher degree of maturity with a cumulative number of fibrocytes and parallel collagen fibers. Healed skin lacked skin adnexa such as hair development follicles, sweat and sebaceous glands after healing.

In conclusion, cod-liver oil was beneficial in healing surgically-induced large-sized wounds by accelerating epithelialization and enhancing healthy scar formation. Therefore, it may be recommended to use cod-liver oil for dressing recent surgical wounds.

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تقييم التأثيرات المعززة لزيت كبد الحوت على التئام جروح المشط كبيرة الحجم فى الخيول

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تتكرر جروح الأطراف السفلية للخيول وتلتئم بعد فترة طويلة مع تطور النسيج الحبيبي المفرط وضعف تقلص الجرح وضعف تكوين الخلايا الظهارية المكونة للجلد. تهدف هذه الدراسة إلى معرفة تأثير التطبيق الموضعي لزيت كبد الحوت على الجروح على التئام جروح المشط الامامي كبيرة الحجم في الخيول. تم تخدير ثلاثة حمير بالغة بشكل كامل وتم إجراء جرح جلدي كبير الحجم (٥ × ١٠ سم) على الجانب الجانبي من القدم الأماميه اليمنى ثم تم وضع زيت كبد الحوت موضعياً ، متبوعاً بضمادة واقية وتم تقييم متابعة التئام الجروح أسبوعيا حتى اكتمال الشفاء ثم تم تقييم الشفاء من خلال الفحص الاكلينيكي والتصوير وتحليل الصور بواسطة برنامج ImageJ وعن طريق التشريح المرضي. أظهرت النتائج أن الأنسجة الحبيبية ملأت فجوة الجرح دون ظهور علامات العدوى ولوحظ الاندمال الظهاري بشكل كبير في اليوم ٣٥ وكان الانخفاض في حجم الجرح ملحوظًا بحلول اليوم ٥٦ (انخفاض بنسبة ٦٠ ٪ من الحجم الأصلي) وظل ينخفض حتى نهاية الدراسة وكشف التشريح المرضي عن وجود أوعية دموية جديدة وتضخم ظهاري، ونسيج ندبي متسلل إلى حد كبير بخلايا التهابية على سطح منطقة الجرح ، وكمية معتدلة من ألياف الكولاجين. خلصت الدراسة بأن زيت كبد

الحوت مفيدًا في التئام الجروح كبيرة الحجم من خلال تسريع عملية التكون الظهاري وتعزيز تكوين الندبات الصحية. لذلك ، يوصى باستخدام زيت كبد الحوت لتضميد الجروح الجراحية الحديثة.