

Randomized placebo-controlled trial of a flavonoid-rich plant extract-based cream in the treatment of rosacea

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ABSTRACT

Background Biological research suggests that vascular changes may play a major role in rosacea pathogenesis. *Chrysanthellum indicum* is a plant-based extract containing a unique combination of phenylpropenoic acids, flavonoids and saponosids, and has a well-documented effect on vascular wall permeability and increase of the mechanical resistance of capillaries.

Objective To determine the efficacy and safety of a cream containing 1% *C. indicum* extract with vitamin P properties in the treatment of rosacea.

Methods This study included 246 patients diagnosed clinically as having moderate rosacea. Patients were randomly allocated to *C. indicum* extract-based cream ($n = 125$) and placebo ($n = 121$) groups. Patients were advised to apply the products on their face twice a day for a 12-week period. The patients were examined at the end of each 4-week period. Severity of erythema (graded by reference to six photographs), surface of erythema and rosacea overall severity scores were recorded at each visit on days 0, 28, 56 and 84. Investigators carried out a final efficacy assessment at the end of week 12. Volunteers' final overall efficacy assessment was recorded in a self-administered questionnaire. Adverse events were identified through examination, interview and collection of comments in patients' questionnaires.

Results Treatment with the *C. indicum* extract-based cream resulted in significant improvement ($P < 0.05$) in severity of erythema, overall rosacea severity compared to baseline and placebo, and investigator and patient overall efficacy assessment scores ($P = 0.046$ and $P = 0.001$, respectively) compared with placebo scores. Adverse reactions were mild, and did not differ between the *C. indicum* extract-based cream and the placebo groups.

Conclusion *Chrysanthellum indicum* extract-based cream is an effective and well-tolerated topical agent for the treatment of moderate rosacea. The mode of action of the active ingredient suggests that additional efficacy might be expected from combination with other topical treatments.

Key words: *Chrysanthellum indicum*, flavonoids, microcirculation, rosacea

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Introduction

Rosacea is a common dermatosis with intricate aetiology involving endogenous, systemic or local, and environmental factors.^{1–4} Based on the hypothesis of the bacterial or parasitic aetiopathogenesis of rosacea, antibiotic and antiparasitic therapies have been demonstrated to be effective in relieving certain rosacea symptoms, and continue to be investigated in

order to improve their efficacy.^{5–8} However results of clinical trials suggest that their mechanism of action is probably not linked to their main antibacterial action.

Biological research suggests vascular changes may play a major role in rosacea pathogenesis.² Degradation of collagen and elastin, particularly by metalloproteinases, under the action of agents such as ultraviolet light, also contributes to the pathophysiology of rosacea. This degradation leads to production of

peptides which, by reacting with immune cells receptors, releases enzymes and free radicals. The presence of these free radicals is thought to deteriorate the elastic and collagen fibers of lymphatic and blood vessels, possibly triggering erythema production.⁹

Chrysanthellum indicum is a plant extract containing a unique combination of phenylpropanoic acids, flavonoids and saponosids, and has a well-documented effect on vascular wall permeability and mechanical resistance of capillaries.^{10,11} Additionally, studies provide evidence of flavonoids being able to penetrate into deep skin layers.¹² Hence, trial of a cream containing 1% *C. indicum* plant extract was considered worth investigating, provided its use would be well tolerated by the sensitive skin of rosacea patients. Cream was chosen as the best-adapted formulation for rosacea.¹³

Methods

This multicentre randomized, double-blind, parallel group, placebo-controlled study compared a cream containing 1% extract of a flavonoid-rich plant – *Chrysanthellum indicum* – vs. placebo applied twice a day over a 12-week period.

The final product had undergone all tests required by European regulatory bodies concerning cutaneous and ocular tolerability (animal model), moisturizing effects, sensitizing potential and comedogenicity. As the active ingredient resulted in a slightly coloured final product, colour of the placebo (vehicle) was adjusted accordingly. Informed consent was obtained from patients prior to participation in the study.

A photograph album was prepared for each investigator to help as a visual reference throughout the trial, with the aim of improving the consistency of investigators' erythema severity assessment over time. From one photograph of a patient with rosacea, six different photographs with growing severity of erythema but similar erythema area, were prepared on a computer. Before final release, the draft photograph album was submitted to 15 dermatologists in order to ensure that the photographs were arranged in a linear fashion in terms of severity. In cases where more than 1/3 of dermatologists found that the photographs did not give an impression of gradually increasing severity, colour adjustments were made accordingly and the album was resubmitted until the order of photographs was acceptable.

As results of former trials have shown that telangectasias call for prolonged therapy before clinical improvement can be observed and because of the limited duration of the trial (12 weeks), improvement of telangectasias was deemed beyond the scope of this trial. Telangectasias were therefore not included in the photograph album. Patients were instructed to fill in a self-administered questionnaire before each examination, and in particular to identify side-effects occurring between visits.

Inclusion criteria were a clinical diagnosis of facial rosacea corresponding to grades 2–4 of the photograph album. Exclusion criteria were the use of any topical facial medication, oral

therapy of any kind within 6 weeks prior to study entry, and use of any cosmetic aimed at improving rosacea within 2 weeks prior to inclusion. Pregnant and lactating women were excluded, as were patients predicting some change in their life-style (outdoor/indoor activity). In addition, the use of any drug, especially vasoactive drugs or CNS drugs was not permitted throughout the duration of the trial.

There was one study site in Greece, one in France, and four study sites in Germany. Each country enrolled, respectively, 94, 56 and 96 patients. One hundred and twenty-five patients were assigned to the *C. indicum* extract-based cream, and 121 were assigned to the placebo. Clinical evaluations were performed at baseline and at 4, 8 and 12 weeks.

Primary efficacy variables evaluated were:

- The severity level of erythema;
- The erythema surface: surface delineated by investigator on a devoted sketch in case report form (CRF), then scanned for automated computerized area calculation (AutoCAD 2000);
- Investigator overall assessment (taking into account erythema severity and surface);
- Investigator final efficacy assessment (based on his experience of other treatments).

The secondary efficacy variable was patient efficacy assessment. Safety and tolerability were evaluated by assessment of adverse event frequency. The variation in severity of erythema, surface of erythema and investigator overall rosacea assessment, was analysed using ANOVA for repeated measures. *P*-values < 0.05 (unilateral) were considered statistically significant for comparison between the two groups. Categorical questions on inclusion and categorical questions asked during the final examination were analysed by χ^2 -test.

The investigators assessed erythema on all four visits using the photograph album. Outlines of areas with erythema were drawn on all four visits, by investigators on face sketches in CRFs. Comparison of erythema grades with reference photographs was made (grades 1–6) to enable implementation of statistical methods (ANOVA for repeated measures).

All statistical calculations were performed using SPSS, version 11.1 with GLM and exact test additional modules (SPSS, Chicago, IL, USA).

Results

Patient demographics

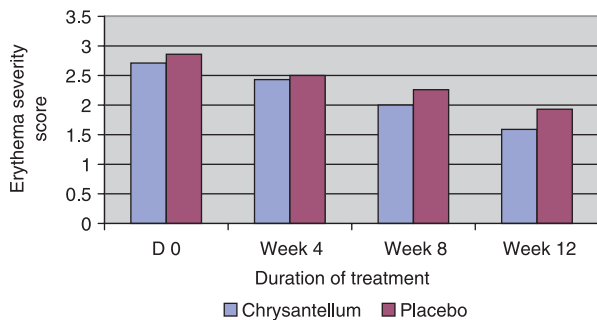
Enrolled subjects were Caucasians with a mean age of 48.9 years (SEM 0.86) (range 18–80 years). Demographic features of patients in both groups at baseline are given in Table 1.

Facial erythema severity

At baseline all patients (*n* = 246) had an erythema grade of 2–4. After 12 weeks of treatment, improvement in facial erythema by

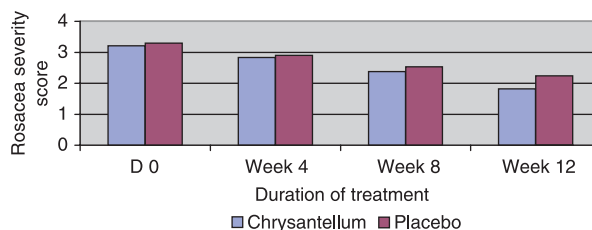
Table 1 Demographic features of *Chrysanthellum indicum*-based cream group and the placebo group at baseline and following 12 weeks of treatment

	<i>Chrysanthellum indicum</i> -based cream group (<i>n</i> = 125)		Placebo group (<i>n</i> = 121)	
Age	48.2 ± 1.2 years		47.8 ± 1.2 years	
Gender	34 male, 91 female		36 male, 85 female	
Erythema severity	At baseline: 2.71 ± 0.07	Following 12 weeks of treatment: 1.59 ± 0.08	At baseline: 2.86 ± 0.07	Following 12 weeks of treatment: 1.92 ± 0.09
Erythema surface (cm ²)	At baseline: 22.49 ± 1.45	Following 12 weeks of treatment: 10.42 ± 1.07	At baseline: 21.14 ± 1.46	Following 12 weeks of treatment: 11.79 ± 1.19
Rosacea overall severity	At baseline: 3.21 ± 0.1	Following 12 weeks of treatment: 1.82 ± 0.11	At baseline: 3.3 ± 0.08	Following 12 weeks of treatment: 2.25 ± 0.09

**fig. 1** Reduction in mean erythema severity scores (grades) for *Chrysanthellum indicum* and placebo over a 12-week period.

at least one score (responders) was noted in 73.3% (*n* = 101) of patients treated with *C. indicum* extract-based cream, compared with 67.6% (*n* = 105) of those on placebo. Mean erythema score at baseline in completed cases for the *C. indicum* extract-based cream group and the placebo group was 2.71 ± 0.07 (mean ± SEM) and 2.86 ± 0.07, respectively. Distribution of grades was not significantly different between the two groups, (Mann–Whitney *U*-test, *P* = 0.12; χ^2 -test, *P* = 0.21). Following 12 weeks of treatment, mean erythema scores (grades) for the *C. indicum* extract-based cream and placebo groups were 1.59 ± 0.08 (41.3% reduction) and 1.92 ± 0.09 (32.8% reduction), respectively (fig. 1). Distribution of grades was significantly different between the two groups, (Mann–Whitney *U*-test, *P* = 0.008; χ^2 -test, *P* = 0.008) (fig. 1).

ANOVA results – encompassing cases without missing grade values for any examination – showed a significant positive association between time and erythema reduction for both groups (*P* < 0.001), and the reduction in the *C. indicum*-enriched cream group (*n* = 96) was significantly (*P* = 0.014) higher than that observed in the placebo group (*n* = 100).

**fig. 2** Rosacea overall severity score reduction for *Chrysanthellum indicum* and placebo over a 12-week period.

Overall rosacea assessment (investigators' assessment)

Clearing or marked improvement (defined as overall rosacea assessment of 0–2 on the same 7-grade scale) on investigator rosacea global assessment by week 12 was observed in 81.2% of the patients treated with the *C. indicum*-based cream and 61% of those treated with placebo. Mean global score at baseline in these completed cases was 3.21 ± 0.10 (mean ± SEM) and 3.3 ± 0.08 for *C. indicum*-based cream group and the placebo group respectively. Distribution of grades was not significantly different between the two groups, (Mann–Whitney *U*-test, *P* = 0.41; χ^2 -test, *P* = 0.21). Following 12 weeks of treatment, mean overall rosacea scores (grades) were lowered to 1.82 ± 0.11 (43.3% reduction) and 2.25 ± 0.09 (31.8% reduction) for the *C. indicum*-based cream and the placebo group, respectively. (fig. 2).

Distribution of levels of severity was significantly different between the two groups (Mann–Whitney *U*-test, *P* = 0.002; χ^2 -test, *P* = 0.016).

ANOVA results showed a significant positive association between time and overall rosacea score reduction for both groups (*P* < 0.001) and the reduction of overall rosacea score was significantly higher (*P* = 0.038) for the *C. indicum*-based cream group (*n* = 96) than for the placebo group (*n* = 100).

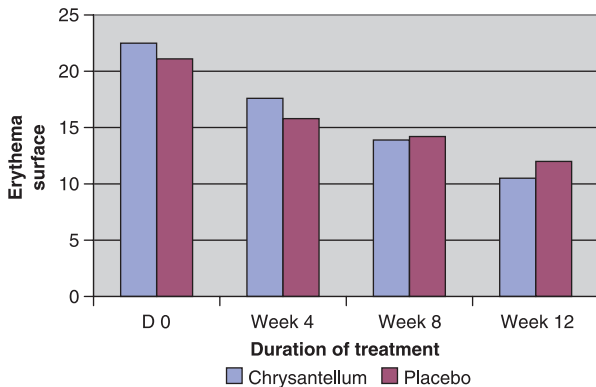


fig. 3 Erythema surface reduction for *Chrysanthellum indicum* and placebo over a 12-week period.

Difference in mean overall severity scores between groups was statistically significant at week 6 ($P = 0.035$) and 12 ($P = 0.002$).

Erythema surface

After 12 weeks of treatment, improvement of erythema surface was noted in 90.8% of patients treated with the *C. indicum*-based cream, compared with 87.3% of those on placebo. Mean erythema surface at baseline for the *C. indicum*-based cream and placebo group was $22.49 \pm 1.45 \text{ cm}^2$ (mean \pm SEM) and $21.14 \pm 1.46 \text{ cm}^2$, respectively. Following 12 weeks of treatment, mean surfaces of erythema for patients in the *C. indicum*-based cream and placebo group decreased to $10.42 \pm 1.07 \text{ cm}^2$ (53.65% reduction) and $11.79 \pm 1.19 \text{ cm}^2$ (44.23% reduction), respectively (fig. 3).

ANOVA results with the baseline as covariate showed a significant positive association between time and surface reduction ($P < 0.001$) for both products, but failed to show any significant difference between evolution of the surface of rosacea in both groups ($P = 0.21$).

Final investigator efficacy assessment

After 12 weeks of treatment a positive judgement about efficacy was noted in 67% of patients treated with the *C. indicum*-based cream compared with 51.5% on placebo. The difference was statistically significant (χ^2 -test, $P = 0.031$).

Final volunteer efficacy assessment

After 12 weeks of treatment, a positive judgement about efficacy was expressed by 60.9% of patients treated with the *C. indicum*-based cream ($n = 98$), compared with 38.8% on placebo ($n = 92$). The difference is statistically significant (χ^2 -test, $P = 0.01$).

Volunteers who were used to treating their rosacea made a positive comparison of the product on trial against their usual

Table 2 Skin sensitivity as declared by volunteers and not verified by stinging test

	<i>Chrysanthellum indicum</i> -based cream group ($n = 125$)	Placebo group ($n = 121$)	P-value
Normal	63	35	0.001
Sensitive	62	86	

product (χ^2 -test, $P < 0.001$) significantly more often in the treated group (75.7%, $n = 32$) than in the placebo group (17.6%, $n = 34$).

Adverse events

During the 12-week period of use 13 of the 125 patients treated with the *C. indicum*-based cream experienced some adverse event that might be attributed to the product. In 11 cases withdrawal was decided.

Eight of the 121 patients in the placebo group experienced some adverse event that might be attributed to the placebo. Six patients in the placebo group were withdrawn because of adverse events.

In all cases the severity of adverse events was rated as mild or moderate. Two of the seven volunteers in the placebo group and seven of the 13 in the treated group with adverse events had defined their skin as sensitive on inclusion. The percentage of so-called sensitive skin on inclusion was statistically higher in the treated group (Table 2).

Discussion

The 41.3% reduction in erythema score for the test cream and 32.5% reduction for the placebo are within the range observed in trials involving metronidazole (35%–90%), and appears to be similar to a recently published trial on metronidazole⁴ (42% on metronidazole and 27% on placebo). This is despite the fact that the current trial investigators' scoring by reference to a 6-grade photo album differs from the commonly found clinical assessment methods.

Figure 1 shows, that a continuous decrease of average erythema scores was observed until the end of the trial, suggesting that duration of treatment beyond 12 weeks could be beneficial. The reduction of erythema surface for the duration of this trial was not significantly different between the *C. indicum*-based cream and the placebo group. This suggests that in this trial, severity of erythema played a more significant role than the erythema surface in rosacea overall assessment. The fact that the photograph album enabled investigators to focus on the severity of erythema may explain this.

The final positive overall efficacy assessment differs between investigators and volunteers in each group: 67% and 60.9% in

the *C. indicum* group, respectively and 51.5% and 38.8%, respectively in the placebo group. The difference in assessment between investigators and volunteers, suggests that other symptoms of rosacea not affected by treatment, have improved differently in the two groups.

The *Chrysanthellum indicum* contained in the cream on trial is reported to possess vitamin P properties, which has been found to be of possible interest in reducing or preventing vascular disorders, and specifically microcirculation disorders involved in erythema of rosacea.

In this trial, the *Chrysanthellum indicum*-containing cream was more effective than the placebo in reducing the erythema of rosacea. In addition, it seems that, even though the cream on trial was applied for an extended period of time (12 weeks), it was fairly safe and well tolerated by the patients.

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