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Investigation of the Anti-Inflammatory Potential of *Aloe vera* Gel (97.5%) in the Ultraviolet Erythema Test

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Key Words

Aloe vera gel · *Aloe vera barbadensis* · Minimal erythema dose · Erythema index · Hydrocortisone · Prednicarbate

Abstract

Background: *Aloe vera* is a natural product that is frequently used in soothing skin care products such as aftersun lotions. In the present study we aimed to explore the anti-inflammatory potential of a highly concentrated *A. vera* gel in the UV erythema test in vivo. ***Methods:*** 40 volunteers with skin types II and III were included in the randomized, double-blind, placebo-controlled, phase III monocenter study. Test areas on the back were irradiated with the 1.5-fold minimal erythema dose of UVB. Subsequently, the test areas were treated occlusively on 2 subsequent days with *A. vera* gel (97.5%), the positive controls (0.25% prednicarbate, 1% hydrocortisone in placebo gel and 1% hydrocortisone cream) and a placebo gel. Erythema values were determined photometrically after 24 and 48 h. ***Results:*** *A. vera* gel (97.5%) significantly reduced UV-induced erythema after 48 h, being superior to 1% hydrocortisone in placebo gel. In contrast, 1% hydrocortisone in cream was more efficient than *A. vera* gel. ***Conclusions:*** In this study after 48 h the *A. vera* gel (97.5%) displayed some anti-inflammatory effects superior to those of 1% hydrocortisone in placebo gel. The *A. vera* gel tested here might be useful in the topical treatment of inflammatory skin conditions such as UV-induced erythema.

Introduction

Aloe barbadensis Miller (synonym: *Aloe vera*) is a perennial succulent plant belonging to the Liliaceae plant family. The plant is the source of two products, gel and latex. The parenchymatous cells in the leaf pulp contain the mucilaginous gel which is extracted by squeezing the leaves. The peripheral bundle sheath cells of the plant produce the yellow bitter juice, *Aloe* latex, mainly containing anthraquinones and their derivatives [barbaloin (aloin A), isobarbaloin (aloin B), aloesin, aloresin A, aloe-emodin]. *Aloe* latex on a dry-weight base additionally contains acid-insoluble resin, a significant amount of ash and essential oil. The most important ingredients of the *A. vera* gel are polysaccharides, mainly acemannan [1]. Although the scientific literature yields little to substantiate claims regarding systemic effects of *A. vera* [2], the consumption of *A. vera* leaf formulations has been shown to display anti-arthritic and antirheumatoid [3], anticancer [4] and antidiabetic [5] properties. *A. vera* gel is used topically for a number of therapeutic purposes including treatment of chronic wounds and thermal injury [6, 7], inflammation [8], treatment of oral ulcers [9], prevention of ultraviolet (UV)-induced immunosuppression [10] and treatment of psoriasis [11] and skin infections [12]. Since published results on the effects of *A. vera* gel on skin conditions are inconsistent [13–15], well-designed scientific studies are needed to address this topic, especially with respect to sunburn treatment.

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The present study aimed to explore the anti-inflammatory potential of a highly concentrated *A. vera* gel in vivo. The most frequently used method in preclinical studies and screenings for active constituents is the UV erythema test [16–18]. Recently we have shown that the back is the best localization to perform the test, and the optimal UVB dose is the 1.5-fold minimal erythema dose (MED) [19]. Here, we investigated a concentrated *A. vera* gel (97.5%) in comparison to 1% hydrocortisone in placebo gel as well as two commercially available corticosteroid preparations, one containing 1% hydrocortisone (Dermallerg-Ratiopharm® cream 1%) and the other containing 0.25% prednicarbate (Dermatop® cream).

Material and Methods

Forty patients were included in this prospective, randomized, double-blind, placebo-controlled study. The study was approved by the local ethics committee and was performed according to established Good Clinical Practice guidelines. All subjects enrolled in the study gave their written informed consent. Included were healthy nonsmoking persons of both sexes, aged at least 18 years, with skin types II and III according to the classification of Fitzpatrick [20]. Exclusion criteria were skin types I and VI, allergic disposition, inflammatory skin diseases, photosensitivity, sunbed tanning, metabolic diseases, use of any drugs (except for contraceptives), alcohol consumption, infections, pregnancy and breast-feeding, and participation in other clinical studies during the last 2 months. No topical corticosteroids were allowed 8 weeks before the onset of the study.

The UV erythema test was performed as described [19, 21]. In brief, for the determination of the MED, gradually increasing doses of UVB were administered on the lower back. Twenty-four hours after irradiation, the first barely perceptible erythema with sharp borders was defined as MED. After the erythema index zero value (baseline) had been measured in the test areas with a Mexameter [19], half of the test areas were irradiated with the 1.5-fold MED of UVB. The other half of the test areas was not irradiated (fig. 1). Immediately after irradiation, the test substances were applied in a blinded manner according to a randomization plan. The substances, each 20 mg per test area, were applied occlusively using extra large Finn chambers (1.8 cm^2, Hermal, Hamburg, Germany) on 6 × 4 cm stripes of Fixomull® (BSN Medical, Hamburg, Germany). The tapes were fixed with larger stripes of Fixomull. To prevent false measurements due to reactions to the tape, the tape was removed 23 h after substance application, i.e. 1 h before evaluation of the test areas. Subsequently, the Mexameter measurement of the erythema index of the test areas and a photographic documentation were performed followed by taping the test areas another time with the substances. Twenty-three hours later, the tapes were removed again, 1 h before the Mexameter measurement and the photographic documentation 48 h after UV irradiation. Each analysis was documented in the case report form.

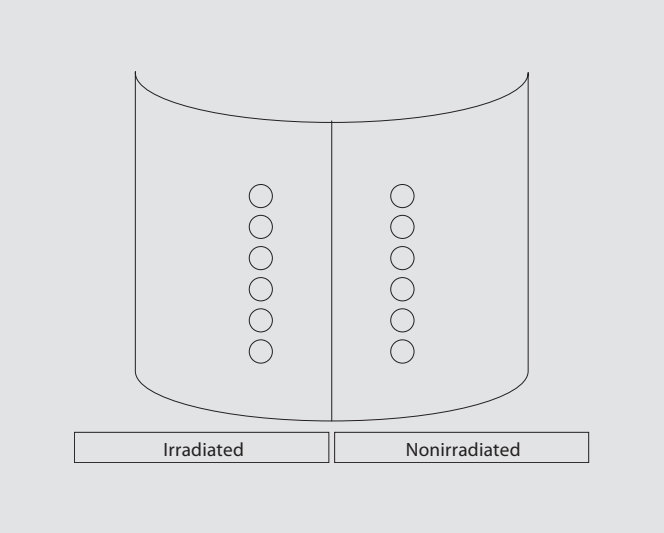

Fig. 1. Arrangement of test areas on the left and right sides of the back.

The following test substances were applied to the irradiated and nonirradiated sites: *A. vera* gel (97.5%) was the primary test substance and was manufactured in May 2004 (batch No. 070504). Dermallerg-Ratiopharm cream 1% (1% hydrocortisone), Dermatop cream (0.25% prednicarbate) and 1% hydrocortisone in placebo gel base were chosen as positive controls. Because the *A. vera* gel (97% v/v) also functions as a vehicle, no identical vehicle could be used as placebo. Therefore, as a negative control a conventional gel base was used (water, glycerol 85%, phenoxyethanol, carbopol ETD 2020, sodium edetate, sodium hydroxide and perfume oil). One untreated test area served as baseline value.

Erythema measurements were performed 3 times in each test site directly before the UV irradiation at time point zero (T_0), after 24 h (T_1) and after 48 h (T_2). All data were recorded in 2 separate databases and compared with each other. The median of the 3 measurements after T_1 and T_2 was taken and averaged over the 40 subjects. The primary endpoint of the study was the difference of erythema between the test substance at time points T_1 and T_2 and the value at time point T_0 in comparison to the untreated area. Secondary endpoints were the comparison of the test substance with the controls, and the skin tolerance on the nonirradiated sites. Statistical analysis was performed by repeated-measures ANOVA (SpSS software package, version 11.0). Due to a significant variety of differences between the measurements T_1 and T_2 and the basic value, univariate analysis with $\Delta_1 = T_1 - T_0$ and $\Delta_2 = T_2 - T_0$ was performed.

Results

Nineteen males and 21 females, aged between 20 and 56 years, participated in the study. Twelve of the females were taking contraceptives. All females were tested nega-

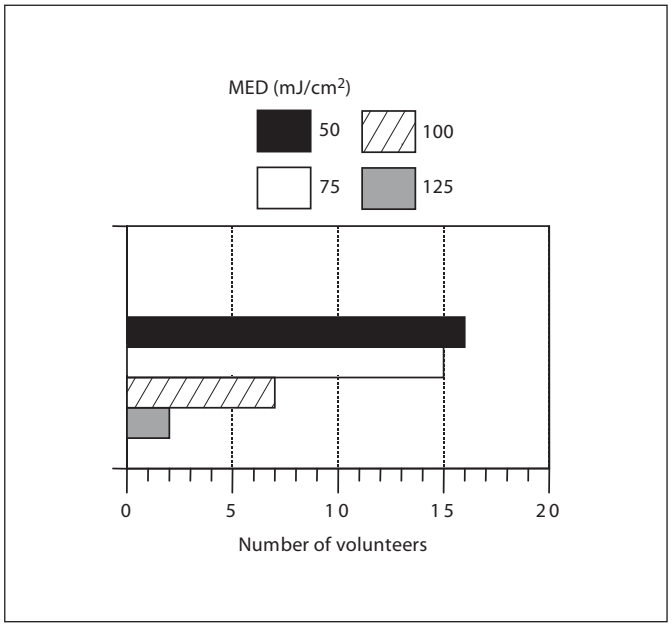

Fig. 2. Distribution of the MED of the 40 volunteers.

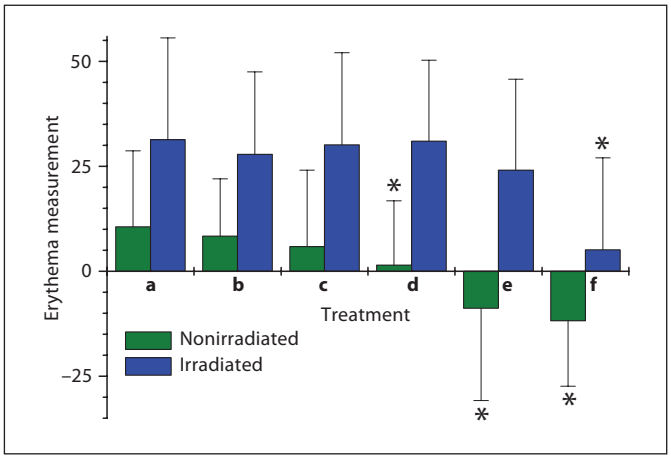

Fig. 3. Erythema values 24 h after irradiation and treatment of test areas with different substances. **a** Untreated. **b** Placebo gel. **c** *A. vera* gel (97.5%). **d** 1% hydrocortisone in placebo gel. **e** Dermallerg-Ratiopharm 1% cream. **f** Dermatop cream. * $p < 0.05$: significant difference compared to untreated area.

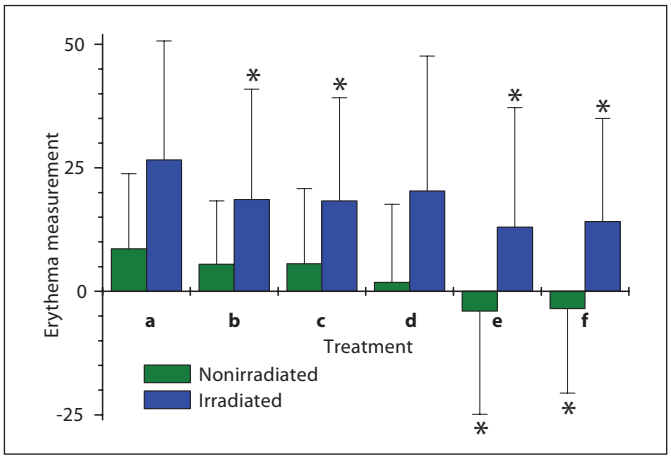

Fig. 4. Erythema values 48 h after irradiation and treatment of test areas with different substances. **a** Untreated. **b** Placebo gel. **c** *A. vera* gel (97.5%). **d** 1% hydrocortisone in placebo gel. **e** Dermallerg-Ratiopharm 1% cream. **f** Dermatop cream. * $p < 0.05$: significant difference compared to untreated area.

tive for pregnancy. All subjects completed the study according to the protocol. The MED of the 40 subjects ranged between 50 and 125 mJ/cm^2 (fig. 2). Irradiation of the skin resulted in a highly significant increase in erythema values. After 24 h, only the treatment with prednicarbate (Dermatop cream) followed by Dermallerg-Ratiopharm cream 1% efficiently reduced the erythema. On the nonirradiated sites, a typical blanching effect of the glucocorticosteroids could be observed. The *A. vera* gel (97.5%), the placebo gel but also 1% hydrocortisone in placebo gel did not show a significant effect 24 h after irradiation (fig. 3). Forty-eight hours after irradiation, all substances including the placebo gel displayed significant erythema-reducing effects (fig. 4). The erythema reduction achieved by the *A. vera* gel (97.5%) was not significantly superior to the effect of the placebo gel. Interestingly, 1% hydrocortisone in placebo gel was not as efficient as the placebo gel or *A. vera* gel (97.5%) whereas 1% hydrocortisone incorporated in a cream (Dermallerg-Ratiopharm cream 1%) resulted in an erythema reduction that was superior to the results of all other test substances.

All test substances were well tolerated. Seven out of 40 subjects showed skin reactions to the tape. The irritation lasted maximally for 84 h and subsided without therapy. One subject had concomitant itching. The adverse events were mild to moderate and appeared isolated. A correlation with the applied test substances was estimated as possible in 2 subjects, but as a result of irritations on several test areas no correlation of the side effect to a single substance could be assessed. Apart from longer-lasting postinflammatory hyperpigmentations of the irradiated areas, no persistent disadvantages were notified. All subjects showed complete remittance. No allergic contact dermatitis attributed to *A. vera* gel (97.5%) or other test substances was observed.

Discussion

For the treatment of acute cutaneous inflammation, predominantly topical corticosteroids are used. In chronic inflammatory frequently relapsing skin conditions, long-term treatment with corticosteroids bears the risk of adverse events like skin atrophy, teleangiectasia and dyspigmentation. Therefore, there is a need for topical preparations containing active ingredients with a comparative anti-inflammatory potential but without the side effects of corticosteroids. On this background there is an increasing scientific interest for herbal ingredients as anti-inflammatory agents. For screening purposes in vivo, the UV erythema test is emerging as a suitable tool [18, 19, 22–24]. Previously, the results of several controlled clinical studies had been in favor of the anti-inflammatory properties of *A. vera* [6, 7, 25, 26]. However, in a small study with 12 volunteers no anti-inflammatory properties of *A. vera* gel were found using the UV erythema test [27]. During this study the assessment of erythema was performed 6 and 24 h after administration of the *A. vera* gel. In the study presented here, we could not detect any anti-inflammatory effect of *A. vera* gel after 24 h either. Forty-eight hours after application of the gel, a significant effect could be detected. Obviously, the onset of the effect of botanical ingredients is delayed. This observation was also made in other studies that tested topical herbal preparations [18, 19].

In the present study, 40 subjects were included in the trial, who were irradiated with the 1.5-fold MED on test areas on the back. This localization is the best test site of the body with the smallest fluctuations of the photometric measurements and the best match of the erythema of the light scale compared to that of the test sites [19]. The effect of *A. vera* gel (97.5%) was compared to Dermallerg-Ratiopharm cream 1% (1% hydrocortisone) and Dermatop cream (0.25% prednicarbate) as well as 1% hydrocortisone in placebo gel as positive controls. As expected, the commercially available potent corticosteroid preparations resulted in significant erythema suppression already after 24 h. Also, the well-known blanching effect of corticosteroids related to vasoconstriction of the superficial vasculature could be observed in nonirradiated test areas. *A. vera* gel (97.5%) also caused a significant inhibition of UVB-induced erythema but only 48 h after the first application. This effect was even stronger than that of 1% hydrocortisone in placebo gel, but weaker compared to that of the commercially available corticosteroids. It is striking that the hydrophilic placebo gel used as negative control also showed a significant anti-inflammatory effect comparable to the effect of *A. vera* gel (97.5%) 48 h after administration. However, the effect of the *A. vera* gel can hardly be attributed to placebo effects because additional constituents make up only 2.5% in the *A. vera* gel. The success of the gel base might be explained by a refrigerant effect or specific effects of the gel compounds, such as glycerol or phenoxyethanol. Interestingly, 1% hydrocortisone in placebo gel was less effective after 48 h than the placebo gel or *A. vera* gel (97.5%) whereas 1% hydrocortisone in the base of a cream efficiently reduced erythema after 48 h. Presumably, the gel base may inhibit the effects of hydrocortisone.

A. vera is known to cause hypersensitivity reactions in the form of contact dermatitis [7, 28]. The *A. vera* gel preparation (97.5%) used in our study was well tolerated without any side effects. No conclusion can be made about the sensitization potential of *A. vera* gel (97.5%) since the occurrence of an allergy after a single application is rather rare.

We conclude that *A. vera* gel (97.5%) has some anti-inflammatory potential with regard to reducing skin inflammation caused by UVB irradiation. The effective use of *A. vera* gel (97.5%) for chronic inflammatory skin conditions cannot be predicted on the base of the present study. Because of the lack of corticosteroid side effects, it might be reasonable to use *A. vera* gel (97.5%) as an additive for skin care products such as aftersun lotions instead of a hydrocortisone-containing gel.

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