Investigation Effect of *Aloe Vera* in Fresh Gel Form on Rabbit's Model Wound

ABSTRACT

Background : Aloe is plant possessing a great therapeutic potential in folk medicine in Yemen namely *Aloe vera* used as a multipurpose skin treatment .

Objective: Therefore, the aim of this study was to investigate the effect of topical *Aloe vera* gel in fresh form on the wound healing of rabbit model in comparison with Mebo .

Methods : The experimental animals as model of excision wound that were classified into four groups. The 1st group was not treated as control , the 2nd group was treated with placebo (petroleum gel) , the 3rd group was treated with Mebo as drug standard , and the 4th group was treated with *Aloe vera* gel in fresh form. This study was carried out in Sana'a city during the period of three weeks . The healing parameters were epithelization period (scar fall day) and percentage of wound contraction (%) and the data obtained were analyzed.

Results : The results showed that the significant different between study group ($p < 0.05$) and the effect of this plant on increase in the percentage (%) of wound contraction was better than the standard drug (Mebo) group and other groups. On the other mean, on the 16th day, the percentage of wound contraction of the treated group with *Aloe vera* was 100 % while in treated group with Mebo was 97.6%. In addition, in placebo and control groups were 76.6 % and 73.8 %, respectively.

Conclusion : Finally, from these findings it could be concluded that application of *Aloe vera* gel in topically administered to an open wound induces significant wound contraction and accelerates wound healing and this herbal may be a promising medication for open wounds.

Keywords : *Aloe vera* , Wound

1. INTRODUCTION

Several plants were tested pharmacologically activity (anti-inflammatory , anti-microbial , anti-diabetes …etc) in Yemen [1 - 4] . This study presents the genus *Aloe* that belongs to the family

Xanthorrhoeaceae that was already mentioned more than 4000 years ago in a collection of Sumerian clay tablets dated 2100 BC [1] . *Aloe* was also mentioned as a laxative in the Egyptian Papyrus Ebers from 1552 BC [2] . *Aloe vera* contains 75 potentially active constituents: vitamins, enzymes, minerals, sugars, anthraquinones , hormones ,lignin, saponins, salicylic acids and amino acids [3 - 5]. Externally, fresh aloe gel often has a very good effect in acne, pimples, eczema and other skin problems, poorly healing wounds, leg ulcers, burns due to excessive heat, sun exposure and in the treatment of radiation dermatitis. Internally, aloe juice can be used in gastro-enteritis and peptic ulcers [6 – 7] . The aim of this research was to study the effect of *Aloe vera* in fresh gel form on wound healing in rabbits in comparison with Moist Exposed Wound Ointment (MEBO) of Julphar Gulf Pharmaceutical Industries, UAE., and SanTou Mebo Pharmaceutical co., ltd., China that reduces evaporation from the wound surface, thereby offering a moist environment for wound healing, Mebo were invented two decades ago by Xu Rong-Xiang of the Beijing Chinese Burn [8] .

2. MATERIALS AND METHODS

2.1. Materials

Mebo was obtained from MSD (UK) in ointment form (Positive control). Ether was supplied from Merck (Darmstadt, Germany) as anesthetic agent to control animals to easy handling . Chlorine solution to mix with clean water and washing *Aloe vera* leaf. Chloroform of Merck (Darmstadt, Germany) was used for sacrificing animals at end of study. Alcohol 70 % as anti-septic agent. Petroleum jelly of Merck (Darmstadt, Germany) was used for dressing the excision wound in group II animals. *Aloe vera* plant from mountain around Sana'a city (Yemen). Sterile cotton , forceps , scraper (spoon) , blender , Knifes , surgical gloves , surgical blade , Gauze swab , electric shaver , weight balance , transparent plastic sheet , permanent markers, graph papers millimeter , digital camera , fine-tipped pen , microscope , clear water , glass container , and metallic dish.

2.2. Preparation Assay

Aloe vera on fresh gel form is the colourless mucilaginous gel obtained from the parenchymatous cells in the fresh leaves of Aloe vera (Liliaceae). At present no commercial preparation has been proved to be stable. Because many of the active ingredients in the gel appear to deteriorate on storage, the use of fresh gel is recommended. Preparation of fresh gel: harvest leaves and wash them with water and a mild chlorine solution. Remove the outer layers of the leaf including the pericyclic cells (Figure 1- A), leaving a "fillet" of gel. Peel the gel and scoop out gel with a spoon (Figure 1- B). Place into a blender (Figure 1- C). Place in a sterilized, clean glass jar, will keep for several months in the refrigerator

(Figure 1- D). . Care should be taken not to tear the green rind which can contaminate the fillet with leaf exudate. *Aloe vera* gel could be kept in the refrigerator to keep it fresh for about 3 months [9] .

Figure 1 : Preparation Assay of Aloe Vera *in Fresh Gel Form*

2.3. Animals handling

Healthy Male rabbits weighing 500 g obtained from Yemen region (Amran city) housed individually with controlled light ,temperature and humidity. before beginning the experiments the animals will be allowed to acclimatize to animal house condition for a period of one week.

2.4. Study design

This pilot study was conducted in four group to determine the effect of topical *Aloe vera* in fresh gel form on rabbit's model of incision wound selected from Yemen where it remains the most frequently used traditional therapeutic to treat the wound . The 1st group (negative control) that the wound was not treated . The 2nd group (placebo) that , the wound was treated with petroleum jelly only . The 3rd group (positive control) that the wound was treated with Mebo ointment ,and the 4th group (tested group) that the wound was treated with the *Aloe vera* gel.

2.5. Wound indication

The rabbits were anesthetized with Ether (Merck, Darmstadt, Germany). this type of anesthesia prevents any movement of the animals, therefore animals were left without being restrained. Hair was

removed by shaving the dorsal back of the rabbit. Ethanol (70%) was applied as antiseptic for the shaved region before wound creation and an excision wound was done by removing a 7x7 mm full thickness piece of the skin from predetermined shaved area on the back of each animal [10] .

2.6. Dose administration

100 % of *Aloe vera* in fresh gel form was applied topically throughout the lesion surface using sterilized tools. The treatment schedule was twice a day for period of 14 days. The photographs on wounds were taken from 4 groups at 0 day,7th day , 14th day , and 16th day . Excessive handling of animals were avoid as it may interfere with the healing process. Proper care was take to avoid infection from external sources [11].

2.7. Measures parameters

The parameters observed were the percentage of wound contraction (%) and the period of epithelization (Day) . The size of lesions (Area) was determined at paper every alternative day after wound excision was well apparent. At this time, each test animal was held in a good position and wound margin was traced on a transparent plastic sheet using a fine-tipped pen without causing any damage to the wound area. Lesion body area was displayed as mm^2 on each experiment day. The area of the wounds on the 1st day was considered as 0 % and the wound areas on subsequent days were compared with the wound area on the first day by the following equation :

$$\text{Wound Closure (\%)} = \frac{\text{Wound area on day (0) - Wound area on day (n)}}{\text{Wound area on day (0)}}$$

Where , n= numbers of days (0th , 2nd , 4th ,6th ,8th ,10th ,12th ,14th , and 16th) . It was monitored by noting the number of days required for the scar to fall off from the excision wound surface without leaving a raw wound behind. the period of epithelization of the wound was expressed as the number of days taken for complete epithelization witch clarify microscopically [12].

2.8. Data analysis

All the values were expressed as the mean ± SD. The data obtained through careful observation were analyzed by one way ANOVA. In addition , T – test were applied in this study at final day of healing. All analyses were performed using SPSS 13.0 (SPSS Inc.,Chicago, IL, USA) and Excel software 2010 . The *p* value of less than 0.05 was considered as significant.

3. RESULTS

Effect of topical *Aloe vera* in fresh gel form on rabbit's model of incision wound in comparison with Mebo was studied and the results were summarized in Table 1. The effect of this plant on increase in the percentage of wound contraction was better than the standard drug (Mebo) group and other groups. On the other mean, on the 16th day , the percentage of wound contraction of the treated group with *Aloe vera* was 100 % while in treated group with Mebo was 97.6% . In addition, in placebo and control groups were 76.6 % and 73.8 %, respectively. On the other hand , the mean period of epithelization (scar fall day) was found to decrease significantly ($p < 0.001$) in treated group with the *Aloe vera* in comparing with all excision wound groups , however the results showed that *Aloe vera* in fresh gel form had healing effect 100 % at the 16th day while the healing effect of Mebo was 100 % at 18th day. Based on parametric test namely T – test , the result showed that non – significant difference ($p > 0.05$) between Mebo and *Aloe vera* at 16th day . In addition , based on non – parametric test namely Wilcoxon test , the result showed that non – significant difference ($p > 0.05$) both products at each day . This result due to the Wilcoxon test more robust than T – test .

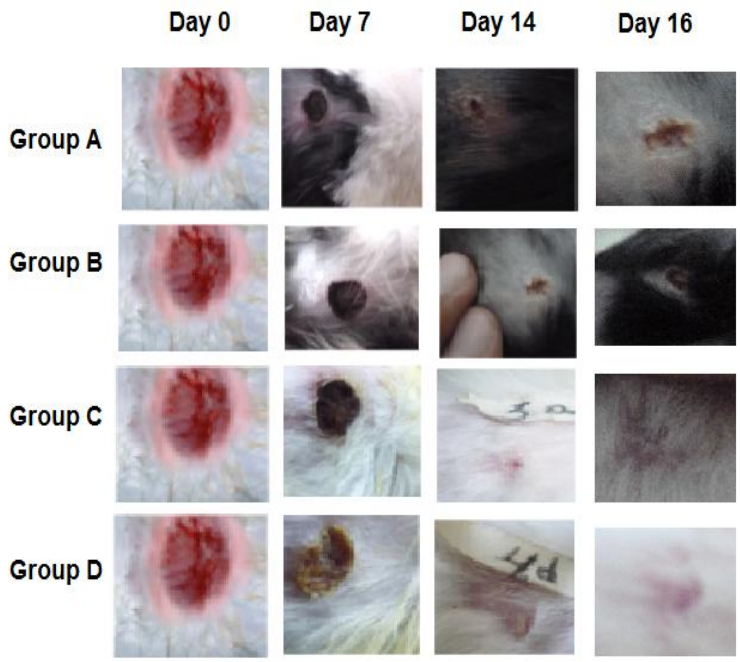

Figure 2 : Wound contraction of normal control, placebo , Mebo , and *Aloe vera* groups

Table 1 : Effect of *Aloe vera* in fresh gel form on wound contraction mean ± Sd (n = 6)

Group	Treatment	Day 0	Day 2	Day 4	Day 6	Day 8	Day 10	Day 12	Day 14	Day 16
Group 1	Control	0	9±0	18.4±0.55	28±0	37.4±0.55	46.4±0.55	55.4±0.55	64.8±1.1	73.8±1.1

Group 2	**Placebo**	**0**	**9.4±0.55**	**18.8±1.1**	**29.2±1.64**	**38.6±2.19**	**48±2.74**	**57.4±3.29**	**66.8±3.83**	**76.6±4.930**
Group 3	***Aleo vera***	**0**	**13.4±0.55***	**26.6±2.19***	**40±2.74***	**53.4±3.29***	**66.2±4.38***	**80±5.48***	**93.4±6.025***	**100±0***
Group 4	**Mebo**	**0**	**13±1.22***	**26±3***	**39±4.18***	**52±5.39***	**64.6±6.69***	**78±8.37***	**91±9.57***	**97.6±5.37***

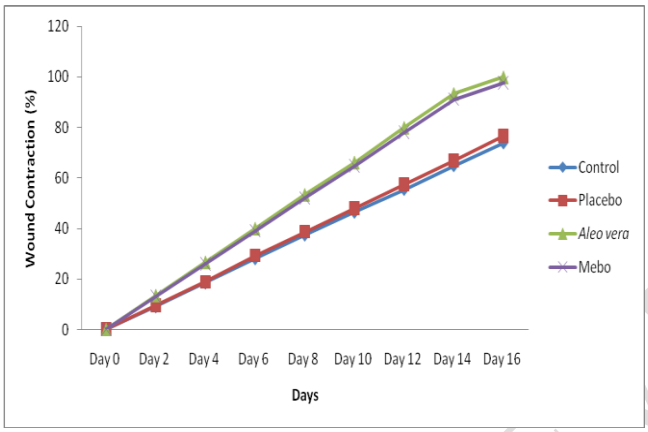

Figure 3 : Effect of *Aloe vera* in fresh gel form on wound contraction mean ± Sd (n = 6)

4. DISCUSSION

The wound healing is a response to injured tissue that results in the restoration of tissue integrity [12] . Several mechanisms have been proposed for the wound healing effects of aloe gel, which include keeping the wound moist, increase epithelial cell migration, more rapid maturation of collagen, anti-inflammatory , immunostimulation effects, wound healing, promotion of radiation damage repair, anti-oxidant effects , anti-bacterial, anti-viral, and anti-fungal [13,14] . This study included testing of *Aloe vera* gel in fresh form on one model of experimentally induced wound , namely, Rabbit's model of incision wound . The appropriate therapeutically concentration was 100 % of extract of the tested plant produced the optimum and maximal effect. The present study showed that *Aloe vera* gel was the best effect on wound healing comparing with other group (100% on 16th day) . Our results were supported from previous published studies. *Aloe vera* may be effective in the treatment of wounds by Vogler and Ernst, [15] . *Aloe vera* promotes the rates of healing that was described by Heggers *et al* and Davis *et al*, 1989 [16,17] . It has been claimed that the polysaccharides in *Aloe vera* gel have therapeutic properties such as anti-inflammatory , immunestimulation effects, wound healing, promotion of radiation damage repair, anti-oxidant effects , anti-bacterial, anti-viral, and anti-fungal [13,14] [19] [20] The enhanced rate of wound contraction and reduction in healing time in treated rabbits might be due to the anti-inflammatory effects of this material together with its effect on maturation and organization of the granulation tissue [21 - 25]. In addition , the Mannose-6-

phosphate has been introduced as the active part of *Aloe vera* responsible in wound healing [26]. On the other hand , in previous studies on mice, *Aloe vera* polysaccharides preserved the number and morphology of immunosuppressive and dendritic cells in skin damaged by ultraviolet exposure [27] . Compounds extracted from *Aloe vera* may act as an immunostimulant in cats and dogs [28]. A number of studies indicated immunomodulating activities of the polysaccharides in *Aloe vera* gel, and suggested that these effects occur via activation of macrophage cells to generate nitric oxide, secrete cytokines (e.g. tumour necrosis factor-alpha (TNF-α) interleukin-1 (IL-1) , IL-6 and interferon-γ (INF-γ) and present cell surface markers [29] . A glycoprotein that was isolated from *Aloe vera* showed an increase in cell migration and accelerated wound healing in a human keratinocyte monolayer. In a raft culture it exhibited stimulation of epidermal tissue formation as well as marked expression of proliferation markers on the immunohistochemical level. The enhanced wound healing effect and cell proliferation of this glycoprotein fraction was confirmed in hairless mice [30] .

Skin damage from radiation treatments has successfully been treated with *Aloe vera* gel [32 , 32] . However, *Aloe vera* extracts might have antibacterial and antifungal activities, which possibly could help treat minor skin infections [33,34] . *Aloe vera* and other plants that contain anthraquinones have an antiseptic effect against a number of bacteria and fungi, e.g. *staphylococci*, *streptococci*, and *Candida albicans* fungi [35,36] . Anthraquinones isolated from the exudate of *Aloe vera* have shown wide antimicrobial activity. The antibacterial activity of emodin against Gram-negative was proposed to be mediated through inhibition of solute transport in membranes [37] .

In a study where the moisturizing effects of cosmetic formulations containing different concentrations of lyophilised *Aloe vera* gel were studied, showed that only formulations with higher concentrations . It was proposed that the *Aloe vera* gel containing products improved skin hydration possibly by means of ahumectant mechanism [38] . Moghbel *et al*. reported that the rate of wound healing of burn wounds treated with *Aloe vera* gel was 50 % faster than routine treatment with silver sulfadiazine. They were not able to propose the exact mechanisms of the action of *Aloe vera* natural gel on burn wounds but suggested that the mannose-6-phosphate present in *Aloe vera*, which contains glucose and mannose chains may be effective in improving the healing rate [39] .

Aloe vera gel was reported to increase microcirculation to the burn area, causing vasodilation and increased post-capillary venular permeability [40] . Also the our study showed the beneficial effects of the *Aloe vera* on the morphology of dermal wound healing in rabbits on days 16 and low scar formation. which are shown in (Figure 1). Low scar formation in rabbits treated with

fresh *Aloe vera* gel might be due to enhanced epithelization facilitated by fresh *Aloe vera* gel ingredients. the study supported these findings, where fresh *Aloe vera* gel was reported significant feature in the treated group was that their newly formed collagen fibers were aligned and were not randomly distributed as in the untreated lesions and reducing the number of adventitious phagocytic cells in the area [27] . [41] [42] . Also study showed that *Aloe vera* cream was more effective than silver sulfadiazine in treating second degree burns [43] **.** In addition , a previous review concluded that the cumulative evidence supports the use of *Aloe vera* for the healing of first to second degree burns [44] .It was proposed that the *Aloe vera* gel containing products improved skin hydration possibly by means of ahumectant mechanism [45] . *Aloe vera* contains vitamins and minerals (including vitamin C, E, and zinc) reported to be beneficial in wound healing [46] .

Aloe vera also contains enzymes, glycoproteins, growth factors, vitamins and minerals [47] that have been shown to improve healing with enhanced epithelization and rapid formation and maturation of granulation tissue in burn wounds [47] . It has been stated that insulin-like growth factor II and mannose-6-phosphate bind to the same receptor on the fibroblast [48] . Finally , our experiment the *Aloe vera* gel was used by fresh prepared method due to avoid deterioration of active ingredients. At present no commercial preparation has been proved to be stable. Because many of the active ingredients in the gel appear to deteriorate on storage, the use of fresh gel is recommended [10]. The enzymes in *Aloe vera* are destroyed at temperatures above 70° C. Therefore carefully made extracts therefore have the greatest effect, while heated, powdered dry extracts have much weaker, or even negative effects [49] . The study supported these findings, the polysaccharides found in *Aloe vera* gel are not stable, especially under stress conditions such as heat, the presence of acid and enzymatic activities. It has been suggested that a standardized method is necessary for production of *Aloe vera* gel products to avoid degradation of the polysaccharides and thereby preventing the removal of high molecular weight molecules. This standardized and consistent production process is vital for preserving the natural biological activity of the *Aloe* gel [50] .

CONCLUSION

Finally, from these findings it could be concluded that application of *Aloe vera* gel in topically administered to an open wound induces significant wound contraction and accelerates wound healing and this herbal may be a promising medication for open wounds.

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