Anti-Inflammatory Effect of Hamamelis Lotion in a UVB Erythema Test

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Key Words
Hamamelis
Anti-inflammatory effect
UVB erythema
Aftersun lotion

Abstract
Background: Although *Hamamelis virginiana* has long been used in the traditional treatment of skin diseases, there are few controlled clinical studies defining the extent of its anti-inflammatory action. **Objective:** The anti-inflammatory efficacy of pH5 Eucerin aftersun lotion with 10% hamamelis distillate, the vehicle and a prior aftersun formulation were tested in 30 healthy volunteers using a modified UVB erythema test as model of inflammation. **Methods:** Four UVB doses ranging from 1 to 2 MED were evaluated in each subject. Test fields on the back were treated occlusively for 48 h following irradiation. Chromametry and visual scoring were used to determine the degree of erythema in the treated fields and an untreated, irradiated control field 7, 24 and 48 h after irradiation. **Results:** Erythema suppression ranged from approximately 20% at 7 h to 27% at 48 h in the hamamelis fields. A suppression of 11–15% was recorded in the fields treated with the other lotions. Significant differences were noted between hamamelis and these lotions. **Conclusion:** These data provide evidence for an anti-inflammatory action of the aftersun lotion with 10% hamamelis and support the usefulness of the UVB erythema test with multiple UV doses for the testing of nonsteroidal anti-inflammatory agents.

Introduction

Preparations containing distillate prepared from leaves and twigs of *Hamamelis virginiana* L. have been used for the clinical treatment of inflammatory skin diseases since the 1800s [1]. It has been possible to provide evidence for an anti-inflammatory action in controlled human clinical trials in both healthy volunteers [2, 3] and patients [2, 4]. In light of the well-documented low toxicity of hamamelis, better understanding of its anti-inflammatory properties is of great clinical interest.

The UVB-induced erythema test is well suited for delivering in vivo evidence of the anti-inflammatory action of topical agents in human subjects. Using this model it has been possible to demonstrate the efficacy of steroidal as well as nonsteroidal preparations [5–8]. In the present study, the model has been used to test the efficacy of an aftersun lotion containing 10% hamamelis distillate. The primary indication for the lotion is the alleviation of the symptoms accompanying a light sunburn.

Using the standard UVB erythema test with uniform exposure of the test fields to a single defined UVB dose, it is

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Table 1. Listing of the test preparation components by INCI

pH5 aftersun lotion with 10% hamamelis distillate	aqua, alcohol denat., octyl stearate, butylene glycol, cyclomethicone, glycine, caprylic/capric triglyceride, tocopheryl acetate, cetearyl alcohol, *Hamamelis virginiana*, panthenol, glyceryl lanolate, laurylmethicone copolyol, PEG-40 castor oil, diammonium citrate, hydroxypropyl methylcellulose, sodium carbomer, sodium cetearyl sulfate, octoxyglycerin, trisodium EDTA, citric acid, lanolin alcohol, bisabolol, *Aloe vera* gel *(Aloe barbadensis)*
pH5 aftersun lotion (hamamelis-free vehicle)	aqua, alcohol denat., octyl stearate, butylene glycol, cyclomethicone, glycine, caprylic/capric triglyceride, tocopheryl acetate, cetearyl alcohol, panthenol, glyceryl lanolate, laurylmethicone copolyol, PEG-40 castor oil, diammonium citrate, hydroxypropyl methylcellulose, sodium carbomer, sodium cetearyl sulfate, trisodium EDTA, citric acid, lanolin alcohol, bisabolol, *Aloe vera* gel *(Aloe barbadensis)*
Prior formulation pH5 aftersun lotion	aqua, alcohol denat., octyl stearate, butylene glycol, cyclomethicone, glycine, caprylic/capric triglyceride, tocopheryl acetate, cetearyl alcohol, glyceryl lanolate, laurylmethicone copolyol, PEG-40 castor oil, diammonium citrate, hydroxypropyl methylcellulose, sodium carbomer, sodium cetearyl sulfate, trisodium EDTA, citric acid, lanolin alcohol

not always possible to demonstrate slight anti-inflammatory effects of nonsteroidal preparations since the sensitivity of the model corresponds approximately to the effectiveness of hydrocortisone. This is especially true since the typical corticosteroid vasoconstrictive effects which contribute to the measurable erythema suppression after short treatment periods are often absent. In order to increase the sensitivity of the model we have modified the standard test using one light intensity to include a range of UVB doses ranging from 1 to 2 minimal erythema doses (MED). Corticosteroids have proved most effective within this dose range [9]. The assessment of erythema suppression was performed using chromametry as well as visual scoring. In our institute we have established that this allows more subtle differentiation between treatment effects than visual assessment alone.

Korting et al. [3] were able to demonstrate a moderate to weak anti-inflammatory action by a hamamelis distillate preparation in a phosphatidylcholine-containing vehicle in a UVB erythema test utilizing a single UVB dose of 1.5 MED. The preparation was weaker than the reference product containing 1% hydrocortisone (oil-in-water, O/W, emulsion) [3]. Two other hamamelis preparations tested simultaneously proved ineffective. In a screening test with a large number of topical preparations, we determined that the UVB erythema suppression by the hamamelis preparation tested in the present study was approximately 30% that of a 1% hydrocortisone cream and in the range of an antihistamine gel containing 0.1% dimethindene maleate at 1 and 2 MED [unpubl. observation]. On the basis of this observation we decided to perform a vehicle-controlled, randomized clinical trial to better define the effectiveness of the test preparation containing 10% hamamelis distillate for the suppression of UVB-induced erythema.

Materials and Methods

Subjects

Thirty-three healthy volunteers (22 women and 11 men; age range 19–64 years, mean 35.6 years) participated in the study. Data from 28 volunteers were available at all test points. Three volunteers discontinued the study prior to the first treatment due to failure to establish the MED. All volunteers had skin types I, II or III according to Fitzpatrick and an individual typological angle >30° [10]. None of them were tanned or had hyperpigmentation or tattoos within the area of the test fields and none had a history of photosensitivity. Treatment with systemic or locally acting medications which might counter or influence the study aim were not allowed within the 2 weeks preceding the study or during the study (e.g. antihistamines or glucocorticosteroids). Pregnant and nursing women were excluded. Written consent was obtained from all subjects. Performance of the study was approved by the Ethics Committee of the Medical Council of Hamburg, Germany.

Test Preparations and Treatments

The newly developed pH5 Eucerin aftersun lotion with 10% hamamelis distillate, the hamamelis-free vehicle and a prior formulation of pH5 Eucerin aftersun lotion also without hamamelis were compared. The components by INCI of the O/W emulsions are listed in table 1. The hamamelis distillate (14% alcohol) was purchased from American Distilling & Mfg., Inc. (East Hampton, Conn., USA). It is accepted as an active product and has been adopted under the name 'witch hazel' into the USP 23 and BPC. Witch hazel is a clear, colorless distillate prepared from recently cut and partially dried twigs of *Hamamelis virginiana* Linné. The exact chemical makeup is unknown.

Approximately 300 µl of each test preparation were applied occlusively to the treatment fields in Finn® chambers (18 mm ∅) immediately following exposure of test fields to UVB and after measurement at 7 and 24 h after irradiation. The irradiated control fields were occluded but untreated. Assignment of the treatment to the test fields was random.

Irradiation

A UV 800 lamp (Waldmann, Villingen-Schwenningen, Germany) emitting mainly UVB and only small amounts of UVA and visible

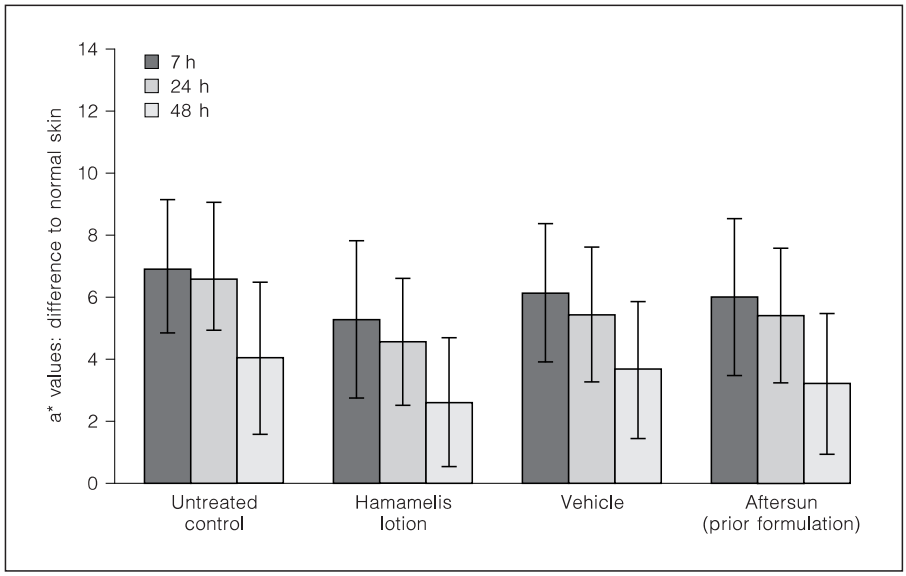

Fig. 1. Adjusted chromametry values following irradiation with 1 MED (mean ± SD).

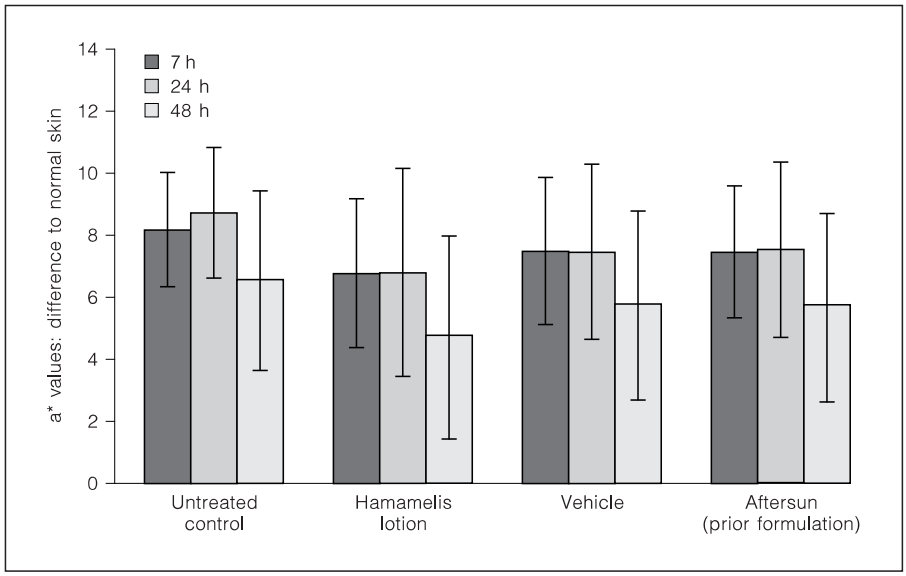

Fig. 2. Adjusted chromametry values following irradiation with 1.25 MED (mean ± SD).

light was used to provide even surface lighting with an intensity of 2 mW/cm^2 UVB. In order to set the required intensity the distance of the source from the plane of the surface to be irradiated was adjusted before every irradiation series with a UVA/B meter (Waldmann).

Twenty-four hours before induction of the UVB erythema, a light scale was performed to determine the individual MED. One MED is the smallest amount of UVB producing distinct erythema. A template with 8 round holes (0.8 cm ∅ each) arranged at least 1 cm from each other was attached to the back. When the desired UVB dose (exposure time) was reached, the individual holes were covered. The dose increased by 20% from one hole to the next. The light scale was read 24 ± 2 h after exposure. The exposure time from the first field showing distinct erythema was taken as 1 MED.

A light-impermeable template with perforated holes (1.2 cm ∅ each) corresponding to 16 test fields and located at least 1.6 cm apart from each other was attached to the back. The entire back was irradiated simultaneously. The 4 fields in each UV dosage group were covered simultaneously with a light-impermeable strip at the end of the exposure time calculated for 1, 1.25, 1.6 and 2 MED.

Measurements

Test field evaluation (chromametry and visual assessment) was performed 7, 24 and 48 h after irradiation. One hour before the measurement periods (6, 23 and 47 h, respectively) the occluding chambers were removed and test preparation residues removed with a soft disposable towel.

Skin color measurements were made with a Chroma-Meter CR 300 (Minolta, Ahrensburg, Germany). Values were recorded in accordance with the L*a*b* system. The value on the 'red-green' axis (a*) reflects the degree of skin reddening. A decrease or increase in the a*

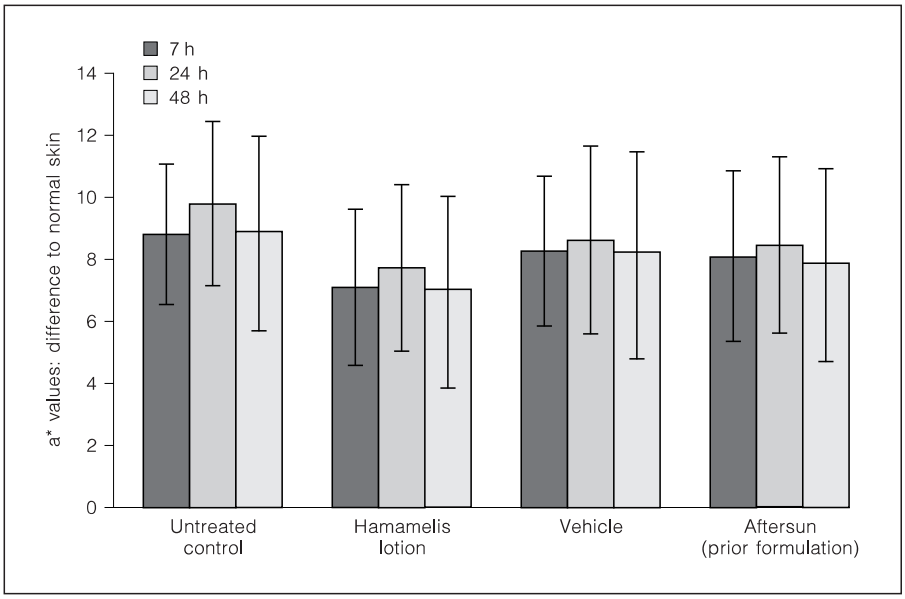

Fig. 3. Adjusted chromametry values following irradiation with 1.6 MED (mean ± SD).

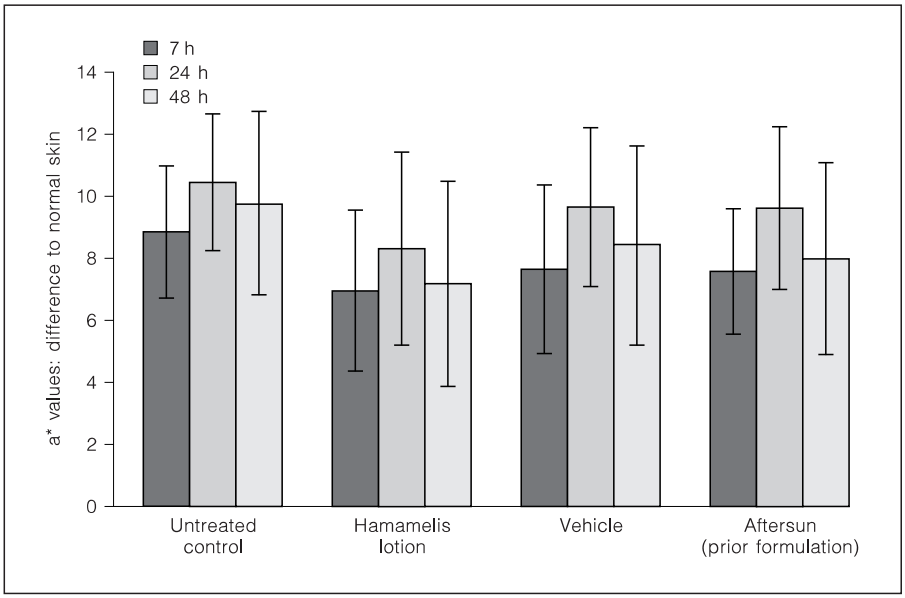

Fig. 4. Adjusted chromametry values following irradiation with 2.0 MED (mean ± SD).

Table 2. Reddening in the test fields expressed as percent of irradiated control

Test point		Hamamelis lotion				Vehicle				Prior formulation			
	MED:	1 n = 30	1.25 n = 30	1.6 n = 29	2.0 n = 28	1 n = 30	1.25 n = 30	1.6 n = 29	2.0 n = 28	1 n = 30	1.25 n = 30	1.6 n = 29	2.0 n = 28
7 h		77	83	80	79	90	92	94	86	88	91	91	86
24 h		69	77	78	79	83	85	87	92	82	85	85	92
48 h		65	71	79	73	91	87	92	86	80	86	88	82

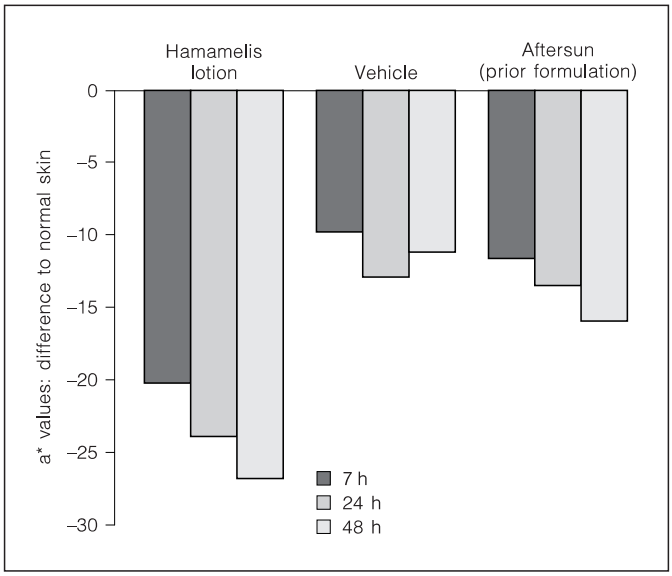

Fig. 5. Suppression of erythema expressed as percent of irradiated control. Adjusted a* values (irradiated site – adjacent nonirradiated skin) from all UVB doses were pooled.

Table 3. Sums of visual scores per test point aud UV dose

Test point		Hamamelis lotion				Vehicle				Prior formulation			
	MED:	1 n = 30	1.25 n = 30	1.6 n = 29	2.0 n = 28	1 n = 30	1.25 n = 30	1.6 n = 29	2.0 n = 28	1 n = 30	1.25 n = 30	1.6 n = 29	2.0 n = 28
7 h		4	2	2	1	3	0	1	1	3	4	4	0
24 h		5	6	7	4	4	2	2	3	7	6	5	4
48 h		1	3	5	5	0	1	4	4	6	6	4	1
Total		10	11	14	10	7	3	7	8	16	16	13	5

Reddening in the treated fields was compared to reddening in the irradiated control field according to the following scale: 0 = no suppression of erythema, no difference to control; 1 = slight, just identifiable suppression of erythema; 2 = clear suppression of erythema but some erythema still present; 3 = complete suppression of erythema.

value (red value) corresponds to a decrease or increase in the degree of erythema. Measurements were performed by lightly placing the measurement head on the test fields and triggering. Three measurements were taken from each test field at each measurement series. Nonirradiated skin adjacent to the test areas was also measured at each test point.

The degree of erythema in the treatment fields in comparison to the untreated control fields was visually assessed according to the following scale: 0 = no suppression of erythema, no difference to control; 1 = slight, just identifiable suppression of erythema; 2 = clear suppression of erythema but some erythema still present, and 3 = complete suppression of erythema.

Statistics

The chromametric data were adjusted by calculating the differences between the a* values measured in the irradiated test fields and at adjacent nonirradiated skin. Normal distribution of the adjusted chromametric data was tested using the Kolmogorow-Smirnow test. Global differences between treatments were tested by performance of an ANOVA F test using the pooled adjusted a* values from all irradiation steps. Multiple comparisons between treatments were made using Tukey's HSD test. All p values were two-tailed.

Results

In figures 1–4, the course of the UVB erythema can be seen for the 4 UVB doses. Even when considering the relatively narrow range of 1–2 MED, it can be seen that the reddening intensifies over a longer time span and the recovery from the erythema is slower at the higher UVB doses. The erythema suppression in the test sites treated with hamamelis tended to increase with longer treatment times in the

fields irradiated with the two lowest UV doses (fig. 1 and 2, table 2). This effect was not apparent in the fields treated with the other preparations.

The percent suppression of erythema for each treatment is shown as a pooled value comprising all irradiation doses in figure 5. The cream containing hamamelis led to a reduction ranging from approximately 20% after 7 h to 27% after 48 h. The other lotions led to a suppression ranging from 10% after 7 h to 15% after 48 h. Percentages for the individual UV doses are listed in table 2.

Hamamelis led to a highly significant reduction in erythema when compared to the prior pH5 Eucerin aftersun lotion ($p = 0.00039$), the vehicle ($p = 0.00001$) or untreated, irradiated skin ($p = 0.00001$). Both hamamelis-free lotions also exhibited significant differences to untreated, irradiated skin (vehicle $p = 0.00007$; prior pH5 Eucerin aftersun lotion $p = 0.00001$). There were no differences between the hamamelis-free lotions.

No clear differences between the test preparations could be detected by visual assessment. Only very low score sums were recorded per test point and irradiation step (table 3).

Discussion

The results of several controlled clinical studies support an anti-inflammatory action of topically applied hamamelis distillate preparations. Sorkin [2] demonstrated a reduction in skin blood flow after an average latency period of 31 min following application of a hamamelis ointment in healthy volunteers as well as patients suffering from atopic eczema or psoriasis. In contrast, the corresponding vehicle mostly led to an increase in skin blood flow. Swoboda and Meurer [4] performed an intraindividual comparison of the clinical efficacy of a hamamelis ointment and bufexamac ointment in 22 patients with neurodermatitis. A similar improvement in the symptoms reddening, scaling, lichenification, pruritus and infiltration was seen for both treatments.

Hamamelis distillate in different O/W emulsions with and without phosphatidylcholine was tested in an experimental study utilizing UVB-induced erythema and stripping as inflammatory models [3]. The hamamelis preparations were compared with a 1% hydrocortisone cream and the active ingredient-free vehicles. A suppression of erythema by the cream with hydrocortisone and one of two hamamelis distillate preparations in a cream containing phosphatidylcholine was reported in both experimental models. The hamamelis preparation was less effective than hydrocortisone cream. Hamamelis distillate in a conventional O/W cream did not prove effective.

Even though the erythema response in the above-mentioned study was assessed by visual scoring as well as chromametry, the authors reported better discrimination with the subjective scoring method [3]. This is in contrast to our own experience with the evaluation of erythematous responses. Even for the experienced observer it is difficult to accurately perceive very slight alterations by eye. By using the difference between the a* values recorded in the test fields and those recorded in adjacent nonirradiated skin, subtle effects due to minor irregularities in the underlying skin color can be corrected. The desirability of objective chromametric measurements for the evaluation of skin color responses is also recognized for other tests, e.g. the blanching assay [11, 12]. Whereas obvious skin color changes such as those observed due to blanching following topical application of moderately to highly potent corticosteroids can be easily verified by visual assessment, finer differences seen with less potent corticosteroids or still weaker phytopreparations are best evaluated objectively. Therefore, the failure of visual scoring to discriminate between the test preparations in the present study is not surprising since the hamamelis test preparation can only be expected to be as effective as an anthistamine gel or about 1/3 as effective as the weak corticosteroid hydrocortisone [unpubl. observation].

It was possible to identify mild but highly significant anti-inflammatory effects for the reference lotions as well as the test preparation with the active ingredient hamamelis. Consistent results were seen at each of the four UVB doses tested (table 1). A slight suppressive effect of the aftersun lotions was already apparent at the earliest test point (7 h after irradiation) and was increased at the second test point by a further 6–7% at 1–1.6 MED. These results can most likely be attributed to the inclusion of tocopherol acetate (vitamin E) in both formulations. Using the same UV erythema test model, it has been possible to demonstrate an anti-inflammatory effect for vitamin E [unpubl. observations].

More pronounced evidence of a progressive suppression with a longer treatment interval was only seen for the hamamelis preparation at the two lowest MEDs. This observation underscores the importance of measurement over a prolonged time span which includes regression of the initial inflammation. At 1 and 1.25 MED, the erythema in the irradiated control field decreases rather rapidly by 48 h and longer after irradiation. In contrast, at the higher UVB doses the phase with a sharper decrease in reddening is only apparent at later time intervals.

In conclusion, in the present study using a modified UVB erythema test as the inflammatory model, an ery-

thema suppression of 20–27% supports an anti-inflammatory effect of the test preparation containing 10% hamamelis distillate. These results provide a further rationale for the topical use of hamamelis distillate for the treatment of inflammatory skin diseases which do not necessitate treatment with potent corticosteroids. In particular, alleviation of the symptoms of inflammation following a light sunburn is a suitable indication for the pH5 Eucerin aftersun lotion with hamamelis. Maintenance therapy for atopic eczema, particularly as a follow-up to treatment with potent steroidal anti-inflammatory agents, may also be considered as an indication. In light of the low toxicity of hamamelis and the absence of known undesirable effects [1], the tested preparation containing hamamelis distillate has a favorable risk/benefit ratio.

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