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Combined Herbal Preparation for Topical Treatment of Herpes labialis

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Key Words

Rhubarb · *Rheum* sp. · Sage · *Salvia officinalis* · Aciclovir · Herpes labialis · Clinical trial

Summary

Background: The efficacy of many preparations for topical use in herpes infections have remained rather disappointing. The development of new antiviral drugs, especially herbal preparations, thus remains desirable. In a screening study with plant extracts, a rhubarb root extract and a sage extract showed a promising activity. ***Objective:*** The efficacy of a combined topical preparation with rhubarb and sage extracts, of a single-agent preparation with sage extract and of a reference treatment was investigated in a double-blind, comparative, randomised trial. ***Patients and Methods:*** A total of 149 patients participated, and 145 patients (111 female, 34 male) of whom 64 received the rhubarb-sage cream, 40 the sage cream and 41 Zovirax cream could be evaluated by intention-to-treat analysis. The dried rhubarb extract (23 mg/g) is a standardised aqueous-ethanolic extract according to the German Pharmacopoeia (DAB) with 4.0–6.0% hydroxyanthracene derivatives. The dried sage extract (23 mg/g) is an aqueous extract. The reference product was Zovirax cream (Zovirax® Creme) with the active ingredient aciclovir (50 mg/g). ***Results:*** The mean time to healing in all cured patients was 7.6 days with the sage cream, 6.7 days with the rhubarb-sage cream and 6.5 days with Zovirax cream. There were statistically significant differences in the course of the symptoms. For the parameter 'swelling', at the 1st follow-up visit there was a significant advantage for Zovirax cream compared to sage cream, and for the parameter 'pain', at the 2nd follow-up visit there was a significant difference in favour of the rhubarb-sage cream compared to the sage cream. ***Conclusion:*** The combined topical sage-rhubarb preparation proved to be as effective as topical aciclovir cream and tended to be more active than the sage cream.

Schlüsselwörter

Rhabarber · *Rheum* sp. · *Salvia officinalis* · Salbei · Aciclovir · Herpes labialis · Klinische Studie

Zusammenfassung

Hintergrund: Die Wirksamkeit vieler bei Herpes-Infektionen lokal angewendeter Präparate ist eher enttäuschend. Die Entwicklung neuer antiviral wirksamer Medikamente und speziell auch pflanzlicher Präparate ist deshalb nach wie vor wünschenswert. ***Ziel:*** Die Wirksamkeit eines topischen Kombinationspräparats mit Rhabarber- und Salbeiextrakt, eines Monopräparates mit Salbeiextrakt sowie eines Referenzpräparats wurde mittels einer komparativen randomisierten Doppelblindstudie untersucht. ***Patienten und Methoden:*** Insgesamt nahmen 149 Patienten an der Studie teil. Die Daten von 145 Patienten (111 weibliche und 34 männliche) konnten in die «Intention-to-treat»-Analyse miteinbezogen werden. Davon erhielten 64 die Rhabarber-Salbeicreme, 40 die Salbeicreme und 41 die Zovirax-Creme. Beim Rhabarber-Trockenextrakt (23 mg/g) handelt es sich um einen eingestellten wässrig-ethanolischen Extrakt nach DAB mit 4,0–6,0% Hydroxyanthracen-Derivaten. Beim Salbei-Trockenextrakt (23 mg/g) handelt es sich um einen wässrigen Extrakt. Als Referenzpräparat diente Zovirax® Creme mit dem Wirkstoff Aciclovir (50 mg/g). ***Ergebnisse:*** Die Heilungszeit aller geheilten Patienten betrug bei der Salbeicreme durchschnittlich 7,6 Tage, bei der Rhabarber-Salbeicreme 6,7 Tage und bei der Zovirax-Creme 6,5 Tage. Im Verlauf der Symptome zeigten sich statistisch signifikante Unterschiede. Für den Parameter «Schwellungen» zeigte sich bei der 1. Kontrollvisite ein signifikanter Vorteil für die Zovirax-Creme im Vergleich zur Salbeicreme. Bei der 2. Kontrollvisite zeigte sich ein signifikanter Unterschied zugunsten der Rhabarber-Salbeicreme gegenüber der Salbeicreme bezüglich dem Parameter «Schmerzen». ***Schlussfolgerung:*** Es konnte gezeigt werden, dass das topische Kombinationspräparat ebenso wirksam wie die Zovirax-Creme und tendenziell besser als die Salbeicreme ist.

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Introduction

Herpes simplex viruses are pathogenic to humans and cause common infections throughout the world. Depending on the site of infection, we speak of herpes labialis on the lips or herpes genitalis in the anogenital area. Herpes simplex viruses are neurotropic, which means that after first infection they spread through the skin or mucosa to the corresponding spinal ganglion and remain inactive there in the latent phase. As a result of various immune stresses they can be re-activated at any time and trigger a characteristic herpes outbreak with the formation of blisters and inflammation. Trigger effects of this type may be: influenza, menstruation, UV challenge, stress, dental treatment, surgery, excessive alcohol consumption, lack of sleep or generally weak immune defences.

In Switzerland, antibodies to type I are found in more than 90% of the adult population, and, depending on the social and sexual risk of transmission, antibodies to type II are found in 20–60% of persons. Transmission is by direct contact with infectious material from the skin or mucosae. Primary infections with Herpes simplex generally have a troublesome course, going as far as herpetic gingivostomatitis with type I and painful ulcerous-oedematous vulvovaginitis with type II. Frequent complications of all herpetic eruptions are super-infection with staphylococci, mycotic infection with *Candida* or herpetic eczema with neurodermatitis.

The early introduction of a systemic therapy with antimetabolites such as aciclovir shortly after the appearance of clinical symptoms is decisive for a successful therapeutic effect. Long-term oral prophylaxis over months and years (especially against herpes genitalis) may be performed with low-dose antimetabolites. The actions of topical preparations have remained rather disappointing. The development of newer antiviral agents and especially those for topical use in herpes infections thus remains desirable just as before.

In a screening study with plant extracts, a rhubarb root extract showed the most promising activity [1]. A prospective, randomised, controlled, double-blind pilot study was therefore performed to investigate the efficacy and tolerability of a cream with rhubarb extract [2]. A total of 66 patients participated in the study, of whom 45 received rhubarb cream and 21 Zovirax cream (active ingredient aciclovir). The results of the study showed no statistically significant difference between the two study products. A clear trend to a better action of Zovirax cream was however seen for the first primary target criterion, i.e. the healing time in all cured patients. The mean healing time was 6.5 ± 2.5 days (mean ± SD) in the Zovirax group (n = 21) and 7.4 ± 3.2 days in the rhubarb group (n = 39) [2]. Due to the rather unsatisfactory results of this study, the study with rhubarb cream was interrupted after the first interim evaluation, and a combined preparation with rhubarb and sage extracts was developed for study. At the same time, a single-agent preparation with sage leaf extract was included in the study. An extract of this type also showed antiviral action in the aforementioned screening study. Sage leaves also have anti-inflammatory activity and, due to their tannin content, may be assumed to have a beneficial action on wound healing.

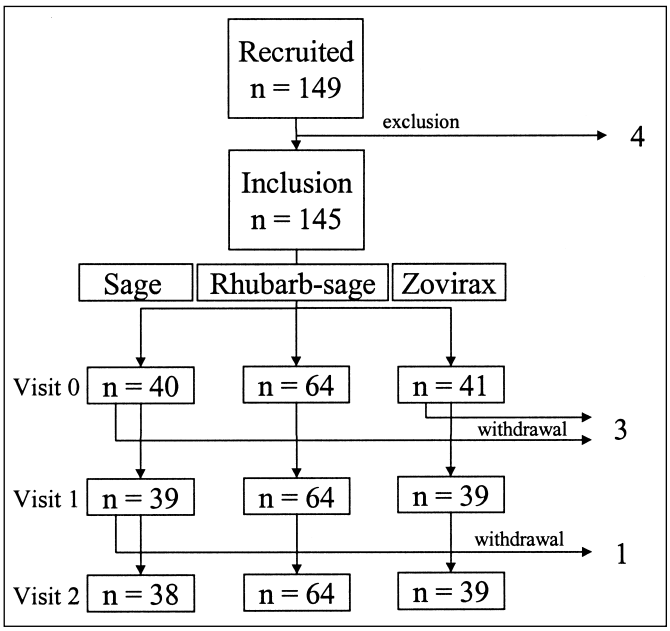

Fig. 1. Patients' flow. Visit 0 = inclusion visit, visit 1 = 1st follow-up visit; visit 2 = 2nd follow-up visit.

Patients and Methods

The Declaration of Helsinki and GCP (good clinical practice) rules were taken into account in the organisation and performance of the study. In addition, the approval of the Medical Ethics Committee of the Graubünden Cantonal Hospital was obtained.

Patients

The following inclusion and exclusion criteria were applied:

Inclusion criteria

- Age: 18–65 years.
- Diagnosis: recurrent herpes simplex labialis, unequivocally diagnosable in the vesicular phase or on appearance of the prodromal signs (itching, smarting, tension, pain) and according to the case history.
- The patients must be informed of the sense and purpose of the study and must have given their consent.

Exclusion criteria

- Any topical use of medicines in the affected area within the last 7 days before the start of treatment.
- Concomitant topical or systemic use of antiviral or immunomodulating medicines.
- Known drug allergies or hypersensitivity to one of the active ingredients (aciclovir, sage leaves, rhubarb root) or one of the excipients (propylene glycol, lanolin, lauryl sulphate, methyl para-hydroxybenzoate (E 218), propyl para-hydroxybenzoate (E 216)).
- Patients expected to show poor compliance.
- Patients in whom delayed healing is possible (immune weakness, diabetes, etc.).

The clinical study enrolled 149 patients, and the results for 145 patients (111 female and 34 male) could be evaluated. The patients' flow is presented in figure 1.

Table 1. Demographic distribution

	Sage	Rhubarb-sage	Zovirax	F[a]	p-value
Mean age, years	35.0	37.5	35.3	0.631	0.53
Mean diameter of lesion, mm	6.2	5.8	6.3	0.236	0.79
Mean number of lesions	1.5	1.6	1.9	0.916	0.40
Mean number of hours in acute state	22.2	25.0	33.1	2.329	0.10

[a]Fisher's exact test.

Table 2. Distribution of symptoms*

Symptoms at 1st visit	Medication						Comparison of all medications[1] (person chi-square[3])	Rhubarb-sage- versus Zovirax[2] (Fisher's exact test[4])
	sage		rhubarb-sage		Zovirax			
	n	%	n	%	n	%		
Total	40	100.00	64	100.00	41	100.00		
Pruritus								
No	15	37.50	26	40.63	21	51.22	0.413	
Mild	17	42.50	30	46.88	12	29.27		
Severe	8	20.00	8	12.50	8	19.51		
Burning								
No	10	25.00	27	42.19	16	39.02	0.193	
Mild	23	57.50	32	50.00	22	53.66		
Severe	7	17.50	5	7.81	3	7.32		
Skin tension								
No	2	5.00	6	9.38	3	7.32	0.712	
Mild	27	67.50	44	68.75	32	78.05		
Severe	11	27.50	14	21.88	6	14.63		
Pain								
No	19	47.50	33	51.56	23	56.10	0.741	
Mild	18	45.00	29	45.31	18	43.90		
Severe	3	7.50	2	3.13				
Blisters								
No	4	10.00	1	1.56	10	24.39	0.001	0.000
Mild	29	72.50	57	89.06	25	60.98		
Severe	7	17.50	6	9.38	6	14.63		
Swelling								
Mild	31	77.50	60	93.75	37	90.24		
Severe	9	22.50	4	6.25	4	9.76		
Erosion								
No	22	55.00	42	65.63	23	56.10	0.468	
Mild	14	35.00	22	34.38	16	39.02		
Severe	4	10.00			2	4.88		
Crust								
No	32	80.00	55	85.94	31	75.61	0.401	
Mild	7	17.50	9	14.06	10	24.39		
Severe	1	2.50						

*For statistical testing, the symptoms were re-coded into a new dichotomous variable that indicates whether a symptom is present or absent.

[1] Comparison of all medications means all three medications are compared and tested for the two states of the symptom variables, resulting in a 2×3 table.

[2] Comparison medication 2 versus medication 3 means that two out of three medications are compared and tested for the two states of the symptom variables, resulting in a 2×2 table. Data are only shown if they are significant without corrections for multiple testing. For Bonferroni correction multiply the p values by two.

[3] Asymptotic 2-sided test.

[4] 2-sided test. p values without corrections for multiple testing. For Bonferroni correction multiply the p values by two.

Table 3. Efficacy and safety parameters

Primary target criteria	Evaluation by*
1. Time to complete disappearance of lesions (duration of therapy in days)	P/D
2. Time to drying and/or to start of crust formation (in days)	P/D
3. Clinical course of the symptoms (itching, smarting, tension, pain, swelling, erosion, diameter of largest lesion) at time of each visit (inclusion, days 4–6, days 10–14)	P/D
Secondary target criteria	
4. Time to next recurrence (in days)	P/D
5. Treatment failure: persistence of lesions at days 10–14	D
6. Appearance of complications, i.e. extension or scatter of lesions, or superinfection (e.g. impetigo) at days 10–14	D
7. Judgement of efficacy	P/D
8. Judgement of tolerability	P/D

*The evaluation was performed by the doctor (D) and the patient (P). The data for the individual symptoms was given in three steps (none, mild and more severe). The judgement of efficacy and tolerability was given in three steps (good, moderate, unsatisfactory).

The three patient groups were comparable at the start of the study with regard to the following parameters: sex, age, diameter of the largest lesions, number of lesions, number of hours in the acute stage as well as symptoms at the time of the inclusion visit (itching, smarting, tension, pain, blister formation, swelling, erosion, crust formation). With the exception of one symptom at the time of the inclusion visit, there were no significant differences with regard to the distribution of patients in the three medication groups. The demographic data are presented in table 1.
The symptoms at the time of the inclusion visit are presented in table 2. The evaluation was performed on a dichotomous basis (no symptoms versus mild and severe symptoms). At this time, blister formation was significantly more marked in the rhubarb-sage group than in the Zovirax group.
The study was performed in 8 study centres. These included a dermatologist, and six general practitioners in their own practices. The eighth study centre was the Davos Dermatology and Allergy Clinic.
In order to determine adverse effects, the investigating doctors questioned the patients during the two follow-up visits.
The study medication was allocated to the patients according to a randomisation scheme developed by the statistician. Randomisation was undertaken in a 1:1:1 ratio (Zovirax:sage:rhubarb-sage) in blocks of 6. After an interim analysis, a new randomisation list was created with a 1:1:2 ratio (Zovirax:sage:rhubarb-sage) in blocks of 8.

Medication

The dried rhubarb extract is a standardised aqueous-ethanolic extract according to the German Pharmacopoeia (DAB) with 4.0–6.0% hydroxyanthracene derivatives, calculated as rhein by reference to the dried extract. This is obtained from the roots of *Rheum palmatum* L. and *Rheum officinale* BAILL. The dried sage extract is an aqueous extract obtained from the leaves of *Salvia officinalis* L. Rosemaric acid, an important constituent of the labiate tannins, serves as the lead substance.
The study medicines were rhubarb-sage cream (23 mg/g rhubarb extract and 23 mg/g sage extract), sage cream (23 mg/g sage extract) and Zovirax cream (Zovirax® Creme, Glaxo Wellcome AG, Schönbühl, Switzerland; 50 mg/g aciclovir). The latter was purchased from a pharmaceutical wholesaler and repackaged.
The rhubarb extract concentration was chosen on the basis of the rhubarb extract concentration in Pyralvex® (NORGINE Pharmazeutische Präparate GmbH, Marburg, Germany), a solution used for conditions of the oral mucosa and gingiva, as well as aphthae. Pyralvex contains 10 mg/ml salicylic acid, and the rhubarb extract has an anthraquinone glycoside content corresponding 3 mg/ml. This concentration led to excessive colouration of the cream and was therefore reduced. The selected concentration of 23 mg/g rhubarb extract for the cream is higher by a factor of 10^2–10^3 than the concentrations that have proved to be antivirally active in vitro. The same concentration was chosen for the sage extract. This is in the same order of size as in the alcoholic extract that can be used undiluted, according to the Commission E monograph of 13.3.1990 [3], for painting on affected parts. Among other things, a virustatic and astringent action may be expected.
At the start of the study it was determined that the creams should be investigated by comparison with an established effective product. Comparison with placebo was rejected for ethical reasons. According to the knowledge at the time, Zovirax cream was the best product available.
The treatment regimen was established as follows: the inclusion visit (day 0) should take place within 1 day after the appearance of prodromal signs. The study medication should be rubbed in gently every 2–4 h while awake until the visit on day 10–14 or until the lesions were judged to be healed by the doctor or the patient. The 1st follow-up visit took place between the 4th and 6th day and the 2nd follow-up visit between the 10th and 14th day. The symptoms were evaluated by questionnaires during the initial visit and during the two follow-up visits. In addition, the symptoms and the use of the medication were recorded in a patient diary.
When dispensed, the study medications could not be distinguished one from the other (labelled tubes with safety closure). Only after opening the tube distinction was possible on the basis of colour. Since the patients did not know which 'chemical' product served as the reference, even after opening their tube it was not possible for them to determine whether they had a 'chemical' or a 'herbal' preparation. Since the tubes were opened only after the visit, it may be assumed that the investigating doctor also could not readily identify the study product.

Course of the Study

The aim of the study was to document the efficacy and tolerability of a cream based on rhubarb extract plus sage extract and of a cream based on sage extract only in patients with labial herpes. This was a prospective, multi-centre, randomised, double-blind trial that ran from 1996 to 1999.
At least 80 cases with the most effective herbal cream and at least 40 cases with Zovirax cream were planned. Since neither of the two herbal creams showed a clear advantage over the other at the time of the interim evaluation after 59 patients (sage cream 19, rhubarb-sage cream 21, Zovirax 19 patients), it was decided to enlarge the study as follows: sage and Zovirax cream at least an additional 20 patients, rhubarb-sage cream at least an additional 40 patients. The interim evaluation and the possibility of an alteration of the randomisation were foreseen in the study protocol. The efficacy and safety parameters are presented in table 3.

The parameters adopted are suitable for determining the course of labial herpes. They correspond to the symptoms usually recorded in clinical studies [e.g. 4–9]. In some studies [e.g. 4, 9] the virus load of the lesions was also determined. This parameter was not adopted in this study since the criteria selected adequately describe the course of a relapse.
External monitoring was performed to ensure the quality of the data. In addition, an investigators' meeting was organised to train the participating investigators at the start of the study. The study sponsor was Parsenn Produkte AG, CH-7240 Küblis.

Statistical Methods
All data analyses were performed using SPSS® for Windows 95/NT, release 6.3 and 9.0 (SPSS Inc., Chicago, IL, USA).
Continuous variables were presented by means of summary statistics. This refers to the number of patients with valid data (n), mean, median, minimum, maximum, SD.
Categorical data were presented using absolute and relative frequencies per category.
To detect possible differences in the baseline characteristics between the treatment groups, data such as age, gender, symptoms, lesions and duration of the infection were subjected to confirmatory statistics (chi-square test, analysis of variance (ANOVA), multinomial logistic regression). To detect possible effects by centres, the parameters for time necessary up to the point where the patient is cured, were additionally tested with an ANOVA model with treatment, centre and their interactions as factors. In order to have centre sizes with 13–19 patients per centre, centres with low number of patients were pooled for this purpose.
An intention-to-treat (ITT) analysis was performed. All patients known to have at least one application of the trial medication were included in the ITT analysis.

Results

The course of the study and the patient numbers are presented in figure 1. The data for 130 patients were available for the evaluation of time to healing. Data for 123 cases were available for the evaluation of time to crust formation. The data for 22 patients could not be used in this case since either there was no crust formation or the diary was missing or not completed by the patients.
The mean time to crust formation was 7.8 days with the sage cream, 7.2 days with the rhubarb-sage cream and 6.3 days with Zovirax cream (fig. 2). The mean time to healing was 7.6 days with the sage cream, 6.7 days with the rhubarb-sage cream and 6.5 days with Zovirax cream (fig. 3). Neither the time to crust formation nor the time to healing differed significantly between the treatment groups. The ANOVA- and Bonferroni-corrected multiple test results are presented in table 4.
For comparison of the healing time, a Kaplan-Meier survival analysis, including also those patients with missing data, was performed, resulting in non-significant differences between the three types of treatments (log rank statistic 2.02, p = 0.36). If the non-inferiority margin for healing, the acceptable inferiority between the plant extracts and aciclovir (Zovirax), is set to 1.5 days, one would conclude non-inferiority for both rhubarb-sage to aciclovir (Zovirax) and sage to aciclovir (Zovirax). Similarly, with the non-inferiority margin for crust

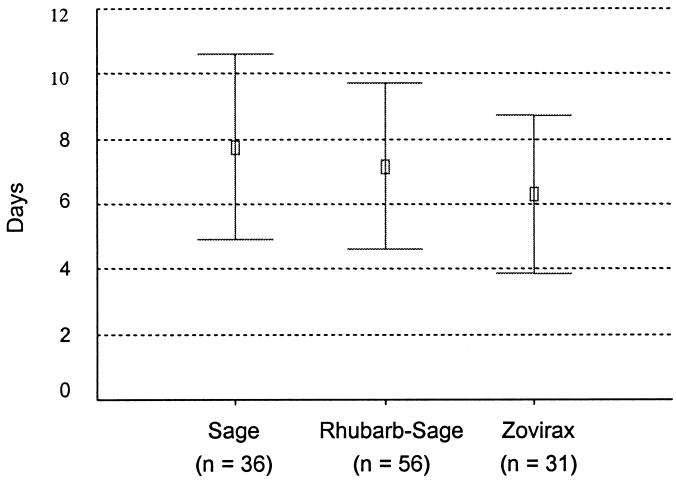

Fig. 2. Time to resolution of crusts.

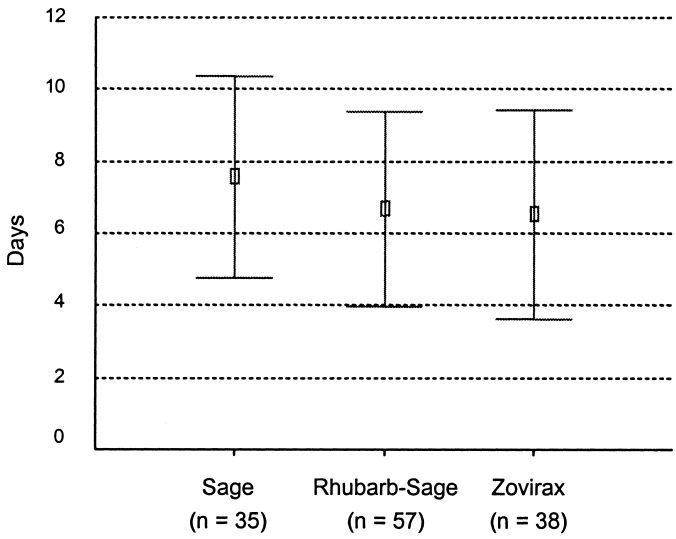

Fig. 3. Time to cure of patient

Table 4. Statistical data for crust formation and healing

	p value	F	95% CI*
Crust formation (ANOVA)	0.078	2.605	
Sage versus rhubarb-sage	0.88		–0.7688 to 1.9474
Sage versus Zovirax	0.07		–0.0980 to 3.0174
Rhubarb-sage versus Zovirax	0.42		–0.5528 to 2.2936
Healing (ANOVA)	0.221	1.572	
Sage versus rhubarb-sage	0.42		–0.5632 to 2.3377
Sage versus Zovirax	0.33		–0.5373 to 2.6275
Rhubarb-sage versus Zovirax	1.00		–1.2567 to 1.5724

*95% confidence interval.

formation set to 1.5 days, non-inferiority can be concluded for both plant extracts to acciclovir (Zovirax).

With one exception each time, the symptoms did not differ significantly between the groups at the time of the 1st and 2nd follow-up visits (tables 5 and 6). With the dichotomous comparison of symptoms (no symptom versus mild to severe

Table 5. Course of symptoms: 1 st follow-up visit*

Symptoms at 1st follow-up visit	Medication						Comparison of all medications[1] (person chi-square[3])	Sage versus Zovirax[2] (Fisher's exact test[4])
	sage		rhubarb-sage		Zovirax			
	n	%	n	%	n	%		
Total	40	100.00	64	100.00	41	100.00		
Pruritus								
No	27	67.50	46	71.88	33	80.49		
Mild	11	27.50	18	28.13	6	14.63	0.402	
Severe	2	5.00			2	4.88		
Burning								
No	24	60.00	52	81.25	34	82.93		
Mild	15	37.50	10	15.63	6	14.63	0.022	0.028
Severe	1	2.50	2	3.13	1	2.44		
Skin tension								
No	22	55.00	36	56.25	26	63.41		
Mild	15	37.50	24	37.50	14	34.15	0.697	
Severe	3	7.50	4	6.25	1	2.44		
Pain								
No	32	80.00	57	89.06	38	92.68		
Mild	8	20.00	5	7.81	2	4.88	0.199	
Severe			2	3.13	1	2.44		
Blisters								
No	31	77.50	56	87.50	38	92.68		
Mild	8	20.00	7	10.94	1	2.44	0.130	
Severe	1	2.50	1	1.56	2	4.88		
Swelling								
No	15	37.50	34	53.13	28	68.29		
Mild	23	57.50	28	43.75	10	24.39	0.021	0.008
Severe	2	5.00	2	3.13	3	7.32		
Erosion								
No	16	40.00	34	53.13	24	58.54		
Mild	21	52.50	29	45.31	15	36.59	0.161	
Severe	3	7.50	1	1.56	1	2.44		
N.A.					1	2.44		
Crust								
No	16	40.00	24	37.50	20	48.78		
Mild	20	50.00	38	59.38	17	41.46	0.508	
Severe	4	10.00	2	3.13	4	9.76		

*For statistical testing, the symptoms were re-coded into a new dichotomous variable that indicates whether either a symptoms is present or absent. For patients where data was not available, the last observation was carried forward.

[1] Comparison of all medications means all three medications are compared and tested for the two states of the symptom variables, resulting in a 2×3 table.

[2] Comparison medication 1 versus medication 3 means that two out of three medications are compared and tested for the two states of the symptom variables, resulting in a 2×2 table. Data are only shown if they are significant without corrections for multiple testing. For Bonferroni correction multiply the p values by two.

[3] Asymptotic 2-sided test.

[4] 2-sided test. p values without corrections for multiple testing. For Bonferroni correction multiply the p values by two.

N.A. = Not analysed.

Table 6. Course of symptoms: 2nd follow-up visit*

Symptoms at 2nd follow-up visit	Medication						Comparison of all medications[1] (person chi-square[3])	Sage versus Zovirax[2] (Fisher's exact test[4])
	sage		rhubarb-sage		Zovirax			
	n	%	n	%	n	%		
Total	40	100.00	64	100.00	41	100.00		
Pruritus								
No	38	95.00	63	98.44	40	97.56		
Mild	1	2.50	1	1.56			0.599	
Severe	1	2.50			1	2.44		
Burning								
No	37	92.50	64	100.00	40	97.56		
Mild	2	5.00			1	2.44	0.075	
Severe	1	2.50						
Skin tension								
No	37	92.50	64	100.00	40	97.56		
Mild	2	5.00			1	2.44	0.075	
Severe	1	2.50						
Pain								
No	36	90.00	64	100.00	40	97.56		
Mild	3	7.50					0.023	0.020
Severe	1	2.50			1	2.44		
Blisters								
No	39	97.50	64	100.00	40	97.56		
Mild	1	2.50					0.449	
Severe					1	2.44		
Swelling								
No	37	92.50	63	98.44	39	95.12		
Mild	3	7.50	1	1.56	1	2.44	0.332	
Severe					1	2.44		
Erosion								
No	37	92.50	62	96.88	40	97.56		
Mild	2	5.00	2	3.13			0.448	
Severe	1	2.50			1	2.44		
Crust								
No	35	87.50	59	92.19	40	97.56		
Mild	2	5.00	5	7.81			0.231	
Severe	3	7.50			1	2.44		

* For statistical testing, the symptoms were re-coded into a new dichotomous variable that indicates whether either a symptoms is present or absent. For patients where data was not available, the last observation was carried forward.

[1] Comparison of all medications means all three medications are compared and tested for the two states of the symptom variables, resulting in a 2×3 table.

[2] Comparison medication 1 versus medication 2 means that two out of three medications are compared and tested for the two states of the symptom variables, resulting in a 2×2 table. Data are only shown if they are significant without corrections for multiple testing. For Bonferroni correction multiply the p values by two.

[3] Asymptotic 2-sided test.

[4] 2-sided test. p values without corrections for multiple testing. For Bonferroni correction multiply the p values by two.

symptom), the values of the 1st follow-up visit showed that in relation to 'burning' and 'burning', healing was more advanced in the Zovirax group than in the sage group. After Bonferroni correction for multiple testing, however, only the difference for the parameter 'swelling' remained significant. At the 2nd follow-up visit there was a significant advantage for the rhubarb-sage group compared to the sage group with regard to the parameter 'pain'.

Table 7. Patients not healed at the time of the 2nd follow-up and patients who dropped out of the study due to insufficient efficacy

Patients	Medication sage- (n = 40)	rhubarb-sage (n = 64)	Zovirax (n = 41)
Not healed at the time of the 2nd follow-up with severe symptoms	3	0	0
Not healed at the time of the 2nd follow-up with mild symptoms	0	7	1
Dropped out due to insufficient activity	2	0	1

Table 8. Efficacy judgement

Evaluation	Medication					
	sage		rhubarb-sage		Zovirax	
	n	%	n	%	n	%
Total	40	100	64	100	41	100
Doctor						
Good	28	70.0	54	84.4	33	80.5
Moderate	9	22.5	8	12.5	6	14.6
Insufficient	1	2.5	1	1.6		
Not stated	2	5.0	1	1.6	2	4.9
Patient						
Good	31	77.5	54	84.4	34	82.9
Moderate	6	15.0	7	10.9	5	12.2
Insufficient	1	2.5	2	3.1		
Not stated	2	5.0	1	1.6	2	4.9

Table 9. Safety judgement

Evaluation	Medication					
	sage		rhubarb-sage		Zovirax	
	n	%	n	%	n	%
Total	40	100	64	100	41	100
Doctor						
Good	35	87.5	63	98.4	39	95.1
Moderate	3	7.5				
Insufficient						
Not stated	2	5.0	1	1.6	2	4.9
Patient						
Good	33	82.5	62	96.9	39	95.1
Moderate	4	10.0	1	1.6		
Insufficient						
Not stated	3	7.5	1	1.6	2	4.9

For the course of symptoms from baseline to the 2nd follow-up visit, the 'area under the curve' (AUC) was calculated by assigning a score of 0 to the 'no symptom' level, a score of 1 to the 'mild symptom' level and a score of 2 to the 'severe symptom' level. Comparison of the AUCs for the three medication groups revealed no significant differences between the treatments (ANOVA: $F = 0.814$, $p = 0.445$).

The results of the supplementary equivalence estimation by the Mann-Whitney test (results not shown) show that the three preparations have comparable efficacy in relation to the main criterion of time to healing.

Judgement of the action of the study medication on the relapse rate had to be renounced since a large number of patients were no longer available for further observation.

149 patients were recruited. The 4 drop-outs concerned 2 protocol violations (no herpes labialis) and 2 patients who did not attend the follow-up visits (lost to follow-up). The following patients could not be taken into account in some respects in the ITT analysis: 4 patients due to withdrawal from the study (Zovirax group: 'severe depression' and 'insufficient efficacy'; Sage group: 'infection became worse' and 'no healing'). In 1 case the withdrawal occurred between the 1st and 2nd follow-up visits so that this patient could still be included in the evaluation of symptoms at the 1st follow-up. Another 11 patients were classed as not healed at the 2nd follow-up (day 10–14) (table 7). The distribution between the three groups showed no significant differences. Comparison between the rhubarb-sage group and the Zovirax group also showed no statistical difference (Fisher's exact test $p = 0.15$).

Two patients had clinical super-infection: both were treated with rhubarb-sage, and both presented the super-infection only at the 1st follow-up visit. In 1 case the super-infection was not confirmed. Conclusive statistical analysis with only 2 cases is not possible.

With regard to the judgement of efficacy and safety by the doctors and patients, no significant differences were found. In any event, it happened that the efficacies of the rhubarb-sage cream and the Zovirax cream were judged to be roughly equal by the doctors and patients and that the sage cream tended to be classed as somewhat poorer. With regard to tolerability, the patients estimated the rhubarb-sage cream and the Zovirax cream to be rather better than the sage cream. The corresponding data are presented in the tables 8 and 9.

A survey of all adverse events observed (a total of 4 cases) is presented in table 10:

All adverse events could be classed as mild and transient. Medical treatment was not necessary, and the patients remained in the study.

Compliance and the degree of patient exposure were checked with the aid of the diaries and the consumed tubes of study medication returned. On average, each patient expressed about 1.2 g of study medication from the tubes and used the study medication 4 times daily for 7.7 days.

Table 10. Adverse events

	Adverse events			
	sage		rhubarb-sage	
	drying of the skin (1st follow-up)	prolonged time of wetness of the skin, drying out not so good (2nd follow-up)	smarting for 1–2 min after application (1st and 2nd follow-up)	smarting for 2 min (1st follow-up)
Severity	mild	mild	mild	mild
Duration	1–2 days	6 days	after each application	5 days
Causal link with the treatment	possible	certain	certain	certain

Table 11. Placebo-controlled studies with Zovirax cream for herpes labialis

Reference	Healing time, days (number of episodes)		p value
	Zovirax cream	Placebo cream	
Van Vloten et al., 1983 [5]	5.4 (29)	6.6 (31)	0.05
Fiddian et al., 1983 [6]	4 (34)	6 (40)	0.01
Shaw et al., 1983 [7]	9 (34)	10 (38)	not significant
Kingsley et al., 1985 [20]	5.9 (75)	7.2 (79)	< 0.05
Raborn et al., 1989 [8]	7.1 (46)	7.9 (56)	not significant

Discussion

The antiviral activity of rhubarb root extract observed during screening was confirmed by the results of various published in vitro antiviral studies with herpes virus and other coated viruses [10, 11]. Anthraquinones could be identified as the active constituents [11–16]. The somewhat weaker activity of sage leaf extract was also confirmed by various publications [17–19].

The symptoms diminished to roughly the same extent between the initial visit and the 1st and 2nd follow-up visits. However, for the parameter 'swelling' there was a significant advantage for Zovirax cream compared to sage cream at the 1st follow-up visit (table 5), and for the parameter 'pain' there was a significant difference in favour of the rhubarb-sage cream compared to the sage cream at the 2nd follow-up visit (table 6).

With regard to treatment failures (table 7), it can be established that the differences are not statistically significant. It is also true that the treatment failures presented only mild symptoms in the rhubarb-sage group, whereas all those in the sage group still resulted in severe symptoms. In addition it has to be considered that, in contrast to the sage and Zovirax groups, there were no drop-outs in the rhubarb-sage group due to insufficient action.

Although the significant differences in the courses of individual symptoms were not clinically relevant, the overall impression was that the Zovirax cream and the rhubarb-sage cream do not differ and that the sage cream is somewhat less effective.

Zovirax cream represents a reference product that has proved its worth in various placebo-controlled studies. These studies show that healing is markedly faster with Zovirax cream than with placebo cream (table 11).

Evaluation of these 5 Zovirax studies shows an advantage of 1.2 days in healing time for Zovirax cream compared to placebo cream. The latest topical herpes remedy is Famvir® (Novartis, East Hannover, NJ, USA) cream (active ingredient penciclovir). For this product, a meticulous placebo-controlled double-blind study with over 2,000 patients showed an advantage of 0.7 days ($p < 0.01$) compared to a placebo cream [9].

The present study is one of the first in which a herbal preparation has been investigated by comparison with aciclovir in the indication of labial herpes. Only placebo-controlled studies with a cream containing melissa extract are known. In the latest work [21], this product was investigated in a double-blind study with 66 patients. The primary target criterion was the comparison of a combined symptom score (pain, blisters, size of lesion) on the 2nd day of treatment. A barely significant advantage ($p = 0.042$) was found for the reference product. Comparison of the symptom scores over 5 days showed no further significant differences between the two groups. This confirmed the results of an earlier study with 116 patients [22], however, this was performed on patients with herpes simplex infections.

Current AIDS therapy shows that much better antiviral action can be obtained with combinations of several active substances than with single substances. In this connection, the following pharmacological studies with herbal combination

products are of interest: It could be shown that a mixture of alcoholic extracts of *Thymus serpyllum* L., *Viscum album* L., *Salvia officinalis* L., *Mentha piperita* L. and *Glycyrrhiza glabra* L. markedly suppressed the multiplication of influenza viruses in vitro and in ovo, whereas the extracts of the single drug plants had only moderate (*Thymus serpyllum* L. and *Salvia officinalis* L.) or no activities. Two other combination preparations showed similar results. The better activity of the combination preparations is attributed to synergistic interaction of the individual components [19].

In a previous study [2] it was found that a group of patients treated with rhubarb cream had a healing time longer by 1.1 days than patients treated with Zovirax cream. The present study shows a healing time 1.2 days longer in the group of patients treated with sage cream compared to the aciclovir (Zovirax) group. The combined rhubarb-sage preparation proved to be as effective as Zovirax cream in this study. The difference in mean healing time was only 0.2 days in favour of Zovirax cream. The non-significant (trend) superiority of the rhubarb-sage cream over sage cream suggests that this is a worthwhile combination. Further pharmacological and clinical studies are, however, desirable to quantify this advantage.

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