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The efficacy of aloe vera used for burn wound healing: A systematic review

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ARTICLE INFO

Article history:

Accepted 10 October 2006

Keywords:

Aloe vera

Burn

Systematic review

ABSTRACT

Aloe vera has been traditionally used for burn healing but clinical evidence remains unclear. We conducted a systematic review to determine the efficacy of topical aloe vera for the treatment of burn wounds. We electronically searched relevant studies in MEDLINE, CINAHL, Cochrane Library, HealthSTAR, DARE, South-East Asia Database, Chinese Databases, and several Thai local Databases (1918–June 2004). Only controlled clinical trials for burn healing were included. There were no restrictions on any language of publication. Two reviewers independently extracted data on study characteristics, patient characteristics, intervention, and outcome measure.

Four studies with a total of 371 patients were included in this review. Based on a meta-analysis using duration of wound healing as an outcome measure, the summary weighted mean difference in healing time of the aloe vera group was 8.79 days shorter than those in the control group ($P = 0.006$). Due to the differences of products and outcome measures, there is paucity to draw a specific conclusion regarding the effect of aloe vera for burn wound healing. However, cumulative evidence tends to support that aloe vera might be an effective intervention used in burn wound healing for first to second degree burns. Further, well-designed trials with sufficient details of the contents of aloe vera products should be carried out to determine the effectiveness of aloe vera.

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1. Introduction

Aloe vera (*Aloe vera* Linn, synonym: *aloe vera* *barbadensis* Mill.) is in family Liliaceae, which is a tropical plant easily grown in hot and dry climates including Thailand. Numerous cosmetics and medicinal products are made from the mucilaginous tissue, called aloe vera gel, located in the center of the aloe vera leaf. Aloe vera gel has been used for many indications since the Roman era or even long before. Burn wound healing is one of major indications of aloe vera gel use in many countries [1,2]. In Thailand, aloe vera gel was included in the Thai Herbal

Fundamental Public Health Drug List as burn wound therapy [3]. Several studies [4–10] suggested that aloe vera, or one or more of its constituents, promote wound healing in various animal models. However, its clinical evidence remains unclear [4]. Recently, there was a systematic review of 10 clinical studies of aloe vera evaluating its clinical effectiveness for a variety of indications was undertaken. They found that oral aloe vera might be valuable for reducing cholesterol or glucose levels. Its topical form might be effective for genital herpes and psoriasis but it is not an effective preventive for radiation-induced injuries [11]. However, the study did not report the efficacy of

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doi:10.1016/j.burns.2006.10.384

aloe vera for burn wounds. The aim of this systematic review was to determine aloe vera efficacy in burn wound healing.

2. Method

2.1. Study selection

We electronically searched in MEDLINE (1966–2004), Cumulative Index to Nursing & Allied Health Literature; CINAHL (1982–2004), Cochrane Database of Systematic Reviews (1996–2004), Cochrane Central of Controlled Trials (1991–2004), Database of Abstract of Reviews of Effectiveness; DARE (2001–2004), Health-Star (1975–2004), Health Source: Nursing/Academic Database (1975–2004), ACP Journal Club (1991–2004), Chinese Science and Technology Database (1989–2004), China Academic Database (1994–2004), Thai Theses Online (1974–2004), Thai Index Medicus Database (1918–2004), South-East Asia Index Medicus, Thai Medical Index, and Medicinal Plant Database. For our search strategy, we used the Medical Subject Headings “Aloe” and the exploded key words “aloe vera” AND “burn” OR “burn wound”. To ensure that our search would be thorough, we reviewed the reference lists of the retrieved articles and any identified review articles. In addition, we consulted the corresponding authors of identified studies, and asked experts working in the field of burn therapy or herbal medicine, for further studies. We included both published and unpublished controlled clinical trials of aloe vera for burn wound healing, regardless of language. All articles were abstracted by two independent investigators. Methodological quality was assessed using the Jadad score [12].

2.2. Statistical analyses

The difference of the length of time required for burn wounds to heal between the control and the treatment groups was an outcome measure used for statistical pooling. The summary weighted mean difference and 95% confidence intervals (CI) were calculated based on a random-effects model using Dersimonian–Laird Method [13]. A statistical test of heterogeneity was performed using the Cochran–Mantel–Haenszel Method. Furthermore, clinical heterogeneity was also investigated through sensitivity analyses.

In some studies where data required for meta-analysis was missing, we attempted to contact the original authors for detailed information. If standard deviation could not be obtained, we assumed equal variance and normal distribution of the data and calculated standard deviations based on *P*-value provided in the articles.

3. Results

3.1. Study selection

A total of 1069 articles was identified. Nine hundred and twenty two studies were excluded because they were not conducted on humans, 124 (not used for burn wounds), 7 (duplications), and 12 (not controlled clinical trials). Four articles [14–17] were located (Fig. 1). Two of the studies [14,15]

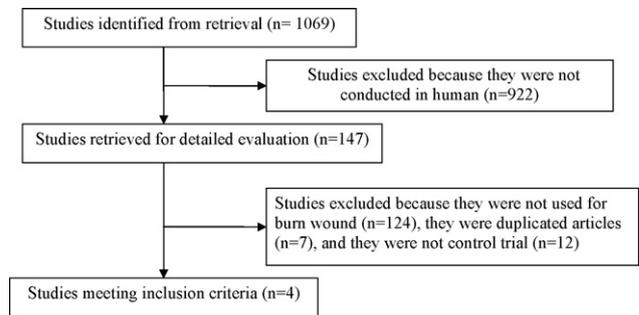


Fig. 1 – Trial flow depicting the selection process of studies included in this study.

were conducted in Thailand while the others [16,17] were performed in India and China. The Thamlikitkul study [14] was published in a Thai local journal while the Visuthikosol study [15] was published in an international journal. The Sun Ji Hai study [17] was published in Chinese local journal while the Akhtar study was available only in abstract form [16].

3.2. Study characteristics

The studies of Thamlikitkul and Akhtar [14,16] used randomized controlled trial design while Visuthikosol [15] used within patient design.¹ Sun Ji Hai et al. [17] used controlled trial design but no information regarding randomization was provided.

Among studies using randomized controlled trial design, Thamlikitkul [14] performed randomization stratified by the depth and the size of the lesions, while Akhtar [16] used a randomization with block size of eight. The subjects in the Akhtar study [16] were blinded but no full description of blinding was provided. Thamlikitkul et al. [14] did not mention whether blinding was performed in their study. None of Both studies [14,16] described the allocation concealment. The JADAD scoring system was used to assess the quality of randomized controlled trials; two studies earned the same score of 2/5 [14,16]. None of the studies addressed the issue of patient drop out from the study.

3.3. Interventions

The Thamlikitkul study [14] compared fresh aloe vera mucilage with silver sulfadiazine cream while the Visuthikosol study [15] compared vaseline gauze alone with gauze saturated with 85% aloe vera gel. In both studies, interventions and controls were applied twice daily. The Akhtar study [16] compared aloe vera cream and framycetin cream; each was applied every 3 days. The Sun Ji Hai study [17] compared vaseline gauze alone with 1% aloe vera powder wrapped with vaseline gauze (Table 1). None of the authors reported the amount of key active ingredient of aloe vera gel in their products.

¹ Within person design is one type of clinical controlled trial design which one patient has an evaluation of both interventions (treatment and control), and hence, a measure of treatment difference for each individual or an individual patient preference.

3.4. Description of population

A total of 371 subjects were included in this systematic review [14-17]. Almost all patients included had thermal burn, except three persons in the Thamlikitkul study [14] and one person in the Visuthikosol study [15] had electrical burns. In terms of severity of burn wound, the study of Sun Ji Hai [17] was the only study which included patients with second or third degree burns. Two studies [14,16] include subjects with first or second degree burns, while the Visuthikosol study [15] specified subjects to have clinically partial thickness burns.²

The percentage of the body surface area with burn was specified in the inclusion criteria of three studies as less than 30% [14], more than 2% [15], and between 10% and 40% [16], respectively. The Thamlikitkul study [14] reported the mean percentage of body surface area in the aloe group and the silver sulfadiazine group as 8%, and 11%, respectively. The mean percentage of body surface area was 20.5% in the Visuthikosol study [15]. Thamlikitkul et al. [14] was the only study specifying that subjects must have burn less than 24 h before admission. The reported median time was less than 1 h in both groups.

Most subjects did not receive previous treatment except all subjects in the Sun Ji Hai study [17] who received skin grafting before treatment. Two studies [14,16] described that the proportions of subjects receiving concomitant treatments were quite comparable between the treatment and the control groups (i.e. 30% versus 33% for intravenous fluid, 60% versus 67% for antibiotics [14]). Visuthikosol et al. [15] specified that all burn wounds were cleaned with chlorhexidine gluconate 2% in detergent-based solution (Hibiscrub[®]).

3.5. Outcomes

Wound healing time was the outcome measure used in the study of Visuthikosaol and Akhtar [15,16]. The study of Thamlikitkul [14] and Sun Ji Hai [17] used the percentage of the success rate of wound healing and rate of epithelialization, measured by the healing size, respectively. Visuthikosol and colleagues [15] specified wound healing as complete epithelialization, whereas Akhtar and colleagues [16] provided no definition of wound healing.

Outcome assessment was based on physician clinical judgment in three studies [14-16], and one study [17] was based on objective definition using a ruler and a pair of compasses as measuring tools. Three studies [14-16] did not describe strategies to minimize subjectivity bias of this outcome assessment process. None of the studies described characteristics and the number of evaluators and whether or not they were blinded. Visuthikosol et al. [15] assessed the wound clinically and performed histological tests based on biopsies collected on the 1st, 7th, 14th, and 21st date of admission. All patients in Thamlikitkul et al. [14] were assessed daily for wound healing. All patients in the Sun Ji Hai study [17] were assessed for the rate of epithelialization on post skin grafting days 5 and 8.

² Partial thickness burn is somewhat equivalent to first and second degree burn [19].

Table 1 – Characteristics and the results of studies

First author, year (location)	Jadad score	Patient sample	Design	Treatment (n)	Control (n)	Frequency and duration	Outcome measure		Comment
							Treatment	Control	
Thamlikitkul et al., 1991 [14] (Thailand)	2/5	38 thermal 1st or 2nd with area ≤30% of BSA ^a	RCT ^b	Aloe fresh mucilage (20)	Sulfadiazine cream (18)	Twice daily until complete epithelialization or patient leave the hospital	% Success rate to healing	95%	Irritation and itching 40% in treatment, 44% in control
Visuthikosol et al., 1995 [15] (Thailand)	-	27 partial thickness burn with area >2% of BSA	Non RCT	Gauze saturated with 85% aloe gel (27)	Vaseline gauze alone (27)	Twice daily until complete epithelialization	Time to healing	11.89 days (S.D. = 4.39)	Comparable to discomfort and minimal transient pain in each group
Akhtar et al., 1996 [16] (India)	2/5	100 thermal 1st or 2nd with area 10-40% of BSA	RCT blinded	Aloe cream (50)	Framycetin cream (50)	Every 3 days until complete epithelialization	Time to healing	18 days (S.D. = 18.9)	-
Sun Ji Hai et al., 1991 [17] (China)	N/A	206 patient with 2nd and 3rd degree burn	Controlled trial	1% Aloe powder + vaseline gauze	Vaseline gauze alone	N/A ^d	Rate of epithelialization on post-skin grafting day 5 and 8	1.29 ± 0.17 mm Day 8; 5.84 ± 0.27 mm Day 5 and 8	-

^a Body surface area.
^b Randomized controlled trial.
^c Standard deviation.
^d Not available.

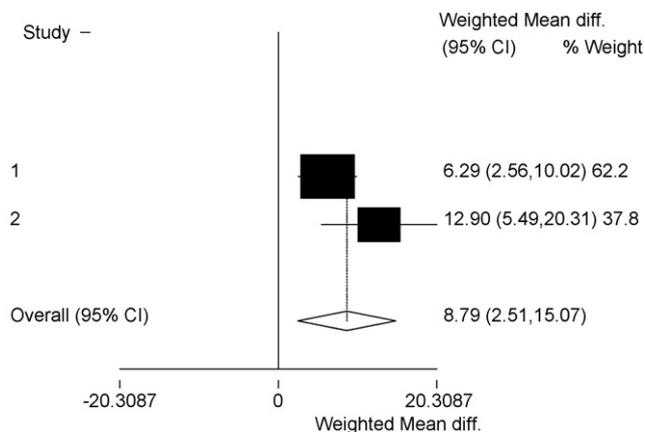


Fig. 2 – Analysis of the difference mean of time to healing between the treatment group and the control group.

3.6. Efficacy and sensitivity analyses

Only studies using time to wound healing as outcome measures were included in a meta-analysis. Based on a meta-analysis of two studies, the summary weighted mean difference in healing time of the aloe vera group was 8.79 days shorter than those in the control group (95% CI: 2.51, 15.07 days; $P = 0.006$) (Fig. 2). The test of heterogeneity was not statistically significant ($P = 0.118$).

The other two studies [14,17] show that the results of the treatment group are better than those in the control group. Thamlikitkul et al. [14] reported that the success rate in the aloe vera group and the silver sulfadiazine group was 95% and 83%, respectively. Sun Ji Hai et al. [17] reported that the epithelialization rate, measured by the healing size, of the aloe with vaseline gauze group was higher than that of the vaseline gauze group on both day 5 (2.695 ± 0.618 mm versus 1.294 ± 0.169 mm), and day 8 (5.837 ± 0.266 mm versus 3.953 ± 0.326 mm) of post skin grafting.

3.7. Safety

Only two studies [14,15] reported adverse effects, while the Akhtar study [16] and Sun Ji Hai study [17] did not provide information related to adverse outcomes. Thamlikitkul et al. [14] reported irritation or itching in 40% in the aloe vera group and 44% in the control (sulfadiazine) group. The other study [15] reported discomfort and minimal transient pains (mild pain was 92.6%, moderate pain was 7.4%) which were relieved by oral analgesic in both groups (acetaminophen tablet). No allergic or eczema was reported in all studies included.

4. Discussion

To our best knowledge, this is the first systematic review conducted to determine the efficacy of aloe vera for burn wound healing. Existing evidence demonstrates that aloe vera used in a variety of dosage forms might be effective in shortening the duration of wound healing in first to second

degree burns, and it tended to increase rate of success to healing and rate of epithelialization.

The promotion of burn wound healing was shown in a study conducted in guinea pig [9]. The study reported that the aloe vera gel extract permitted faster healing of burn, and reestablished the vascularity of burn tissues. These effects might be due to several mechanisms including an increasing collagen synthesis and rate of epithelialization by the effect of acemaman (mannose-6 phosphate) to stimulate fibroblasts [8,9,18,20], an anti-inflammatory effect [21,22], an antimicrobial effect [19,23], and a moisturizing effect [19,24].

Our finding demonstrates that aloe vera products are safe for topical use. There was no withdrawal or serious adverse reaction reported in the included studies. Only irritation, itching, discomfort, and minimal transient pain were reported. However, these events were common signs and symptoms in burns, and they were present in both the aloe and the control groups. Important things to notice for safety of topical fresh aloe vera was contamination with anthraquinone. It was a potential cause of the irritation as reported in previous studies [20,25,26].

One might expect a large amount of evidence investigating aloe vera used for burn wounds; however, our search results found only four studies. We performed a comprehensive search by attempting to contact experts in the field of burn therapy or herbal medicine, as well as other potential sources for the further papers. Despite this endeavor, we are uncertain that publication bias is eliminated. Due to a small number of studies, a test for publication bias cannot be performed. Publication bias is one concern in systematic reviews since its existence can result in biased conclusions [27,28].

The standardization of product is necessary for the quality control of the products. Our study revealed that none of the included studies standardized the amount of active ingredients of aloe vera in the product. The amount of active ingredient in aloe vera varies depending on the age of plants [18], growing and harvesting conditions, parts of plants, and extraction methods [4,20]. In addition, it has been reported that many of the active ingredients in aloe vera appeared to deteriorate during storage and preparation [25,29,30]. It is therefore, very important that the active ingredient be measured for standardization in all studies.

One of the major limitations of this study is the possible existence of measurement bias. All patients enrolled in two of the studies [14,15] were evaluated by clinicians who were not blinded. In addition to the absence of blinding, the outcome of interest (complete epithelialization) is very subjective, thus increasing a chance of measurement bias. If any clinical studies are to be conducted to assess this type of outcome, having at least two independent outcome assessors may lessen the bias and increase the validity of research studies.

Selection of proper outcome measures is a key step in clinical trials. In patients with partial thickness burns, most of the patients fully recovered after appropriate treatment. As the success rate of wound healing was generally high in patients with partial thickness burn, the room for outcome improvement might be too small for aloe to show its effects. This can be seen in a study conducted by Thamalikitkul et al. [14]. Because, the success rate of wound

healing was chosen as an outcome measure in patients with partial thickness burn, a statistical significance was not found. The duration of wound healing has been advised to be the outcome measure in patients with partial thickness burn [31]. This outcome is more clinically meaningful for partial thickness burn persons than the success rate because it can capture the difference of outcome in this type of patients.

All studies compared aloe vera with different conventional treatments, including vaseline gauze, silver sulfadiazine cream, and framycetin cream. Despite this clinical heterogeneity, our findings demonstrated the benefits of aloe vera over all types of comparators. From theoretical standpoint, we understand that combining studies using different comparators may not be methodologically sound. However, its superiority indicated its potential use in real situations, where a variety of conventional treatments may be chosen for burn wound healing therapy.

5. Conclusion

Existing evidence demonstrates that aloe vera used in a variety of dosage forms might be effective in speeding up the wound healing process and tend to increase the rate of success of healing, and the rate of epithelialization in first and second burns when compared with conventional treatments. However, because of the differences of products used and an absence of studies with a quality score accepted as good quality, further well-designed trials with sufficient details of the contents of aloe vera products should be carried out for determining the effectiveness of aloe vera for burn wound healing.

Acknowledgements

We thank Thailand Research Fund and School of Pharmacy Grant for Young Researcher for their grant support, Yingzi Zeng M.Sc. (The medical librarian in Sichuan University, China: Database searching assistant), Wang Feng M.Ed. (The Assistant Professor of Beijing Foreign Studies University, China: Translator), and Visanu Thamlikitkul, M.D., M.Sc., Siriraj Hospital, Mahidol University, Thailand.

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