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Evaluation of the healing process in experimentally induced wounds treated with *Aloe vera* in sheep

Avaliação do processo de cicatrização em feridas induzidas experimentalmente tratadas com *Aloe vera* em ovinos

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Animal skin trauma can lead to significant tissue loss, requiring specialized treatment for proper healing, *Aloe vera*, known for its healing properties, has potential benefits for wound treatment in small ruminants. The objective of this study was to evaluate the healing effect of *Aloe vera* on experimentally induced wounds in sheep. Skin wounds were made in the right and left paralumbar fossa and the animals were subjected to: Negative control group (NC): 1 mL of 0.9% saline solution, Positive control group (PC): 0.1 gram of allopathic ointment based on 35% Lauryl dimethyl benzyl ammonium Chloride and *Aloe vera* Group (AV): 1g of 10% *Aloe vera* extract. Topical treatment was carried out in the three experimental groups for 22 days every 24 hours. For macroscopic evaluation, hemorrhage, crust, granulation tissue, swelling, color, hair growth in the area adjacent and epithelialization were evaluated. For microscopic evaluation, morphological aspects such as mononuclear cells and edema epithelialization were evaluated. Macroscopically, it can be inferred that the 10% *Aloe vera* extract for the treatment of skin wounds in sheep was effective and therefore its use can be suggested as a treatment. In the microscopic analyses, the three groups presented similar results in the evaluation on the 1st, 8th, and 15th day, differing only on the 22nd postoperative day. Therefore, it is concluded that macroscopically and microscopically, *Aloe vera* 10% presented a satisfactory healing effect, and can be indicated as an alternative in the treatment of skin wounds in sheep.
Keywords: aloe, skin, small ruminants.

Traumas na pele de animais podem levar a perdas significativas de tecido, exigindo tratamento especializado para uma cicatrização adequada, *Aloe vera*, conhecida por suas propriedades cicatrizantes, tem benefícios potenciais para tratamento de feridas em pequenos ruminantes. O objetivo deste estudo foi avaliar o efeito cicatrizante de *Aloe vera* em feridas induzidas experimentalmente em ovinos. Feridas cutâneas foram feitas na fossa paralombar direita e esquerda e os animais foram submetidos a: Grupo controle negativo (NC): 1 mL de solução salina 0,9%, Grupo controle positivo (PC): 0,1 grama de pomada alopática à base de 35% de Cloreto de Lauril dimetil benzil amônio e Grupo *Aloe vera* (AV): 1g de extrato de *Aloe vera* 10%. O tratamento tópico foi realizado nos três grupos experimentais por 22 dias a cada 24 horas. Para avaliação macroscópica, foram avaliados hemorragia, crosta, tecido de granulação, inchaço, coloração, crescimento de pelos na área adjacente e epitelização. Para avaliação microscópica, foram avaliados aspectos morfológicos como células mononucleares e epitelização do edema. Macroscopicamente, pode-se inferir que o extrato de *Aloe vera* 10% para tratamento de feridas cutâneas em ovinos foi eficaz e, portanto, seu uso pode ser sugerido como tratamento. Nas análises microscópicas, os três grupos apresentaram resultados semelhantes na avaliação no 1º, 8º e 15º dia, diferindo apenas no 22º dia pós-operatório. Portanto, conclui-se que macroscopicamente e microscopicamente, o *Aloe vera* 10% apresentou efeito cicatrizante satisfatório, podendo ser indicado como alternativa no tratamento de feridas cutâneas em ovinos.
Palavras-chave: babosa, pele, pequenos ruminantes

1. INTRODUTION

The skin of animals can be exposed to trauma that triggers lesions with extensive tissue loss, resulting in healing in an attempt to restore its functional integrity. The extent of skin loss makes it difficult to approximate the edges, resulting in what we know as second intention healing, which is a slower process, often producing extensive scars and increasing the cost of treatment [1].

In small ruminants, skin wounds are of particular concern, as they may lead to complications such as secondary bacterial infections, myiasis, stress-related immunosuppression, and reduced productivity due to pain and discomfort. Additionally, cutaneous lesions are frequent entry points for opportunistic pathogens, resulting in economic losses due to decreased growth rates and treatment expenses, particularly in semi-intensive or extensive systems where wound monitoring is challenging [2].

Most authors classify healing into three phases: inflammatory, proliferative, and maturation [3]. The inflammatory phase begins with an immediate capillary constriction to the wound, aiming for intravascular coagulation, followed by capillary dilation with increased vascular permeability produced by inflammatory mediators such as histamine, prostaglandins, and cytokines like TNF-α and IL-1β. Platelets adhere and aggregate, forming a clot that restores homeostasis. Clot, fibrin, and exudate fill the wound, forming a matrix on which fibroblasts and newly formed endothelial cells will constitute the granulation tissue [4].

Another phase of healing is fibroplasia or repair, characterized by the proliferation of a specific cell population, which are fibroblasts. With the local presence of macrophages derived from monocytes and the production and release of chemical mediators produced by them, including transforming growth factor beta (TGF-β) and vascular endothelial growth factor (VEGF), the migration and activation of fibroblasts are intensified [5].

The final phases of the healing process consist of contraction and increased scar strength. Contraction is the reduction of part or all of the open wound area, occurring centripetally from the edges of the lesion, caused by the actin filaments of myofibroblasts. When collagen production and arrangement of its molecules occur, the number of myofibroblasts decreases, observing the relationship between the contraction mechanism and collagen maturation [6].

Different existing alternatives allow accelerating the wound healing process. Regardless of the chosen method, it should provide a favorable environment, allowing spontaneous progression to avoid delaying the repair process [7]. Among the healing plants, *Aloe vera*, popularly known as aloe, has been used for a long time due to its healing effect [8].

Aloe vera has a gel in its parenchyma whose main healing substrate is mannose-6-phosphate, a proliferative stimulant of fibroblasts, macrophages, and angiogenesis, in addition to containing anthraquinones, known for their antibacterial, antiviral, and antifungal properties [9]. Studies in laboratory animals, such as rats and rabbits, have demonstrated accelerated wound closure, enhanced fibroblast activity, neovascularization, and reduced inflammation with the use of *Aloe vera* [10, 11].

Currently, it is common to administer synthetic substances such as anti-inflammatories and drugs that aid in healing, but in this context, little is known about the effects of *Aloe vera* when administered to wounds in small ruminants. Given the biological importance of skin integrity, its relevance in disease prevention, and the scarcity of studies in sheep and goats, this study aims to evaluate the effectiveness of *Aloe vera*-based formulations in promoting skin wound healing in small ruminants, contributing to the search for accessible and effective alternatives.

2. MATERIAL AND METHODS

This study was approved by the Ethics and Animal Experimentation Committee - CEEA of the Veterinary Medicine Course at UEMA, according to protocol no. 15/2021.

2.1 Study area, selection of animals and separation of batches

The field experiment was conducted at a private sheep farm located at the geographical coordinates 2°30’42.7"S and 44°02’24.6"W, in the state of Maranhão.

Fifteen sheep, all castrated males, crossbred, aged between 6 to 12 months, were used. They were standardized into three groups of 5 animals each. Each batch was numbered sequentially from 1 to 15, as follows: 1 to 5 belonging to the negative control group (NC); 6 to 10 belonging to the positive control group (PC); and 11 to 15 to the *Aloe vera* group (AV).

2.2 Stall preparation and handling of confined animals

All animals underwent an eight-day confinement period in collective pens for acclimatization and adaptation. They were dewormed with Doramectin (1% at 1 mL/kg body weight), administered subcutaneously. Afterward, a mineral multivitamin supplement (5mL/animal) containing mephentermine sulfate (600mg), calcium pantothenate (500mg), cobalt sulfate (200mg), and nicotinamide (10000mg) was given orally. The animals were fed forage, concentrate, and mineral salt, with water available ad libitum. Forage, primarily Pennisetum purpureum schum, was provided three times daily in wooden troughs, either chopped by a forage cutter or manually. The concentrate (200g/animal/day) contained 20% soybean meal, 15% urea, 19% ground corn, and 30% common salt. Mineral salt was available all day.

2.3 Demarcation of the area and creation of skin wounds

The animals underwent trichotomy of the right paralumbar fossa using an electric device and a manual trichotome with a steel blade. They were then weighed on a mechanical scale to determine the appropriate anesthetic doses based on their individual weight. The site was antiseptically prepared with gauze soaked in iodized alcohol before anesthesia. Anesthesia was induced using an inverted L local infiltrative technique with 2% lidocaine hydrochloride (with a vasoconstrictor) at a dose of 7mg/kg body weight.

A 2.5 cm circular mold was used to mark the right paralumbar fossa, and incisions were made with a scalpel. Wound hemostasis was maintained using sterile gauze throughout the procedure. Topical treatment was applied daily for 22 days to animals in the three experimental groups, and macroscopic evaluations were conducted on days 1, 8, 15, and 22.

Using a digital camera, the wounds on the right paralumbar fossa were photographed for subsequent detailed macroscopic evaluation and measured with a manual caliper. Macroscopic evaluation and measurement were performed every 24 hours until reepithelialization, totaling 322 observations.

The following aspects were evaluated: hemorrhage (presence or absence), crust (partial or total, exuberant or non-exuberant, dry or with secretion, and color); granulation tissue (presence or absence, and color), swelling, color, hair growth in the area adjacent to the wound, and epithelialization.

2.4 Topical therapeutic substances used in treatments

The following were used: 10% *Aloe vera* extract; a commercial product based on 35% Lauryl dimethyl benzyl ammonium chloride; and 0.9% saline solution. The animals were divided into three experimental groups, and each group received the following treatment: Negative control group (NC) – animals treated with 1 mL of 0.9% saline solution; *Aloe vera* group (AV) – animals treated with 1g of 10% *Aloe vera* extract; Positive control group (PC) – animals treated with 1g of 35% Lauryl dimethyl benzyl ammonium chloride ointment.

2.5 Data analysis

To obtain the wound areas, they were measured daily using the formula $A=(2D)\cdot(2d)\cdot\pi$, where $\pi=3.14$; D = largest diameter of the wound; d = smallest diameter of the wound. These results were used to evaluate the quantification of wound area contraction. Subsequently, these data were organized in Excel spreadsheets and the experimental design was in randomized blocks. Data analysis was performed using the Minitab Statistical Software version 21.1.0, where the mean comparison test for the measured areas was conducted through analysis of variance and the paired Tukey test with a 95% confidence interval ($p < 0.05$).

2.6 Collection of material and histological processing

For collection, the wound was divided into four quadrants, the skin segments were removed using a dermatological punch with the aid of a scalpel and rat-tooth forceps, and then preserved in collection jars with a 10% formalin solution for 24 hours. After the fixation period, the samples were transferred to new collection jars containing a 70% alcohol solution for dehydration.

After dehydration, the segments were inserted into histological cassettes and dehydrated in increasing solutions of ethyl alcohol (70%, 80%, 90%, absolute alcohol I and II), then diaphanized in xylene and embedded in histological paraffin. The histological sections were sectioned at 4 μm thickness, using a HM 360 MICROM rotation microtome. The slides were then stained with Hematoxylin-Eosin (HE) and Picrosirius Red for subsequent morphological analysis, where microscopic aspects such as mononuclear cells and edema were evaluated on the 1st, 8th, 15th and 22nd postoperative day.

3. RESULTS AND DISCUSSION

Before the start of confinement for the adaptation of the animals in the pens, one animal from the negative control group (NC) died, and due to the property not having another male animal, it was not replaced. No signs of infection were detected in the wounds during the experimental period. The animals showed good health, with characteristics of physical disposition, good behavioral and nutritional temperament.

On the 1st day of macroscopic evaluation of the wounds, some characteristics were absent in the three experimental groups, namely: crust, granulation tissue, epithelialization, and swelling. On the 5th day of evaluation, the presence of myiasis was observed in the left paralumbar fossa of animal four from the NC.

On the eighth day of evaluation, all wounds exhibited a dark reddish tone without swelling. Hemorrhagic points, partial and total crust formation, and epithelialization at the wound edges were observed. Hair and foreign bodies were present on the wound surface, along with occasional serous exudate. On the 15th day, the absence of hemorrhagic points, swelling, and exudate was observed in all groups, and all wounds appeared pink and pale. On the 22nd day, the absence of hemorrhagic points, swelling, and exudate was recorded, with wounds appearing pink and pale. The observations described in the macroscopic evaluation of the wounds are illustrated in Figure 1.

The first response to an injury is hemostasis, which involves vasoconstriction, formation of the platelet plug, and activation of the coagulation cascade with the formation of the fibrin plug, resulting from activated platelets, red blood cells, fluid, and fibrin. Over time, the surface of the fibrin plug will dry and form a crust, allowing the wound healing to continue underneath [12]. The presence of a more serous exudate in the AV and PC groups evidenced more efficient hemostasis, unlike the NC group, which presented bloody exudate. A similar result was found by Brandão et al. (2016) [9], who observed that wounds in rats treated with 10% *Aloe vera* extract showed light yellow exudate with a serum-like appearance.

Regarding the formation of crusts, it was observed that, on the first day of evaluation, they were absent in 100% of the animals in the experimental groups. On subsequent days, the

presence of crusts varied between the groups and periods evaluated. The animals in the AV and PC groups had more homogeneous and prevalent crusts compared to the NC group, suggesting that both groups had a satisfactory effect on crust formation.

Crusts are composed of coagulated blood, fibrin, dried collagen, and cellular debris, formed by the desiccation of the wound surface. More exudative wounds tend to form thicker and more easily removable crusts, which provide less protection to the lesion. Therefore, according to Hussini et al. (2010) [13], it is more appropriate for there to be less exudation in the wound bed, remaining dry and with the formation of an adhered protective crust.

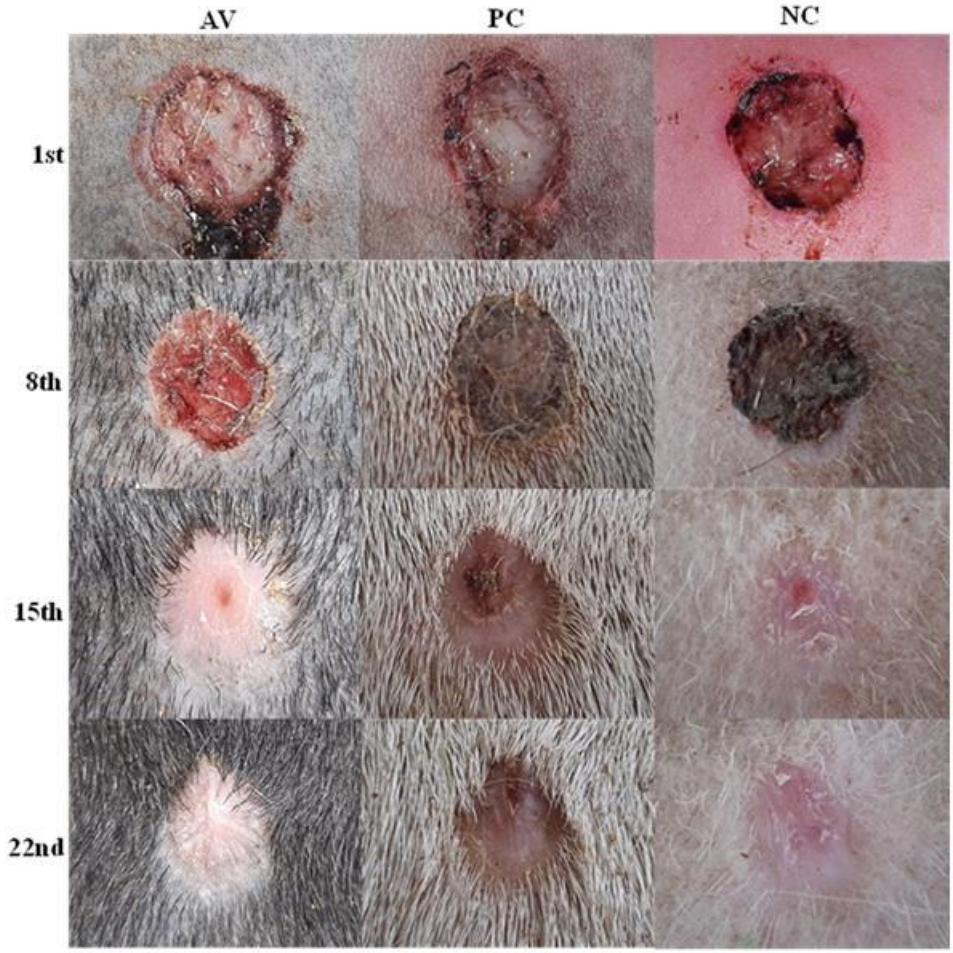

Figure 1: Wound contraction on the 1st, 8th, 15th, 22nd days, in the three experimental groups.

About reepithelialization, on the first day of evaluation, it was absent in 100% of the animals in the experimental groups. On subsequent days, the progression of reepithelialization varied between groups and evaluation periods. The animals in the AV and PC groups demonstrated a gradual and satisfactory reepithelialization process over time, with a higher prevalence of complete epithelialization by the 22nd day, compared to the NC group.

Regarding the wound area, there was a statistically significant difference on the eighth day of measurement ($p=0.042$) between the AV and PC groups, demonstrating that *Aloe vera* provided greater wound contraction at the beginning of the healing process. On the other measurement days, there was no statistical difference, as we can observe in Table 1.

Table 1: Mean and standard deviation of the area of experimentally induced wounds in the skin of sheep from AV, NC, and PC on the 1st, 8th, 15th, and 22nd days of evolution.

Groups		Days			
		1st	8th	15th	22th
Negative Control	Average	4,392[a]	1,698[ab]	0,079[a]	0,002[a]
	Standard Deviation	0,393	0,188	0,168	0,004
Positive Control	Average	4,343[a]	2,060[a]	0,113[a]	0,028[a]
	Standard Deviation	0,773	0,285	0,045	0,014
Aloe vera	Average	4,200[a]	1,397[b]	0,138[a]	0,063[a]
	Standard Deviation	0,253	0,496	0,050	0,140
	Combined Standard Deviation	0,532	0,359	0,108	0,085
	p-value	0,851	0,042	0,976	0,576

The wound contractions based on their averages in the AV group showed better results at the beginning of the healing process. However, on the 17th day of evaluation, there was a loss of crust in animal 11 due to a traumatic process, justified by the presence of hemorrhagic points in the wound. This fact may have influenced the results, as the other animals in this group showed fully reepithelialized wounds by the 20th day, and after the crust fell off, there was a significant increase in the wound area.

Regarding the average wound contraction, it was observed that on the 22nd day of evaluation, the group treated with *Aloe vera* showed a reduction value of 98.75%, the positive control group 99.50%, and the negative control group 99.96%. The results of wound contraction at the beginning of the healing process were similar to those described by Jettanacheawchankit et al. (2009) [14], who found that on the 7th day of the experiment, wounds treated with 0.5% *Aloe vera* showed significant closure compared to treatments with saline solution and 0.1% triamcinolone acetonide, due to its anti-inflammatory properties by prostaglandin production, through the inhibition of arachidonic acid action [15].

The high percentage of contraction in wounds treated with *Aloe vera* corroborates the results of Brandão et al. (2016) [9], who, when analyzing the healing process in wounds of rats using 10% *Aloe vera*, obtained a higher contraction percentage for the group treated with 0.9% saline solution. In their study evaluating the healing process with glycolic extract of *Aloe vera* in guinea pigs, Lira et al. (2020) [16] obtained very close results regarding the contraction of wounds in the group treated with 0.9% saline solution compared to the other evaluated groups, attributing this to the fact that the healing and tissue remodeling mechanisms of the organism are capable, to a certain extent, of restructuring the entire skin matrix without the need for additional agents.

On the first postoperative day, the presence of mononuclear cells and edema varied among the experimental groups. The NC group exhibited a greater prevalence of moderate to intense mononuclear cell infiltration, while the AV and PC groups showed a more balanced distribution across mild, moderate, and intense grades. Regarding edema, the AV group predominantly presented mild grades, suggesting a potentially favorable effect of *Aloe vera* on reducing inflammatory responses.

On the 8th postoperative day, the distribution of mononuclear cells and edema varied among the experimental groups. The AV group demonstrated a predominance of moderate mononuclear cell infiltration, with one animal showing an intense grade, while the NC and PC groups exhibited higher grades of infiltration overall. Regarding edema, the AV group showed the most favorable results, with one animal showing no edema, three with mild grades, and only one with moderate edema, indicating a potential anti-inflammatory effect of *Aloe vera*.

On the 15th postoperative day, the presence of mononuclear cells and edema was more evenly distributed across the experimental groups. The AV and PC groups had a predominance of mild to moderate mononuclear cell infiltration, suggesting similar inflammatory responses. Regarding edema, the AV group presented the most favorable outcome, with one animal showing no edema, three with mild grades, and only one with moderate edema, indicating a potential reduction in inflammation associated with *Aloe vera*.

On the 22nd postoperative day, the inflammatory response, indicated by mononuclear cell infiltration and edema, showed significant improvement across all groups. The AV group exhibited the most favorable results, with two animals showing no mononuclear cells and three with mild infiltration. Regarding edema, the AV group also had the best outcomes, with three animals showing no edema and two with mild grades, suggesting a pronounced anti-inflammatory effect of *Aloe vera* by this stage of recovery.

This anti-inflammatory effect may be attributed to *Aloe vera*'s ability to modulate cytokine production, reduce prostaglandin synthesis, and inhibit cyclooxygenase pathways. Additionally, its bioactive components such as acemannan and mannose-6-phosphate are known to stimulate macrophage activity and fibroblast proliferation, promoting tissue regeneration and reducing inflammatory cell infiltration [17, 18].

The presence of edema can be justified by the large number of inflammatory cells. With vasodilation at the initial stage of the healing process, permeability also occurs, which allows the transport of proteins and components to the extravascular space. This causes an osmotic imbalance resulting in the extravasation of fluids and cell migration [19].

Figures 2 and 3 shows the evolution of the healing process in the three groups, where both groups present re-epithelialization. Thus, the *Aloe vera* group was shown to be ahead in the healing process by presenting a lower inflammatory process, indicating stability in the fibroblast formation process and also presenting total re-epithelialization. Also presented higher collagen fiber deposition compared to the control group and the ointment group used during the evaluation period.

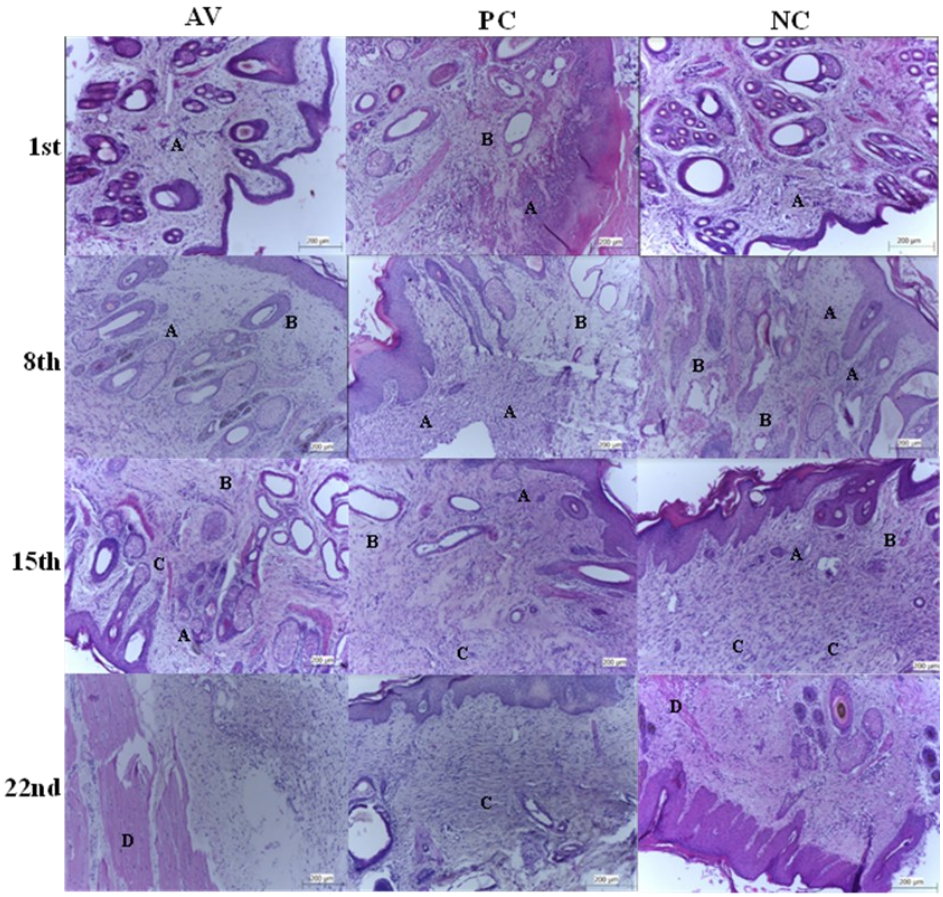

Figure 2: Photomicrographs of histological sections of skin wounds in sheep of NC, PC e AV groups on the 1st, 8th, 15th, 22nd days postoperatively with presence of mononuclear cells (A), edema (B), fibroblasts (C), collagen fibers (D) and the reepithelialization process can be noted. HE staining, scale: 200 µm (10x).

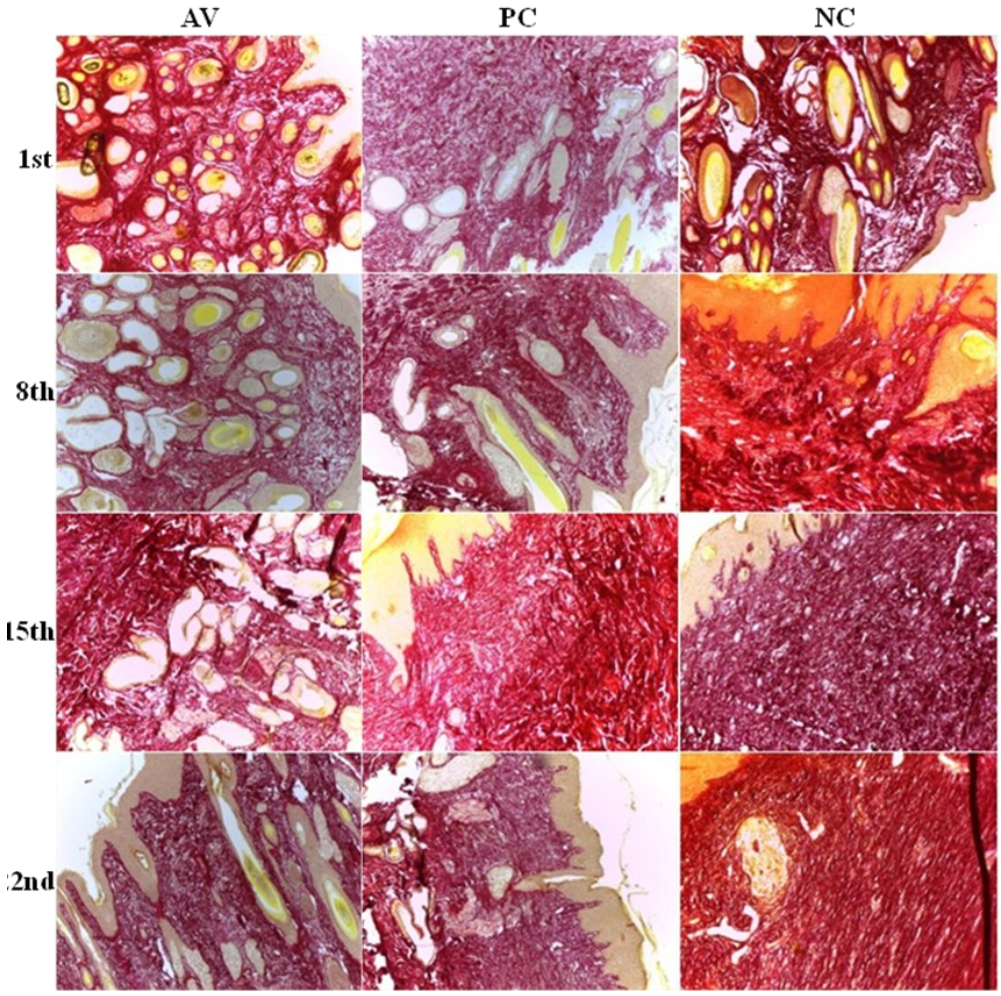

Figure 3: Photomicrograph of sheep skin, showing the arrangement and quantity of collagen fibers quantified of NC, PC e AV groups on the 1st, 8th, 15th, 22nd days postoperatively. Picrosirius Red staining, scale: 200 µm (10x).

In an experiment carried out by Gomes et al. (2016) [20], where they evaluated the effect of *Aloe vera* on wound healing by secondary intention, they observed that the lesions of the treated group healed in 7 days, while the other groups healed on day 14, which differs from the results presented. In a study conducted by Lizzi and Bragança (2021) [21], where he evaluated the tissue regeneration of post-surgical incisions in dogs and cats with the use of *Aloe vera*, he showed the effectiveness of its use after three weeks of the surgical procedure, where the *Aloe vera* group had a greater number of fibroblasts than the control group, in addition to presenting a greater amount of defense cells with reduced inflammation.

The presence of the inflammatory process during the 22nd postoperative day can be explained by the previous collections. However, even with this, it was possible to observe the process of re-epithelialization of the wound and the presence of collagen fibers. One of the functions of macrophages is to stimulate the formation of fibroblasts, consequently the synthesis of collagen [22].

The constituent of *Aloe vera* responsible for increasing macrophage activity and fibroblast proliferation, mannose-6-phosphate, increases its action in the remodeling phase, where fibroblasts are transformed into myofibroblasts that act in wound contraction [23]. The *Aloe vera* group showed higher collagen fiber deposition compared to the control and ointment groups used during the evaluation period. These results suggest that, in addition to the healing process being in the maturation phase, the deposition of these fibers in the extracellular matrix favored the re-epithelialization of the wounds, since epithelial migration is guided by collagen fibers [22].

Despite the promising results, certain limitations should be acknowledged. The relatively small sample size may reduce the statistical power of the findings and limit their generalizability. Additionally, the absence of an alternative control group treated with a different healing agent restricts comparisons between *Aloe vera* and other potential therapies. A strength of this study was the effective control of external variables that could influence wound healing, however, future studies should consider evaluating additional physiological variables, such as metabolic status or subclinical conditions, which may subtly affect the healing process.

Moreover, incorporating a cost-benefit analysis of the treatments would add practical value to the study. Depending on the associated costs, a treatment may prove less feasible in real-world applications. Further research should also explore different concentrations or formulations of *Aloe vera*, as well as its effectiveness in treating infected wounds. These approaches could provide a more comprehensive understanding of its therapeutic potential and inform its application in both veterinary and human medicine.

4. CONCLUSIONS

Based on the results obtained, it can be concluded that a 10% *Aloe vera* extract is effective for treating cutaneous wounds in sheep, as demonstrated by macroscopic and microscopic evaluation.

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