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Review Article

The Effect of Aloe Vera Clinical Trials on Prevention and Healing of Skin Wound: A Systematic Review

CME Article

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Abstract

Background: Aloe vera is an herbaceous and perennial plant that belongs to the Liliaceae family and used for many medicinal purposes. The present study aimed to systematically review clinical trials regarding the effect of Aloe vera on the prevention and healing of skin wounds.

Methods: To identify all related published studies, we searched SID, IRANDOC, Google Scholar, PubMed, MEDLINE, Scopus, Cochrane Library, and ScienceDirect databases in both the English and Persian languages from 1990 to 2016. The keywords used were Aloe vera, wound healing, and prevention. All clinical trials using Aloe vera gel, cream, or derivatives that included a control group with placebo or comparison with other treatments were included in the study. The PRISMA checklist (2009) was used to conduct the review.

Results: In total, 23 trials that met the inclusion criteria were studied. The results of the studies showed that Aloe vera has been used to prevent skin ulcers and to treat burn wounds, postoperative wounds, cracked nipples, genital herpes, psoriasis, and chronic wounds including pressure ulcers.

Conclusion: Considering the properties of Aloe vera and its compounds, it can be used to retain skin moisture and integrity and to prevent ulcers. It seems that the application of Aloe vera, as a complementary treatment along with current methods, can improve wound healing and promote the health of society.

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Keywords ● Aloe ● Clinical trial ● Wound healing ● Prevention ● Wounds and injuries ● Systematic review

What's Known

- Aloe vera is a medicinal plant, traditionally used to improve skin integrity.
- Aloe vera is known for its anti-inflammatory, skin protection, anti-bacterial, anti-viral, antiseptic, and wound healing properties.

What's New

- Aloe vera can be used to retain skin moisture and integrity, and to prevent ulcers. However, there are limited studies on this topic.
- The use of Aloe vera to improve wound healing is recommended as the main or complementary treatment alongside other methods.

Introduction

The process of wound healing is a complex biological process and promotion of tissue recovery is the main objective of medical interventions. Skin lesions are caused due to different reasons such as burns, arterial diseases, surgery, and trauma.[1] Wound healing is a dynamic process that takes place in three phases. The first phase is inflammation, congestion, and leukocyte infiltration. The second phase involves the removal of dead tissue and the third phase of proliferation includes epithelial regeneration and fibrous tissue formation.[2] Several studies on Aloe vera have been conducted and shown to be effective in the prevention and healing of skin wounds.

Aloe vera is a medicinal plant traditionally used since 1500 BC in many countries such as Greece, China, and Mexico. It also has

been used for centuries as a traditional medicine for various diseases and skin lesions.[3] Aloe vera is an indigenous plant from tropical Madagascar, Saudi Arabia, and Iran. It belongs to the Liliaceae family; it is similar to Cactus and is an herbaceous and perennial plant with thick, fleshy and long leaves. The Egyptian queens Nefertiti and Cleopatra used Aloe vera as part of their regular beauty regime.[4] So far, 75 known compounds have been identified in Aloe vera, including 20 minerals, 20 amino acids, vitamins, and water.[5, 6] In vitro studies and studies conducted on living organisms have shown that Aloe vera can inhibit thromboxane (an inhibitor of wound healing), improve the wound healing process, and reduce inflammation.[3, 7] Magnesium lactate available in the gel can prevent the production of histamine that causes itching and irritation of the skin.[8, 9] It also enhances the immune system and the synthesis of cytokines. Aloe vera is effective in inhibiting inflammatory reactions by the inhibition of IL-6 and IL-8, the reduction of leukocyte adhesion, an increase of IL-10 levels, and decrease of TNF alpha levels.[10] Its regenerative properties are due to the compound glucomannan, which is rich with polysaccharides like mannose. Glucomannan affects fibroblast growth factor receptors and stimulates their activity and proliferation, which in turn increases the production of collagen. Aloe vera gel can not only increase the amount of collagen in wounds but also change the composition of collagen, increase collagen cross-linking and thereby promote wound healing.[11] Scientific studies have shown that the gel can increase the flexibility and reduce the fragility of the skin since 99% of the gel is water.[4] Additionally, mucopolysaccharides along with amino acids and zinc present in Aloe vera can lead to skin integrity, moisture retention, erythema reduction, and helps to prevent skin ulcers.[12] Several studies have shown the positive effects of Aloe vera to treat wounds such as psoriasis, mouth sores, ulcers, diabetes, herpes, bedsores, and burn wounds.[1, 4, 6, 13-15] Aloe vera is known for its anti-tumor, anti-inflammatory, skin protection, anti-diabetic, anti-bacterial, anti-viral, antiseptic, and wound healing properties.[6]

Considering the availability of several clinical trials on the effect of Aloe vera on the prevention and healing of skin wounds, as well as its popularity among people and widespread use in the cosmetic industry, the present study aimed to review research studies on this topic.

Materials and Methods

Search Strategy

The present study is a review of clinical trials on the effect of Aloe vera in preventing and healing of skin wounds. Articles published in both national and international journals were considered. Articles published online (1990-2016) were selected from the national databases (SID, IRANDOC) and international databases (Google Scholar, PubMed, MEDLINE, Scopus, Cochrane Library, and ScienceDirect). Moreover, the references of the identified articles were searched for additional sources of information. The used keywords were Aloe vera, wound healing, and prevention. All keywords were searched electronically, the titles and abstracts of all identified articles were screened, and duplicated articles were omitted. Each article was independently screened by four reviewers and possible disagreements were resolved in a joint review meeting. The language of the articles was either Persian or English.

Inclusion Criteria

All clinical trials using Aloe vera gel, cream, or derivatives that included a control group with placebo or comparison with other treatments were included in the study. The sample size of at least 30 cases was considered sufficient.

Exclusion Criteria

All studies using animal models, lack of access to full text, lack of transparency of statistical results, and sample size less than 30 cases were excluded.

Methodological Appraisal

The PRISMA checklist (2009) was used to conduct the review. Articles that were performed on animals, duplicated articles, non-transparent statistical results (without mean, standard deviation, confidence interval, test, P value, etc.), incomplete articles (duration of intervention, dosage, frequency, lost to follow-up, type of control groups, number of treatment sessions, and with no results based on its goals), and all articles with less than 30 sample size were removed. Eventually, 23 trials that met the inclusion criteria were studied (figure 1).

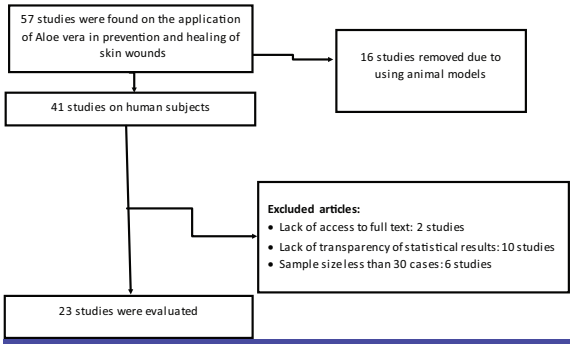

Figure 1: The PRISMA checklist for article selection.

Data Extraction

Data such as the author's name, year of publication, study region, study design, sample size, age of participants, sex, type of wound, type of intervention, duration of treatment, intervention and control groups, and main results were extracted.

Results

In total, 57 articles were identified out of which 16 were conducted on animals, 2 lacked access to the full text, 10 lacked transparency of statistical results, and 6 had a sample size less than 30 cases. These articles were removed and eventually, 23 articles were evaluated.

Wound healing and preventive effects of Aloe vera have been reported in several studies.[16] Topical application of Aloe vera to prevent ulcers and enhance the healing process of dermal injuries (e.g., burns, frostbite, skin infections, surgical wounds, inflammation, herpes ulcers, diabetic foot ulcers, pressure sores, and chronic wounds) has been reported.[17] Aloe vera is highly suitable for wound dressings.[18] Most of the studies were conducted on burn wounds. Aloe vera is considered as the traditional therapy for burns. Five studies investigated burn wound healing. In these studies, Aloe vera was more effective than petroleum jelly gauze dressing, silver sulfadiazine 1% ointment, and framycetin cream. Moreover, it reduced the recovery time, prevented infection in the wound area, and prevented redness and itching.[4, 14, 19-21] In these studies, Aloe vera was more effective in first- and second-degree burn wounds than in the other degrees. As described in table 1, it is concluded that Aloe vera can reduce the healing time of first- and second-degree burns to 9 days (P=0.006).[15]

As described in table 2, Aloe vera was used on postoperative wounds such as episiotomy, cesarean section, skin biopsy, hemorrhoidectomy, gynecologic laparotomy surgery, and graft.[22-28] In these studies, the use of Aloe vera gel and cream reduced the pain and recovery time compared to other conventional treatments. Only one study group, Aloe vera dressing for skin shave biopsy, did not show any difference in terms of improvement compared to the combined dressing group.[27]

Table 1: Analysis of studies using Aloe vera for first- and second-degree burns

Authors	Year	Sample size	Methods	Results
Malek Hosseini et al.[4]	2013	64 patients with second-degree burns	32 patients were dressed with Aloe vera gel and 32 other patients were dressed with silver sulfadiazine 1% cream, daily. Parameters of the wound on the 1st, 7th, and 15th days were studied using Bates-Jensen wound assessment tool.	By comparing the average improvement in both groups at baseline and on the 15th day, a significant difference was found between the two groups (P<0.0001). Finally, it was reported that wounds healed faster using Aloe vera gel dressing than silver sulfadiazine
Khorasani et al.[19]	2009	30 patients with burns on two areas of the body	In each patient, one part of the body was randomly used to apply Aloe vera cream 0.5% and the other part with sulfadiazine 1%. In both groups, Aloe vera and sulfadiazine were applied twice a day. The healing time was 19 days.	80% of the SSD group and 100% of the AV group were cured after 19 days. The mean days of recovery in the AV and SSD groups were 15.9±2 and 18.73±2.56 days, respectively. In addition, no infection was observed in both groups (P<0.0001).
Moghbel et al.[14]	2007	30 patients with second-degree burn wounds	The patients applied Aloe vera dressing and silver sulfadiazine 1% ointment on each hand as the experimental and control groups, symmetrically.	They reported improvements within 10 days in 90.6% of the experimental group and 28.7% of the control group (P<0.001).
Akhtar et al.[20]	1996	100 patients with burns	100 patients were divided into two groups. The AV group applied Aloe vera dressing three times a day and the control group applied framycetin ointment.	The average improvement for the AV group was 18 days versus 30.9 days.
Tamlikikal et al.[21]	1991	38 patients with first- to third-degree burns in which less than 30% of their body surface area was burned.	The samples were assigned into two groups by random allocation; in SSD group silver sulfadiazine was applied twice a day and in the AV group Aloe vera was applied twice a day.	55% (11/20) with mucilage AV and 39% (7/18) with SSD were recovered.

Table 2: Analysis of studies using Aloe vera on postoperative wounds

Authors	Year	Sample size	Methods	Results
Malazem et al.[22]	2015	90 women undergoing cesarean section	Aloe vera gel dressing was used in the intervention group and a simple dressing on the wound immediately after cesarean section was applied in the other group. The pain and improvement in the first 24 hours and the 8th day were compared.	In the Aloe vera group, wound healing was faster than the control group in the first 24 hours (P=0.003). However, no difference was observed on the 8th day (P=0.283). Finally, the positive effect of Aloe vera treatment was confirmed.
SabzAli Gol et al.[23]	2014	84 women undergoing nulliparous episiotomy	In the intervention group, Aloe vera gel was used twice a day for 10 days and betadine bath was used for the control group twice a day for 10 days.	In the Aloe vera group, 57.1% on the 7th day and 30% on the 10th day had complete remission. The pain intensity average was 2.3 on the 7th day and 1.21 on the 10th day.
Eghdam Poor et al.[24]	2013	74 women undergoing nulliparous episiotomy	Aloe vera ointment every 8 hours for 5 days was applied in the intervention group and the control group used betadine bath every 4 hours for 5 days.	The average improvement in the Aloe vera group was 1.62, which was significantly high (P<0.0001).
Jahdi et al.[25]	2011	74 women undergoing nulliparous episiotomy	In the intervention group, Aloe vera ointment (3 cc) was applied every 8 hours for 5 days and betadine bath used in the control group every 4 hours for 5 days.	Regarding pain intensity, the average pain score was 1.86 in the Aloe vera group, which was significantly low (P<0.001).
Khorasani et al.[26]	2011	45 skin graft donor sites	A group using Aloe vera cream (three times daily), a placebo group (three times daily), and the other group without any topical agent were studied. Dressing was applied daily in all three groups.	It was concluded that the effect of Aloe vera gel on the donor sites resulted in a significant improvement in recovery time between the control group (without any topical agent: 17±8.6), the placebo group (without Aloe vera cream: 8.8±2.8), and the experimental group (cream without Aloe vera: 9.7±2.9). However, there was no difference in the placebo and experimental group, which can be due to the moisturizing effect of both creams.
Eshghi et al.[27]	2010	49 patients after hemorrhoidectomy	Aloe vera gel 0.05% was used in the intervention group and placebo was used in the control group 12 hours after hemorrhoidectomy three times a day for 28 days.	The complete time of remission was considered as 14 days. 100% of the intervention group and only 4% of the control group cured after 14 days.
Philips et al.[28]	1995	49 patients undergoing skin shave biopsy	The intervention group used Aloe vera gel dressing and the control group used the combined dressing (hydrogel parkside, antibiotic ointment, and absorbent dressing) twice a day.	After 14 days, no difference was observed between the two groups in terms of the healing and 24/24 in the AV group and 23/23 in the control group recovered.

As described in table 3, Aloe vera was used for healing of cracked nipples in 2 studies and it reduced the pain and discharge in the area.[29, 30]

Aloe vera has been effective in chronic wounds such as pressure ulcers, diabetic ulcers, chronic anal fissure wounds, chronic wounds caused by accidents, psoriasis, and genital herpes. In this regard, 7 articles were studied and Aloe vera was more effective compared to saline gauze dressing, phenytoin, and current treatments.[31-37] Only in one study, no differences were found between the two groups which can be due to the small sample size compared to the other studies.[36] Aloe vera reduced the pain, bleeding, and recovery time in chronic wounds (table 4).

Aloe vera has also been effective in the prevention of ulcers. Mucopolysaccharides along with amino acids and zinc available in Aloe vera can lead to skin integrity, moisture retention, erythema reduction, and helps to prevent skin ulcers. As described in table 5, two studies were reviewed.[12, 38]

Table 3: Analysis of studies using Aloe vera for healing of cracked nipples

Authors	Year	Sample size	Methods	Results
Alamolhoda et al.[29]	2013	110 nulliparous lactating women	In one group, after each breastfeeding, lactating women applied 0.5 ml of Aloe vera gel on their nipples and around the areola. The control group applied 4 drops of their breast milk. Both groups were evaluated at days 10 and 14 postpartum.	The pain and damage of the nipple and discharge in the Aloe vera group were much less than the control group and Aloe vera improved the fissure (P<0.001).
Tafazoli et al.[30]	2009	100 lactating women with breast fissure	Two groups were divided into lanolin ointment or Aloe gel groups (three times a day for 1 week).	There was a statistically significant difference between the two groups on the 3rd day (P=0.048) and 7th day (P=0.003). Aloe vera gel was more effective than lanolin ointment in healing cracked nipples.

Table 4: Analysis of studies using Aloe vera on chronic wounds

Authors	Year	Sample size	Methods	Results
Avijegan et al.[31]	2016	60 patients with chronic wounds	In the intervention group, 30 patients used Aloe vera gel twice a day in combination with current treatments and the control group only used conventional treatments. Patients were evaluated 1 week and 3 months after treatment.	After 3 months follow-up, wound healing occurred in 28 (93.3%) of patients in the Aloe vera group and 14 (46.7%) patients in the control group (P<0.05). The overall mean time of wound healing was 31.25±11.2 and 63.2±20.4 in the Aloe vera and control groups, respectively (P<0.05). The mean hospitalization time was 35.2±6.4 and 67.4±8.9 in the Aloe vera and control groups, respectively (P<0.05).
Panahi et al.[32]	2015	60 patients with chronic wounds (41 patients with pressure ulcers, 13 patients with diabetic ulcers, and 6 patients with ulcer caused by venous disorders)	Aloe vera cream in combination with olive oil was used in the intervention group and the control group used phenytoin cream for 30 days. The pain, depth, size, edema around the wound area, the amount of exudate, and necrotic tissue were examined using Bence Jones and VAG tools.	The pain, depth, size, edema around the wound area, the amount of exudate, and necrotic tissue in the intervention group showed a statistically significant difference compared with the control group (P<0.001). Aloe vera gel in combination with olive oil was much more effective in reducing pain and wound healing compared with phenytoin.
Rahmani et al.[33]	2014	60 patients with a confirmed diagnosis of chronic anal fissures	Aloe vera cream 0.5% (3 grams) was used in the intervention group three times a day for 3 weeks and the control group used the placebo.	A statistically significant difference was observed in the pain, bleeding, and wound healing of chronic anal fissure before and at the end of the 1st week of the study compared with the control group (P<0.001) and topical application of Aloe vera was considered effective in treating wounds.
Choonhakarn et al.[34]	2010	80 patients with a diagnosis of psoriasis vulgaris	Mucilage from Aloe vera (70%) twice a day without any treatment was used in the intervention group and triamcinolone cream 0.1% was used in the control group for 8 weeks.	Aloe vera cream was at least as effective in reducing psoriatic plaque in patients as triamcinolone acetonide cream with significantly more reduction in psoriasis area severity index and equal reduction in dermatology life quality index.

(Contd...)

Table 4: (*Continued*)

Authors	Year	Sample size	Methods	Results
Thomas et al.[35]	1998	30 patients with two-, three- and four-degree ulcer with a wound size≥1 cm^2	16 people used carrasyn dressing derived from Aloe vera gel (along with the acemannan Aloe vera) and 14 of the patients used saline gauze dressing, daily. They were followed up for 10 weeks.	63% of the Aloe vera group and 64% of the saline gauze dressing group recovered after 10 weeks. The mean time of improvement was 5.3±2.3 for AV group and 5.2±2.4 for saline gauze dressing group and there was no difference.
Syed et al.[36]	1996	120 patients with a diagnosis of genital herpes	0.05% cream or Aloe vera gel was used in the intervention group three times a day and the placebo was used for 2 weeks in the control group.	Both Aloe cream and gel were effective in reducing healing time compared to placebo (4.8 vs. 7.0 vs. 14.0 days, respectively), Aloe cream was more efficacious in the number of cured patients compared to gel (70% vs. 45% vs. 7%, respectively.
Syed et al.[37]	1996	60 patients with a diagnosis of psoriasis vulgaris	The intervention group used 0.05% cream or Aloe vera gel maximum three times a day (or 15 times a week) and in the control group, the placebo was used for 4 weeks.	Aloe hydrophilic cream cured 83.3% of patients treated versus 6.6% in the control group. Psoriatic plaques were significantly (P<0.001) reduced and biopsies presented with reduced inflammation and parakeratosis.

Discussion

Based on a detailed review of articles, the application of Aloe vera as a medicinal plant for skin wound healing is confirmed.[1-40] Aloe Vera is widely used for its antibacterial, anti-viral, anti-inflammatory effects and has been considered in medical sciences.[2, 3, 6] Dat and colleagues (2012) showed that Aloe vera is more effective in chronic than acute wounds.[1] Aloe vera is mainly used to treat first- and second-degree burn wounds resulting in reduced recovery time to 9 days. Aloe vera dressing for once or twice a day has been more effective than the current treatments, including petroleum jelly gauze dressing, silver sulfadiazine 1% ointment, and framycetin cream. It has resulted in reduced recovery time, the absence of wound infection, and the lack of redness and itching.[4, 14, 21] Aloe vera has long been used to treat burns and is commonly known as the burn tree and first aid plant.[39] Due to anti-inflammatory, increased immune activity, anti-bacterial and anti-viral effects, and decreased histamine activity properties of Aloe vera, it accelerates the healing process of burn wounds. The outcome of the present review study shows that Aloe vera is unanimously considered as the ideal dressing. Most studies have been performed on grade 1 and 2 ulcers and there are limited studies on grade 3 ulcers. The latter could be due to full thickness skin loss in grade 3 wounds and possible onset of wound infection.

Aloe vera gel or cream on postoperative wounds (three times a day for 5-10 days) could reduce pain and recovery time.[22-28] Only one study indicated that there was no difference between the experimental and placebo groups.[28] This could be due to inappropriate placebo or the optimal time point for improvement. Cracked nipples could also be treated using Aloe vera if applied 3 times a day or after each breastfeeding. It would reduce the pain due to cracked nipples.[29, 30] This finding was also confirmed in a study by Eshgizade and colleagues (2016).[40]

It is indicated that Aloe vera (as a gel or cream) can be effective to treat chronic wounds such as psoriasis lesions (twice a day for 4-8 weeks),[34, 37] pressure ulcers (1-3 months), venous, diabetic,[31, 32] and herpes ulcers and chronic anal fissure (2-3 weeks).[33-36] In these articles, in addition to the recovery time, the following factors were also checked: Lesion scores;[34] depth, size, edema around the wound area, the amount of exudate and necrotic tissue,[32] inflammation,[34, 37] pain and bleeding,[33] and infection.[19] It was shown that Aloe vera could have a positive effect on the above-mentioned factors and their reduction. Only Thomas and colleagues found no healing difference between saline and Aloe vera in the

Table 5: Analysis of studies using Aloe vera to prevent ulcers

Authors	Year	Sample size	Methods	Results
West et al.[12]	2003	30 adult females with bilateral occupational dry skin with or without irritant contact dermatitis (with or without erythema, fissures, and excoriations)	The intervention group wore a glove containing Aloe vera gel 8 hours a day for 30 days on one hand and the control group (the other hand) did not use any material. The patients rested for 30 days and the intervention was repeated for an additional 10 days.	Average recovery of the dry skin time was 3.5 days for the intervention group and no event occurred in the control group. Aloe vera could help in preventing the onset of erythema, dryness and eczema, and scarring (P<0.0001).
Williams et al.[38]	1996	194 women receiving radiation therapy for breast cancer	Aloe vera gel was used in the intervention group (98%) in combination with common treatments. The control group only used common treatments.	No difference was observed between the two groups.

treatment of pressure ulcers. Perhaps the small sample size (30 cases) was the reason behind their findings.[35] As the secondary objective, many studies measured the length of hospitalization, cost of scar treatment, and redness and itching of the wound area. They indicated that Aloe vera is superior to other treatments.[14, 21, 31]

Several studies noted the traditional belief that a wound should not be covered, allowing it to become dry and detach itself from the wound area since it inhibits the migration of cells and growth factors leading to wound healing. Aloe vera as a wound cover would keep the wound area moist and allows optimal migration of fibroblasts and epidermal. Aloe vera (1 to 100 mg/kg) can improve wound healing.[41]

The main limitations of the present systematic review were the quality of available literature, lack of access to all articles, and unpublished reports. Moreover, only the literature in English and Persian were reviewed. These have considerably reduced our sample size regarding various data parameters and consequently hindered our ability to determine statistically significant results. Furthermore, not all articles were blind experiments, which is a challenge to determine the true effect of Aloe vera on wound healing. In total, 57 articles had to be excluded since they involved multiple procedures or multiple indications without providing specific outcomes data for the Aloe vera effect on wound healing. Since the present study was not a meta-analysis and had no major summary, data analysis to determine publication bias with the STATA software was not performed. However, qualitative analysis of both the survey responses and the focus group discussion identified possible ways of reducing publication bias. This was done through increased transparency, improvements in trial registries, search engines and databases, enhancing the role of the institutional review boards, and positive support from the scientists. The above-mentioned approaches minimized publication bias.

Conclusion

Due to the properties of Aloe vera and its compounds, it can be used to retain skin moisture and integrity. It also prevents skin ulcers as it contains mucopolysaccharides, amino acids, zinc, and water. In terms of quality and speed of wound healing, Aloe vera is much more effective and less costly compared to the currently available alternative treatments. Considering the tendency to promote traditional medicine as well as rare side effects of Aloe vera, the use of this medicinal plant to improve wound healing is recommended as the complementary treatment alongside other methods.

Conflict of Interest: None declared.

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