International Journal of Life Science Research Archive

ISSN: 0799-6640 (Online)

Journal homepage: https://sciresjournals.com/ijlsra/

(RESEARCH ARTICLE)

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Comparison of healing effects of aloe vera gel and aloe vera leaf pulp extract on burn-wound rats

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International Journal of Life Science Research Archive, 2023, 04(02), 006–013

Publication history: Received on 18 February 2023; revised on 29 March 2023; accepted on 31 March 2023

Article DOI: https://doi.org/10.53771/ijlsra.2023.4.2.0047

Abstract

Aloe Vera has anti-inflammatory, anti-oxidant, anti-viral, and anti-microbial properties. It has been demonstrated that Aloe Vera use could accelerate healing of burn injuries in rats. The current study evaluates the effects of Aloe Vera gel and Aloe Vera leaf pulp extract (LPE) alone and together with silver sulfadiazine on third degree burn wound injuries in rats. In an experimental study, 70 male Wistar rats weighing 200–250 g were divided into 7 groups to receive topical placebo, silver sulfadiazine, Aloe Vera gel, Aloe Vera LPE and their combination. Treatment results were evaluated according to wound healing on days 3, 10, and 21 and according to pathologic findings on day 21. Wound size differed significantly between groups on day 3 (p= 0.001), day 10 (p= 0.001), and day 21 (p= 0.001). The study's findings indicate that Aloe Vera gel alone, compared to LPE, and the combination of Aloe Vera gel or LPE with silver sulfadiazine had a more significant reduction in wound size. The combined treatment of Aloe Vera LPE and silver sulfadiazine has shown several advantages, including enhanced epithelialization and reduced cell infiltration, granulation tissue formation, and vascularization in the treatment of burns. However, additional research is necessary to determine the most effective treatment for third-degree burns.

Keywords: Aloe Vera; Burn; Wound healing; Chi-squared test; Rat

1 Introduction

Damage caused by burns is a public health problem worldwide, especially in underdeveloped and developing countries with limited medical facilities. Burn injuries are a significant cause of death and disability, with high healthcare costs. Although numerous antiseptics have been discovered, healing burn wounds is still a challenge for modern medicine. Burn management includes the hospitalization period, expensive treatments, multiple surgical operations, and an increased recovery period. These cares make burns costly, and every endeavor should be made to reduce inpatient care for burn patients (1).

Skin wound healing is done by skin contraction and epithelialization. Infection is one of the important complications of burns, which can result in more complications and cause the burn area to fail to heal. Therefore, different types of antibiotics are used to reduce the proliferation of microbes; however, their use can damage fibroblasts and keratinocytes and cause a delay in skin restoration (2, 3, 4, 5 and 6).

In addition to systemic antibiotic treatment, preventing the infection of the burn area by using local antibiotics reduces the degree of inflammation and damage and accelerates the healing process. Local use of antibiotics reduces the systemic side effects and further tissue penetration. Silver sulfadiazine is an essential local antibiotic, the most widely used drug in this field. This drug is oligodynamic; silver ions cause antimicrobial properties even in deep burns (7).

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In previous studies, different drugs have been used to reduce the damage caused by burns and speed up healing. One of these medicines is Aloe Vera, which is of the Liliaceae family. It has been shown that using Aloe Vera can accelerate the healing process after burn damage in rats. Furthermore, it has been indicated that Aloe Vera has anti-inflammatory, antioxidant, antiviral, and antimicrobial properties (8). The use of medicinal plants as medicinal substances and food supplements to improve general health and cure diseases has a special position. Aloe Vera, with the scientific name Aloe Barbadensis (Miller) and of the Liliaceae family, is one of the medicinal plants used since the old days and has numerous applications (9 and 10). The leaves of this plant contain a high concentration of anthraquinone compounds, which are used as laxatives in many countries (10 and 11).

Aloe Vera has many properties. Some of these properties include wound healing (12 and 13), anti-inflammatory (11 and 14), anti-cancer (9, 15, and 17), anti-diabetes (10, 11, and 18), antioxidant (19 and 20), and anti-ulcer (21). Aloe Vera effectively prevents inflammatory reactions by inhibiting the production of interleukin-6 and interleukin-8, reducing the adhesion of leukocytes, increasing the level of interleukin-10, and decreasing the level of a necrotizing factor in alpha tumors (11, 22 and 23). In animal models, Aloe Vera has been used for treating diabetes, wound healing, tumors, and inflammatory bowel disease (IBD) through injection and oral administration (13, 18, 23, and 24). Aloe Vera extract is widely used in cosmetic-health products due to its rejuvenation, healing, and emollient properties. Preliminary studies indicate that oral consumption of Aloe Vera gel reduces inflammation symptoms in patients suffering from ulcerative colitis. The compounds extracted from this plant have been used as an immune system stimulant, effectively treating cancer in cats and dogs. However, these experiments have not been scientifically studied on humans (25).

It should be mentioned that Aloe Vera extract has antibacterial (Streptococcus, Shigella) and antifungal effects. It has been shown that this plant extract inhibits the fungus causative agent that leads to tinea. The biologically active components in this plant's leaves include manan, polymanan, anthraquinone c-glycosides, and anthrone derivatives (25). When using Aloe Vera gel locally or orally, glucomannan, a polysaccharide enriched with mannose and gibberellin (a growth hormone), affects fibroblast growth factor receptors and stimulates their activity and proliferation, which in turn causes an increase in collagen production. Aloe Vera gel not only increases the amount of collagen in the wound, but it also changes the composition of collagen (mainly type III) and increases the collagen cross-links; as a result, wound healing is accelerated.

Furthermore, an increase in the synthesis of hyaluronic acid and dermatan sulfate in healing wounds after oral or local use of Aloe Vera has also been reported (8). Maenthaisong et al. (2007) observed that the healing period in the Aloe Vera group was 8.79 days shorter than that of the control group. Cumulative evidence indicates that Aloe Vera is a suitable intervention in healing burn wounds for first- to second-degree burns (25).

Oryan et al. (2010) evaluated the healing properties of Aloe Vera on the skin wounds of 40 rats, which were randomly divided into two groups. Treated animals showed insignificant wound contracture and histopathology improvement on the 10th day. A significant difference between the wound contractures of the two groups is observed after the 15th day. Lesions of the treated animals showed better alignment, less infiltration of inflammatory cells, and significantly improved biochemical properties on the 10th day. The results showed that using Aloe Vera liquid extract in open wounds causes wound contracture and facilitates healing (26).

To determine the wound healing and microcirculation effects of Aloe Vera in second-degree burn wounds in rats, Somboonwong et al. (2000) divided 48 male Wistar rats into 4 equal groups, including a control group, a group of rats with untreated burn wounds, a group of rats treated with normal saline, and a group of rats treated with Aloe Vera gel. On the 7th day, vasodilatation and the increased postcapillary vascular permeability observed in untreated wounds were significantly reduced in the normal saline and Aloe Vera groups. The stickiness of leukocytes was the same among the groups, and vascular contraction occurred after the wound was left untreated on the 14th day of study. Only in the groups treated with Aloe Vera did the arteriolar diameter usually increase, and the postcapillary vascular permeability was not different from the control group without burns. The degree of leukocyte stickiness was less compared to the untreated groups and the groups treated with normal saline. In addition, the healing area in the Aloe Vera group was better than the other two groups on the 7th and 14th days after the burn. This study states that Aloe Vera can cause wound healing and has anti-inflammatory effects on second-degree wounds (27).

Hosseini Mehr et al. evaluated Aloe Vera cream's effectiveness in treating thermal burn wounds in rats. They compared it to the results obtained in the group treated with silver sulfadiazine. On the 25th day, the average wound size was 5.5, 4, 0.78, and 4.1 square centimeters in the control, base, Aloe Vera, and silver groups, respectively. The wound size was significantly smaller in the Aloe Vera group compared to other groups. The histological comparison showed that Aloe Vera significantly increased re-epithelialization in burn wounds compared to other treated wounds. This study also

showed that Aloe Vera cream significantly increases re-epithelialization in burn wounds compared to the group treated with silver sulfadiazine (28).

Muller et al. (2003) investigated the effects of Aloe Vera and silver sulfadiazine on wound healing. They showed that the simultaneous use of Aloe Vera extract and silver sulfadiazine caused more tissue repair than using either of them alone (12). Khorasani et al. (2009) also conducted a clinical study to evaluate the effectiveness of Aloe Vera cream for burn wounds with a relative thickness and compared its results with the silver sulfadiazine group in 30 patients with similar types of second-degree burns in different parts of the body. In each patient, one wound was treated with silver sulfadiazine and one with Aloe Vera cream. The rate of re-epithelialization and repair of burns with a relative thickness was significantly faster in the area treated with Aloe Vera than in those treated with silver sulfadiazine (15.9 ± 2 and 18.73 ± 2.65 days, respectively). The areas of the patients' bodies treated with Aloe Vera were restored entirely in less than 16 days, compared to 19 days with silver sulfadiazine. These results clearly show the evidence and excellent effect of Aloe Vera cream compared to silver sulfadiazine cream in treating second-degree burns (29).

According to the previous studies as well as the proof of the beneficial effect of this plant in healing burn wounds, we decided to study and compare the effect of the simultaneous use of Aloe Vera gel and Aloe Vera leaf pulp extract (LPE), comparing them with each other according to their simultaneous use with silver sulfadiazine, on the burn damage in rats so that its results can be used in the preparation of a more efficient product made out of the different parts of this plant to be used clinically in the future. The study aims to compare the effect of Aloe Vera gel extract with the extract obtained from leaf pulp in healing burn wounds in rats. The specific aims of the study are:

- To determine the effect of using the gel obtained from the subcutaneous tissue of Aloe Vera and LPE obtained from its deep tissues in healing burn wounds.
- To compare the effect of the gel obtained from the subcutaneous tissue of Aloe Vera with silver sulfadiazine in healing burn wounds.
- To compare the effect of the extract obtained from the leaf pulp of Aloe Vera with silver sulfadiazine in healing burn wounds.

On the basis of the results of the present study, it would be possible to provide useful medicinal products obtained from the different parts of this plant for healing burn wounds, and in the future, they can be used for the production of medicine. We hypothesize that there is difference between the two types of products obtained from Aloe Vera and silver sulfadiazine in healing third-degree burn wounds.

2 Material and methods

70 male Wistar rats weighing 200–250 g were purchased from Pasteur Animal Care Center and kept in the animal center of the Applied Pharmaceutical Research Center. The selection of the sample size was made based on the previous studies carried out in this field. The mice were divided into seven groups of 10, as follows:

- The group receiving the topical product without effective substances;
- The group receiving the topical product containing silver sulfadiazine;
- The group receiving the topical product containing Aloe Vera gel;
- The group receiving the topical product containing Aloe Vera LPE;
- The group receiving the topical product containing silver sulfadiazine and Aloe Vera gel;
- The group receiving the topical product containing silver sulfadiazine and Aloe Vera LPE; and
- The group receiving the topical product containing Aloe Vera gel and Aloe Vera LPE.

The diet of all rats and the method of maintaining them were exactly the same, and there was no difference among them. Ketamine 50 mg/kg and Xylazine 10 mg/kg were used to sedate the rats, and their hair was shaved from the neck to the back. To induce burns, a metal plate with a diameter of 2 cm was prepared at a temperature of 100 degrees centigrade; then, it was placed on the backs of the rats in an anesthetized state for 20 seconds, and a standard 3rd-degree burn was created. After the burn was formed, the treatment was done with two methods: Aloe Vera, LPE, and silver sulfadiazine (1%) as described below. In order to prepare the topical product containing Aloe Vera gel extract, first, the gel is obtained from the leaf and is completely dried by a rotary operator; finally, the topical product containing a dry extract of Aloe Vera gel is prepared on carbopol, and is packed in 30-gram tubes.

Furthermore, to prepare the topical product containing the pure Aloe Vera leaf pulp extract (LPE) extract, Aloe Vera leaves are thoroughly dried in the laboratory environment away from direct sunlight. Then, they are changed into fine powder. Then, the obtained powder is distilled by the maceration method with the help of a hydroethanolic solvent (70%). The distillation process is repeated three times, and a rotary evaporator machine entirely dries the obtained extract under low pressure. A topical product containing dry Aloe Vera leaf extract (5%) is prepared on Carbopol base and is packed in 30-gram tubes.

After using two types of products and the silver sulfadiazine drug, at least on the 21st day, the rats were euthanized with sodium thiopental, and a biopsy was prepared from the wound area; the pathologist analyzed the samples taken in terms of the number of vessels, collagen deposition in the wound bed, the degree of acute inflammation, and the degree of chronic inflammation. During the study, one case from group 1 and one from group 7 died after day 3, and the remaining study was continued with 68 rats. The studied variables include the number of vessels, collagen deposition, degree of acute inflammation, and degree of chronic inflammation.

All the procedures and investigations followed the Iranian Society for Laboratory Animals guidelines and the principles of laboratory animal care (No. 86-23, revised 1985, Publication NIH). All rats were examined under complete anesthesia and after anesthesia. A veterinarian was mandatorily present in all stages, and at the time of extermination, all rats will have free access to water and food.

3 Discussion

All collected data were analyzed using SPSS 16 statistical software. Descriptive statistical methods (frequency, percentage, mean, standard deviation) were used for statistical investigations. A Chi-squared statistical test was used to compare the qualitative findings. Furthermore, the Kruskal-Wallis non-parametric statistical test was used to compare the quantitative findings among the groups. A P value less than 0.05 was considered significant in the present study. Figure 1a shows the size of the wound on the 3rd day after the burn. As it can be seen in the graph, there is a statistically significant difference among the groups in terms of wound size ($p = 0.001$). However, no significant statistical difference was observed in comparing the results among different groups. Figure 1b shows the size of the wound on the 10th day after the burn. In this case, a statistically significant difference was observed among the groups regarding the wound size ($p < 0.001$). Figure 1c shows the size of the wound on the 21st day after the burn. As it can be seen in the graph, there is a statistically significant difference among the studied groups ($p < 0.001$).

70 cases of male rats were studied in 7 groups. Furthermore, the wound size in the group without an effective substance was significantly smaller than the wound size in the groups containing Aloe Vera and LPE ($p = 0.001$) and silver sulfadiazine and Aloe Vera gel ($p = 0.001$), and also in the Aloe Vera gel group in comparison to the groups containing Aloe Vera LPE ($p = 0.01$) and silver sulfadiazine and Aloe Vera gel ($p = 0.005$).

It was also observed that the size of the wound in the group without an effective substance was significantly smaller than the wound size in the silver sulfadiazine group ($p = 0.002$), the Aloe Vera gel group ($p = 0.006$), the Aloe Vera LPE group ($p < 0.001$), and the group with a combination of Aloe Vera gel and silver sulfadiazine ($p < 0.001$).

Furthermore, the size of the wound was significantly smaller in the silver sulfadiazine group, compared to the Aloe Vera extract group ($p<0.001$), in the Aloe Vera gel group, compared to the Aloe Vera extract group ($p<0.001$), in the group with a combination of Aloe Vera gel and silver sulfadiazine, compared to the Aloe Vera extract group ($p =0.03$), compared to the group with a combination of Aloe Vera extract and silver sulfadiazine ($p=0.002$) and the group with a combination of Aloe Vera gel and extract ($p=0.005$), also in the group with a combination of Aloe Vera extract and silver sulfadiazine, compared to the Aloe Vera extract group ($p= 0.002$), and also in the group with a combination of Aloe Vera extract and gel, compared to the group of Aloe Vera extract alone ($p<0.001$). Figure 1 shows the size of the wound on (a) 3rd day (b) 10th day and (c) 21st day after the burn.

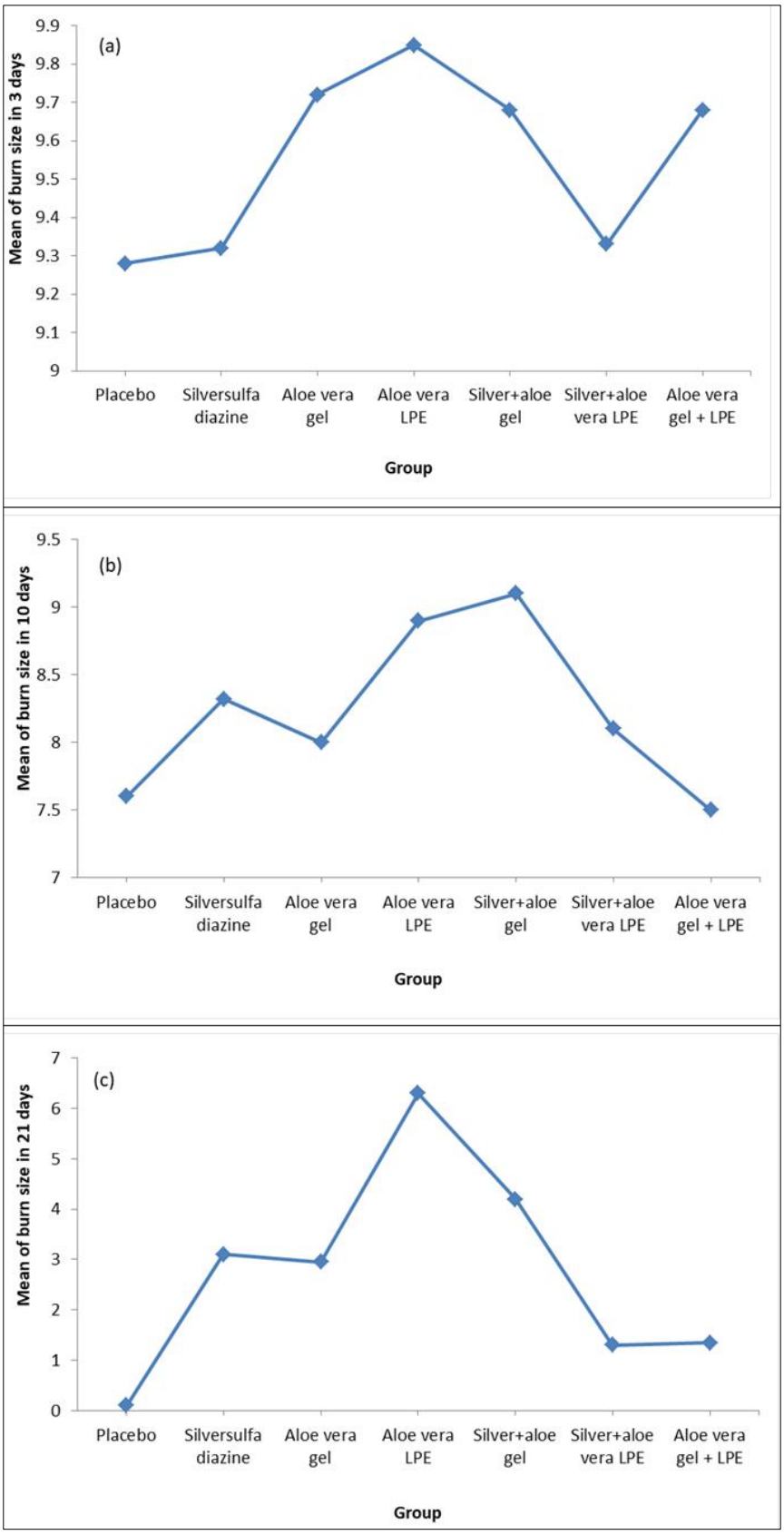

Figure 1 The size of the wound on (a) 3rd day (b) 10th day and (c) 21st day after the burn

Figure 2 shows the degree of hair growth in the studied groups. Due to the disproportionate distribution of the data, it was not possible to evaluate the statistical difference; however, it can be seen that in most groups, the hair growth was avarage (≤ 2).

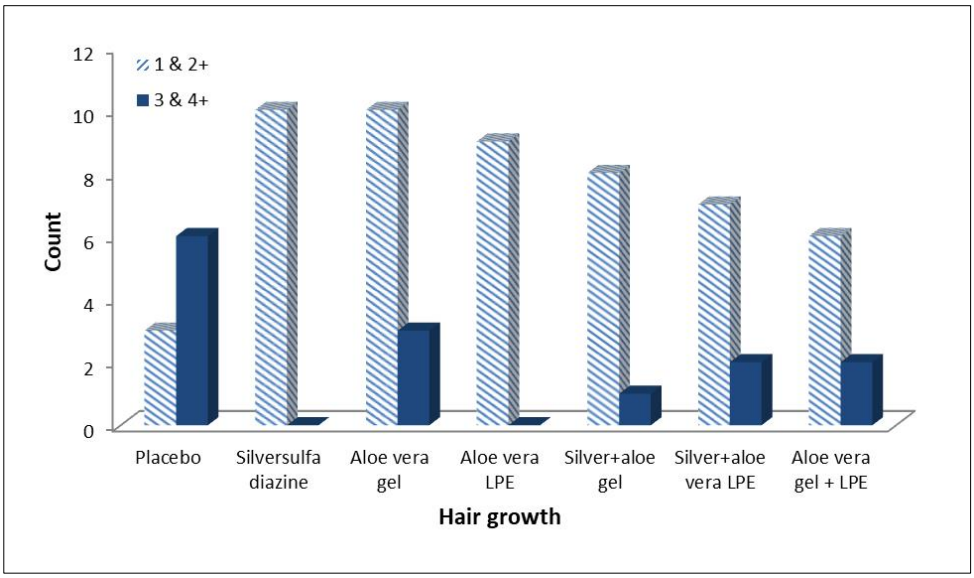

Figure 2 The amount of hair growth in the studied groups

Table 1 shows the pathological findings among the studied groups. It was not possible to evaluate the statistically significant difference among the groups due to the disproportionate distribution of the data. However, as can be seen in the table, the amount of appropriate epithelialization has been the highest in the group without an effective substance and the group with a combination of Aloe Vera LPE and silver sulfadiazine, and in the next level, in the group with a combination of Aloe Vera LPE and gel. In addition, the degree of the inflammatory response has been of the lowest degree in the above case. The amount of granulation tissue formation in the groups receiving Aloe Vera gel and also in the group with a combination of Aloe Vera gel and silver sulfadiazine has been the highest. In the aforementioned two cases, there was the highest inflammatory response. Moreover, proper vascularization has been the highest degree in the group with a combination of Aloe Vera gel and silver sulfadiazine.

Table 1 Pathological findings between the studied groups

Group	Epithelialization		Inflammatory response		Formation of granulation tissue		Vascularization	
	without	appropriate	without	appropriate	without	appropriate	without	appropriate
1	0	100%	100%	0	100%	0	66.7%	33.3%
2	30%	70%	50%	50%	50%	50%	50%	50%
3	70%	30%	30%	70%	30%	70%	70%	30%
4	70%	30%	30%	70%	100%	0	50%	50%
5	90%	10%	10%	90%	30%	70%	30%	70%
6	0	100%	100%	0	100%	0	100%	0
7	22.2%	77.8%	77.8%	22.2%	77.8%	22.2%	100%	0

4 Conclusion

The study found that Aloe Vera gel, Aloe Vera leaf pulp extract (LPE), and silver sulfadiazine either alone or in combination had different effects on reducing the size of wounds in third-degree burns. On the third day after treatment, there was a statistically significant difference among the groups in terms of wound size. However, on the 10th and 21st days after treatment, significant differences were observed. Aloe Vera gel alone, compared to LPE, and the combination

of Aloe Vera gel or LPE with silver sulfadiazine had a more significant reduction in wound size on the 10th day. On the 21st day, the size of the wound was significantly reduced in the silver sulfadiazine group and the Aloe Vera gel group. Combined treatment with Aloe Vera LPE and silver sulfadiazine had advantages such as more epithelialization and less cell infiltration, granulation tissue formation, and vascularization.

In summary, this study has the potential to benefit society by providing new and effective treatments for burn injuries. However, further research is needed to determine the safety and efficacy of Aloe Vera in humans before it can be widely used in clinical practice.

Compliance with ethical standards

Acknowledgments

The Authors wish to acknowledge National Veterinary Research Laboratory Iran for their technical support and research equipment.

Disclosure of conflict of interest

We declare that we have no conflicts of interest to disclose.

Statement of ethical approval

We confirm that the appropriate ethical approval was obtained from the Iranian Society for Laboratory Animals guidelines and the principles of laboratory animal care (No. 86-23, revised 1985, Publication NIH) and the study was conducted in accordance with their guidelines.

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