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Clinical and Histopathological Evaluation of the Effectiveness of Lavender oil Compared with Black seed oil, Ostrich oil and Cod liver oil on the Second Intention Wound Healing in Dogs

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Key words
Wound healing, Lavender oil, Black seed oil, Ostrich oil, Cod Liver oil, Histopathology.

ABSTRACT:
The natural compounds that stimulate wound healing are valuable aim for many researchers. The current experimental study was designed to evaluate the effectiveness of lavender oil compared with black seed oil, ostrich oil and cod liver oil for treatment of surgically induced full-thicknesses skin wounds in the back region in dogs. Clinical wound characters following lavender oil treatment proved good and showed marked reduction in wound dimension and formation of healthy scar. The quantification of observations concerning the histopathological parameters involved in wound healing indicates significant increase in cellular infiltration, neovascularization and collagen production, with early onset for re-epithelialization and significant decrease in thickening of epithelial layers over wound surface in group treated with lavender oil compared to control and treated groups. It could be concluded that lavender oil accelerated wound healing within a short period without any complication and is therefore advisable to be used as a dressing for wounds in dogs.

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1. INTRODUCTION

Wounds are common in animals with various causes. The variety of wound types has resulted in a wide range of wound dressings with new products. Therefore, wound management still remains an important focus of researches. In the last few decades, using of natural products as an alternative treatment has been on the rise (Kirui et al., 2004; Tan et al., 2009 and Haryanto et al., 2012). Wound healing progresses through a series of interdependent and overlapping stages in which a variety of cellular and matrix components act together to reestablish the integrity of damaged tissue and replacement of lost tissue (Rothe and Falanga, 1989 and Shakespeare, 2001).The healing process has four phases: blood clotting, inflammation, new tissue formation, and tissue remodeling (Monaco and Lawrence, 2003 and Theoret, 2004). Many traditional medicinal plants used in Africa to treat wounds exhibit antibacterial activity (Kudi et al., 1999). The increased interest in complementary therapies has led to the investigation of products traditionally believed to have a beneficial effect in wound healing. Several studies have demonstrated improved wound healing with traditional medicinal oils treatment (Dursun et al., 2003; Kietzmann and Braun, 2006; Pei et al., 2006 and Wang, 2006). Documented evidence for the use of lavender as a therapeutic agent can be traced back to the ancient Romans and Greeks, and the continuing popularity and commercial value of lavender was recently confirmed when it was named 'Herb of the Year 1999' by the Herb Growing and Marketing Network in the United States of America (Evelegh, 1996 and Anonymous, 1999).The flowers and the essential oil derived from them are antibacterial, antifungal, sedative, anti-depressant and effective for burns wounds and insect bites (Cavanagh and Wilkinson, 2002), beside its anti-inflammatory and analgesic properties (Vakiliana et al., 2011, Denner, 2009, Lusby et al., 2006 and Jones, 2011). Vakilian et al. (2011) reported that lavender was effective in wound healing and wound pain relief. The current experimental investigation was designed to evaluate the effectiveness of lavender oil compared with black seed oil, ostrich oil and cod liver oil for treatment of surgically induced full-thicknesses skin wounds in the back region in dogs.

2. MATERIALS AND METHODS:

2.1. Animals and Wounds

Seven apparently healthy male and female mixed breed (mongrel) dogs, aging 1-2 years and weighting 15-20 kg were used in the present experimental investigation. They were physically controlled in sterna recumbent position after sedation by xylazine HCl injected intramuscular in a dose rate of 1 mg/ kg body weight. Local analgesia was performed using 10% lidocaine spray (10 mg ⁄dose) at the site of skin incision. After routine aseptic preparation of the wound area in each dog, 5 neighboring rectangular full-thickness skin wounds measuring 2 cm width and 3 cm length for each were conducted (Fig.,1). Hemorrhage was controlled by pressure on the wound surface for 2 minutes. The wounds were bandaged with adhesive tape to protect them from contamination and flies for 24 hours (Fig., 2). Immediately before treatment application, each wound was irrigated with 0.9% saline solution as a start point.

2.2. Wound management

Wounds were treated in the following manner; each dog (5 wounds) received all treatments. One wound treated with 0.9% saline solution as a control, one wound treated with lavender oil, one wound with black seed oil, one wound with ostrich oil and the last wound was treated with cod liver oil. Application of the medicament was carried out by direct topical application over the wound surface which was then covered with sterile piece of gauze followed by a protective bandage changed day after day in the first week, every fourth day for two weeks and then once weekly till complete healing took place.

2.3. Wound Evaluation

Evaluation of wound healing based on; clinical wound characters, wound contraction % and histologic features. Mean reduction in wound dimensions (length and width) was determined at day 7, day 14 and day 21 for calculating wound contraction % according to the equation described by Ramsey et al. (2005). Wound Contraction (WC %) = W0 – WI / W0 X 100 Where: - W0 = the initial wound measurement (1st measurement in cm).

- WI = the wound measurement on day of measurement (2nd measurement in cm).

2.4. Histopathological evaluation

Skin wound specimens were obtained after 3, 7 and 19 days for the histopathological evaluation. They were thoroughly washed with a physiological saline (0.9% saline solution) then immediately fixed in 10% neutral buffered formalin for at least 24 h. specimens were processed through the conventional paraffin embedding technique and stained with hematoxylin and eosin (H & E) for light microscopic examination according to Bancroft et al. (2013).

2.5. Histopathological scoring system

Several histopathological parameters could be used to assess the progression of healing from the inflammatory to the repair stage, the cellular infiltration, angiogenesis, epithelization and level of collagen production were selected, each parameter were recorded in five high power field (HPF-X400) and scored according to the scoring system described by Karayannopoulou et al. (2011) and discussed in the following (tables. 1&2):

Table (1): Scoring system for cellular infiltration and collagen production.

Histopathologic observation	Score 0	Score 1	Score 2	Score 3	Score 4	Score 5
Degree of cellular infiltration: number of inflammatory cells (neutrophils, lymphocytes, plasma cells, macrophages, eosinophils and mast cells) detected per high power field (HPF-X400)	≤ 3 Inf. cells	4 to 10 Inf. cells	11 to 20 Inf. cells	21 to 30 Inf. cells	31 to 40 Inf. cells	≥ 41 Inf. cells
Collagen production (amount and maturation of produced collagen)	Normal	Mild increase	Mild to moderate increase	Moderate increase	Moderate to marked increase	Marked increase (involves deep tissues)

Table (2): Scoring system for newly formed blood vessels and thickness of epithelium over the wound.

Histopathologic observation	Score 0	Score 1	Score 2	Score 3
Number of newly formed blood vessels and capillary buds (as indicator of neovascularization or angiogenesis) evaluated in 5 HPFs per section)	≤ 3 New vessels	3 to 10 New vessels	11 to 30 new vessels	≥ 31 New vessels
Thickness of epithelium over the wound (compared with normal epidermis of excised skin on 0 day (control specimen)	Thickness similar to normal epithelium	Slightly increased thickness	Moderately increased thickness	Markedly increased thickness

Fig. (1): Five experimentally induced wound in the back region of each dog. The wounds are full-thickness skin wounds.

Fig. (2): Wounds covering using piece of gauze fixed to the skin.

3. RESULTS:

3.1. Clinical wound characters

Throughout the period of treatment, clinical wound parameters including inflammatory signs, bleeding tendency, exudation, infection and granulation tissue showed low significant difference between different drugs. Wounds treated with lavender oil provided good healing parameters as compared with other oils, it characterized by absence of inflammatory signs, exudation and infection *(*Fig. 3) Granulation and epithelial tissue formation were moderate to complete and rapidly seen after lavender oil. The scab flacked out leaving smooth epithelial surface without scar formation (Figs. 3).

3.2. Wound contraction

Change in the wound dimensions varied according to different treatments at different weeks (Table 3). The percent of wound contraction showed great varieties responding to each treatment are summarized in (Table 4).

Lavender oil showed significant reduction in wound dimensions than other oils, also the wound contraction percent was significantly increased in lavender with faster healing than other wounds.

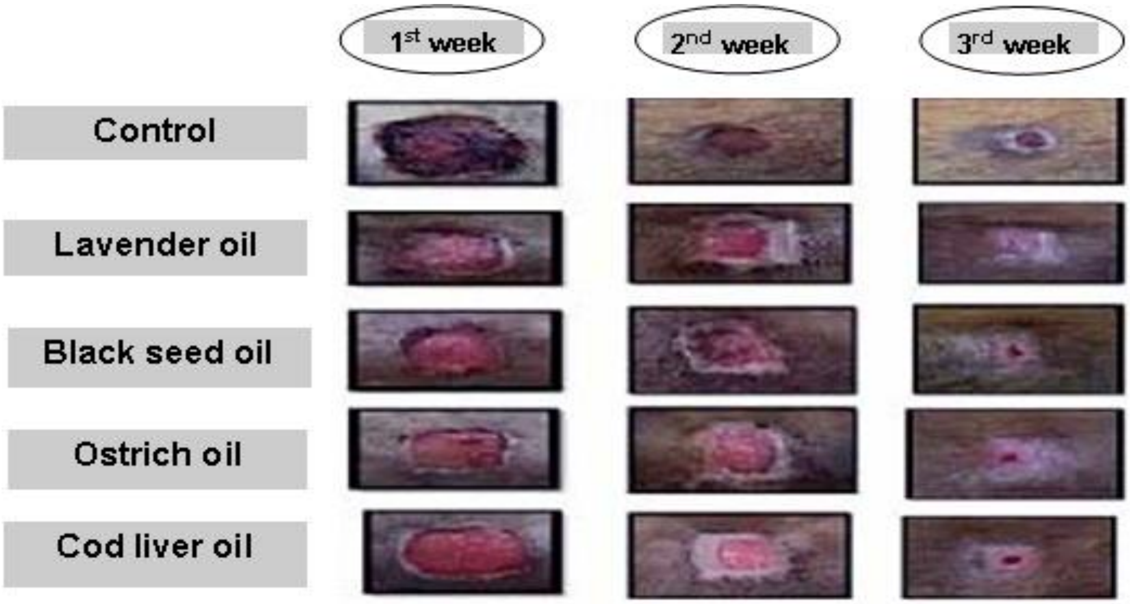

Fig.(3): progress in wound healing from 1st to 3rd week in control, lavender oil, black seed oil, ostrich oil and cod liver oil wound.

Table (3): Wound dimensions of different treatments at different weeks.

Treatment	1st Week		2nd Week		3rd Week	
	Length	Width	Length	Width	Length	Width
	Mean ± S.E					
Saline	3±0.30 Aa	1.8±0.70 Aa	2±0.20 Ab	1.1±0.10 Ab	1±0.01 Ac	1±0.01 Ab
Lavender oil	2.5±0.55 Ca	1.3±0.30 Ca	1.8±0.80 Bb	0.5±0.01 Bb	0 Dc	0 Cc
Black seed oil	2.8±0.18 Ba	1.5±0.50 Ba	2±0.10 Ab	0.5±0.01 Bb	0.2±0.01 Cc	0.1±0.01 Ac
Ostrich oil	2.8±0.14 Ba	1.5±0.50 Ba	2±0.10 Ab	0.6±0.01 Bb	0.4±0.01 Bc	0.1±0.01 Ac
Cod liver oil	2.9±0.19 ABa	1.5±0.50 Ba	2±0.10 Ab	1±0.01 Ab	1±0.01 Ac	0.7±0.02 Bc

Capital litters: Indicated that: Means within the same column of different litters are significantly different at (P < 0.01). -Small litters: Indicated that: for each parameter within the same week: Means within the same row of different litters are significantly different at (P < 0.01). Mean ±S.E: Means ± Standard Error

Table (4): Percentages of wound contractions of different treatments at different weeks

Treatment	1st Week	2nd Week	3rd Week
	Mean ± S.E		
Saline	4±0.1 Ec	38±3.44 Eb	60±6.12 Ea
Lavender oil	24±2.44 Ac	54±3.55 Ab	100±10.12 Aa
Black seed oil	14±1.22 Bc	50±4.55 Bb	94±4.99 Ba
Ostrich oil	12±1.22 Cc	48±4.12 Cb	90±9.14 Ca
Cod liver oil	6±1.66 Dc	40±4.11 Db	66±6.16 Da

Capital litters: Indicated that: Means within the same column of different litters are significantly different at (P < 0.01). Small litters: Indicated that: Means within the same row of different litters are significantly different at (P < 0.01).

3.3. Histologic features

During the inflammatory and proliferative stage, after 3 days, the control wound showed partial re-epithelization with few underlying neovascularization and slight inflammatory cells infiltration mainly neutrophil (Fig. 4B), while, the same results were recorded for cod liver and ostrich oil treated wounds where the covering epithelial cells proliferate and 'crawl' atop the wound bed, providing cover for the new tissue with underlying neovascularization and considerable number of inflammatory cells mainly neutrophil (Fig.4C & D). Furthermore, similar description was obtained for Black seeds and Lavender oil treated wounds where the covering epithelial cells proliferate and 'crawl' atop the wound bed, providing cover for the new tissue with marked underlying neovascularization and considerable number of inflammatory cells mainly macrophages (Fig.4E & F).

After 7 days (during the proliferative stage), the control group showed incomplete re-epithelization with underlying neovascularization and slight infiltration of macrophage (Fig. 5B). Cod liver oil treated group showed complete re-epithelialization with underlying neovascularization and considerable number of inflammatory cells mainly neutrophil and few fibroplasia (Fig. 5C).While, ostrich oil treated group showed complete re-epithelialization with underlying neovascularization and considerable fibroplasia (Fig. 5D). Moreover, black seed and lavender oil treated groups showing complete re-epithelialization with underlying neovascularization and considerable fibroplasia admixed with collagen bundles (Fig. 5E & F).

During the wound contraction stage (after 19 days), the control group showed complete epithelization with rete ridges formation under scab formation; with underlying granulation tissue formation featuring immature stellate shape fibroblast and few collagen perpendicular to new blood vessel and parallel to wound surface (Fig. 6B). Cod liver oil treated group showed complete epithelization with rete ridges formation under scab formation; with underlying granulation tissue formation featuring fibroblast and collagen perpendicular to new blood vessel and parallel to wound surface (Fig. 6C). While, ostrich and black seeds oil treated groups showed complete epithelization with rete ridges formation; with underlying granulation tissue formation featuring fibroblast and collagen perpendicular to new blood vessel and parallel to wound surface (Fig. 6D & E). Furthermore, Lavender oil treated group showed complete epithelization with rete ridges formation with underlying ***fibrous tissue*** where fibroblast and collagen bundles devoid of new blood vessels and parallel to wound surface (Fig. 6F).

The quantification of observations concerning the selected histological parameters involved in wound healing allowed detection of a number of differences between the 5 groups described in table (5).

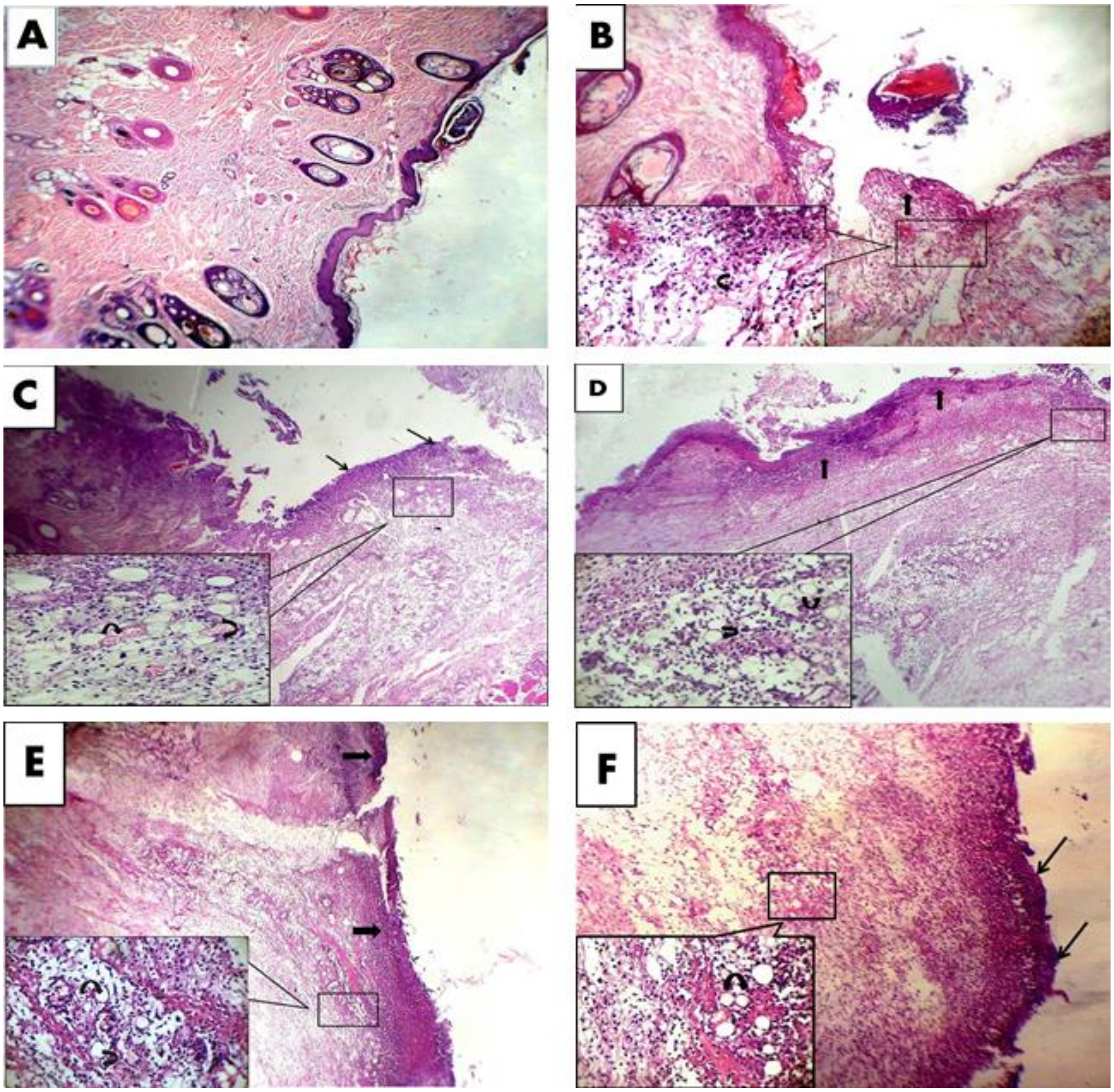

Fig (4): Representative photomicrograph for proliferative stage of surgically induced skin wound in dog (after 3 days) treated with cod liver, ostrich, black seeds and lavender oil and stained with hematoxylin and eosin (H&E): (A) Normal skin histology (X40). (B): Control wound with saline dressing showing focal re-epithelization (arrow; X40) with mild underlying neovascularization (curved arrow) and slight inflammatory cells infiltration mainly neutrophil (inset; X400). (C): Cod liver oil treated wound showing covering epithelial cells proliferate and 'crawl' atop the wound bed, providing cover for the new tissue (arrows; X40) with underlying neovascularization (curved arrows) and considerable number of inflammatory cells mainly neutrophil (inset; X400). (D): Ostrich oil treated wound showing covering epithelial cells proliferate and 'crawl' atop the wound bed, providing cover for the new tissue (arrows; X40) with underlying neovascularization (curved arrows) and considerable number of inflammatory cells mainly neutrophil (inset; X400). (E): Black seeds oil treated wound showing covering epithelial cells proliferate and 'crawl' atop the wound bed, providing cover for the new tissue (arrows; X40) with marked underlying neovascularization (curved arrows) and considerable number of inflammatory cells including macrophages (inset; X400). (F): Lavender oil treated wound showing covering epithelial cells proliferate and 'crawl' atop the wound bed, providing cover for the new tissue (arrows; X40) with marked underlying neovascularization (curved arrow) and considerable numbers of inflammatory cells mainly macrophage (inset; X400).

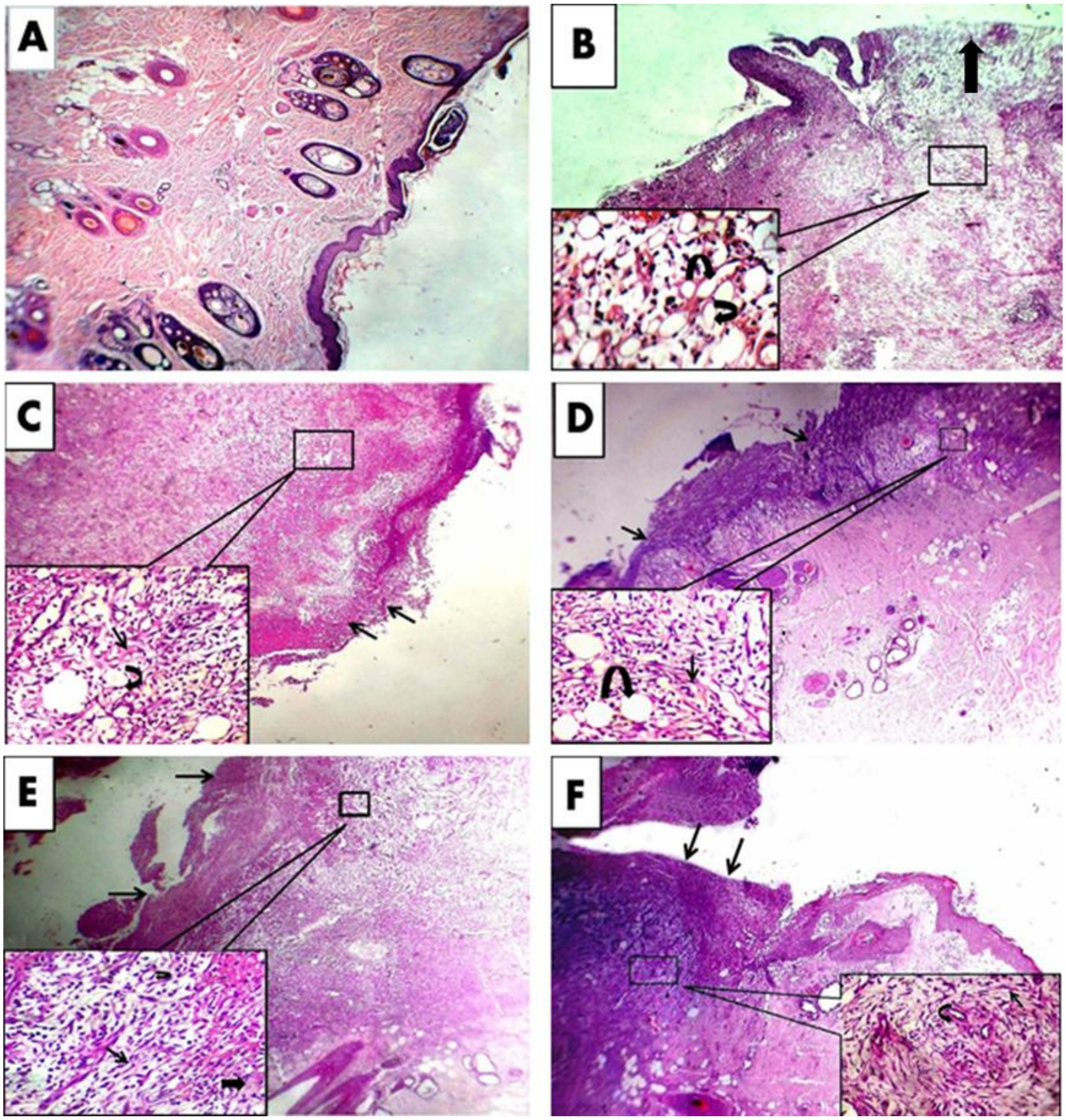

Fig (5): Representative photomicrograph for proliferative stage of surgically induced skin wound in dog (after 7 days) treated with cod liver, ostrich, black seeds and lavender oil and stained with hematoxylin and eosin (H&E): (A) Normal skin histology (X40). (B): Control wound with saline dressing showing incomplete re-epithelization (thick arrow; X40) with underlying neovascularization (curved arrow) and slight infiltration of macrophage (inset; X400). (C): Cod liver oil treated wound showing complete re-epithelialization (arrows; X40) with underlying neovascularization (curved arrow) and considerable number of inflammatory cells mainly neutrophil and few fibroplasia (thin arrow, inset; X400). (D): Ostrich oil treated wound showing complete re-epithelialization (arrows; X40) with underlying neovascularization (curved arrow) and considerable fibroplasia (thin arrow, inset; X400). (E): Black seeds oil treated wound showing complete re-epithelialization (arrows; X40) with underlying neovascularization (curved arrow) and considerable fibroplasia (thin arrow) admixed with collagen bundles (thick arrow, inset; X400). (F): Lavender oil treated wound showing complete re-epithelialization (arrows; X40) with underlying neovascularization (curved arrow) and considerable fibroplasia (thin arrow, inset; X400) admixed with collagen bundles.

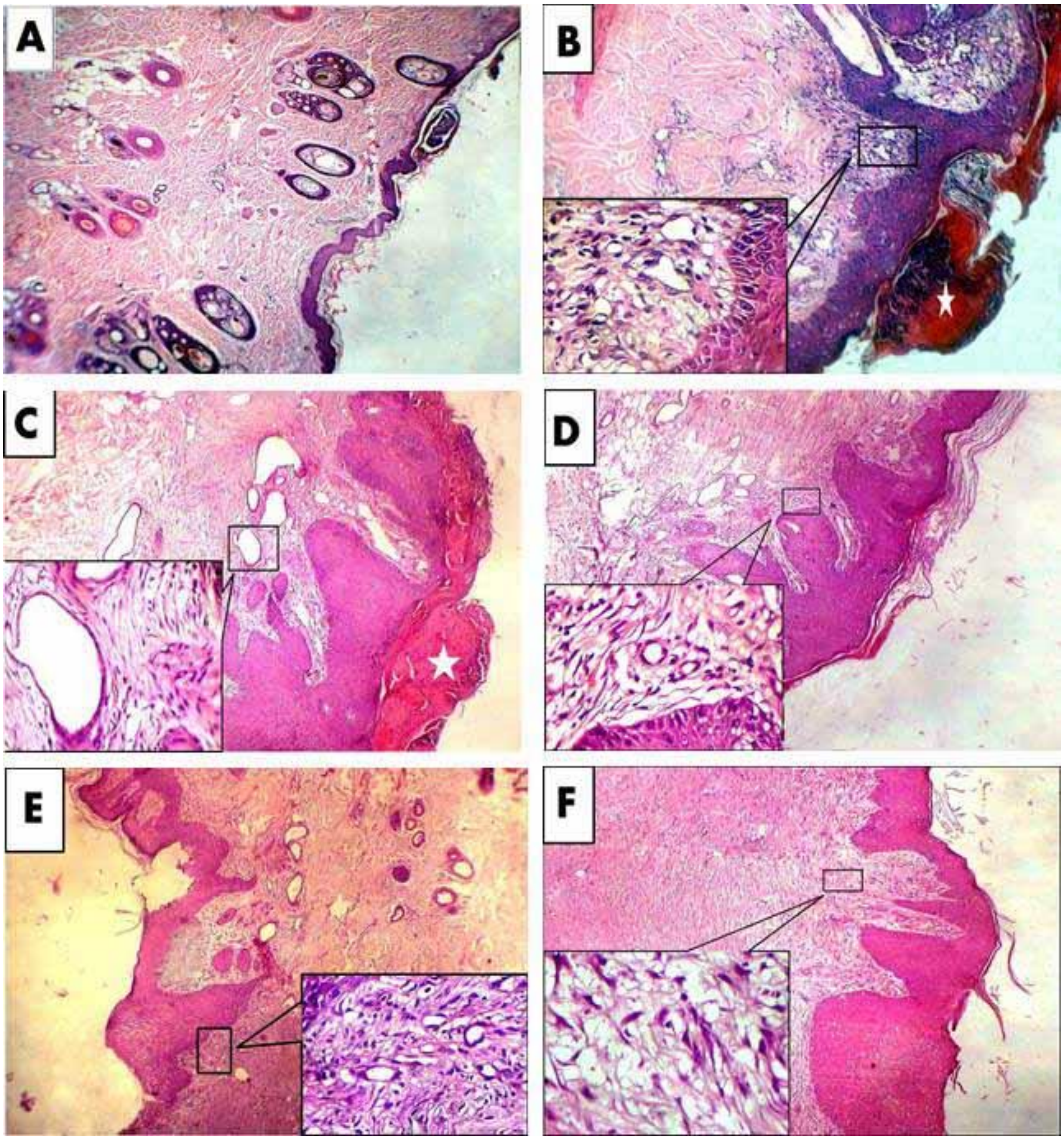

Fig (6): Representative photomicrograph for wound contraction stage of surgically induced skin wound in dog (after 19 days) treated with cod liver, ostrich, black seeds and lavender oil and stained with hematoxylin and eosin (H&E): (A) Normal skin histology (X40). (B): Control wound with saline dressing showing complete epithelization with rete ridges formation under complete scab formation (star) ; with underlying granulation tissue formation featuring immature stellate shape fibroblast and few collagen perpendicular to new blood vessel and parallel to wound surface (inset; X400).(C): Cod liver oil treated wound showing complete epithelization with rete ridges formation under scab formation (star); with underlying granulation tissue formation featuring fibroblast and collagen perpendicular to new blood vessel and parallel to wound surface (inset; X400). (D): Ostrich oil treated wound showing complete epithelization with rete ridges formation; with underlying granulation tissue formation featuring fibroblast and collagen perpendicular to new blood vessel and parallel to wound surface (inset; X400). (E): Black seeds oil treated wound showing complete epithelization with rete ridges formation; with underlying granulation tissue formation featuring fibroblast and collagen perpendicular to new blood vessel and parallel to wound surface(inset; X400). (F): Lavender oil treated wound showing complete epithelization with rete ridges formation; with underlying ***fibrous tissue*** where fibroblast and collagen bundles (devoid new blood vessels) parallel to wound surface (inset; X400).

Table (5): Means of scoring system of wound healing among different treatments at different periods

Parameters	No	Control group	Cod liver oil group	Ostrich oil group	Black seed oil group	Lavander oil group
		Mean ± S.E				
Cellular infiltration	5	Be 2.40±0.24	Ad 3.20±0.37	Bc 3.40±0.51	Bb 3.60±0.24	Ba 4.40±0.24
Neovascula-rization	5	Ee 1.40±0.24	Dd 1.80±0.20	Ec 2.00±0.32	Eb 2.20±0.49	Ea 2.60±0.24
Collagen production	5	De 1.60±0.24	Cd 2.40±0.24	Cc 2.60±0.24	Cb 2.80±0.37	Ca 3.40±0.24
Thickness of epithelium over the wound	5	Ce 1.80±0.20	Ed 2.20±0.37	Dc 2.40±0.24	Db 2.60±0.24	Da 3.00±0.01

Small litters: Indicated that: Means within the same row of different litters are significantly different at (P < 0.01).
Mean ±S.E: Means ± Standard Error.

4. DISCUSSION

The aim of wound care is to promote wound healing in a shortest time with minimal pain, discomfort and scarring to the patient, and it must occur in a physiologic environment conductive to tissue repair and regeneration (Priya et al., 2007). Despite numerous treatments available for deteriorated cutaneous wound healing, there still the need for more effective therapy (Lee et al., 2011). Several drugs for the management of wound healing take their origin from plants as lavender oil (Kutlu et al., 2013; Abu-Ahmed 2015), black seed oil (Sarkhail et al., 2011) or from animal origin as ostrich oil (Politis and Dmytrowich, 1998) and cod liver oil (Ali and Radad, 2011). The result of this study showed that wounds treated with lavender oil characterized by absence of inflammatory signs, exudation, pain and infection. This result could be attributed to antimicrobial, anti-inflammatory, analgesic properties of lavender (Lusby et al., 2006). Alpha-terpineol and terpinen-4-ol and camphor which are the chemical constituents of lavender essential oil have antibacterial effects (Lis-Balchin and Hart, 1999 and Gilani et al., 1998). On the other hand, exudation and bleeding are evident in other wounds. Significant decrease in wound dimensions with significant increase in wound contraction percent were observed in wound treated with lavender than other oils and healing appeared to faster without scar formation, this result agreed with Cavanagh and Wilkinson (2002) whose reported that lavender oil reduce scar tissue formation. Accelerated re-epithelization and faster wound closure in lavender oil wounds may be due to the lavender oil enhancing EGF (epidermal growth factor) secretion (Kutlu et al., 2013). EGF stimulates granulation tissue formation and re-epithelization and increase wound resistance to stretching (Li et al., 2007). Histopathological features of this study showed early onset of inflammatory and proliferative phases of lavender treated wound which confirmed statistically by significant increase in cellular infiltration, neovascularization, and collagen production, with complete re-epithelialization and significant decrease in thickening of epithelial layers over wound surface. Thick vascular granulation tissue, fibrous tissue formation, collagen deposition and epithelial migration that met with wounds treated with lavender oil are the most characteristic histologic features of good and accepted wound healing (Meagher, 1981). It could be concluded that lavender oil accelerated wound healing within a short period without any complication and is therefore advisable to be used as a dressing for wounds in dogs.

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