



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

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Ambroise Paré (1510-1590) : Clinical description of « gutta rosacea »



- **CHRYSANTHELLUM INDICUM**

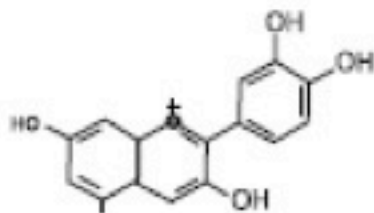
Excellence in its composition:

- Flavonoides
- Saponosides

- **PHARMACOPEE**

- Anti Radicals
- Anti Poperoxydant
- Anti inflammatory
- Action Vitaminic P

- **UE PATENT – INTNL PATENT**



Impossible d'afficher l'image. Votre ordinateur manque peut-être de mémoire pour ouvrir l'image ou l'image est endommagée. Redémarrez l'ordinateur, puis ouvrez à nouveau le fichier. Si le x rouge est toujours affiché, vous devrez peut-être supprimer l'image avant de la réinsérer.



- EUROPEAN CLINICAL STUDY

Multicentric study:

- Germany
- France
- Greece

- Under UE Committee

(OSEO ANVAT)

- CLINICAL TRIAL :

- Double Blind
- Versus Placebo
- 2 Applications Daily
- 12 weeks
- Clinical Evaluation at W4, W8 and W12
- Colorimetric Evaluation by Spectrometer
- Panel randomised of 246 Patients
- Specific schema analysis: Clinical scores
 - Scores for Erythro-Couperosis
 - Scores for Rosacea-Erythro-Telangiectasic

ORIGINAL ARTICLE

JEADV (2005) 19, 564–568

DOI: 10.1111/j.1468-3083.2005.01248.x

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

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Multicentric Study

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

- *Rosacea* = from Latin meaning « like a rose »
- 5 to 10% of population (increasing in winter time)
- 3rd to 4th motive of consultation in Europe
- Mechanism of action is not due to bacterial action
- Biological research suggests vascular changes (degradation of collagen and elastin)
- *Chrysanthellum Indicum* = effect on vascular wall permeability and mechanical resistance of capillaries

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 phenylpropenoic 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 (A)

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.

- Study in Greece (1 center), France (1 center) and Germany (4 centers)
- Each country enrolled respectively, 94, 56 et 96 patients.
- 125 patients were assigned Chrysanthellum Indicum
- 121 patients were assigned Placebo
- Clinical evaluation were performed at W4, W8 and W12 (Photograph album & computer area calculation *autocad 2000*)

Methods (B)

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).



Results (A)

Rosacea Severity Evaluation

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 \pm 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).

Multicentric Study

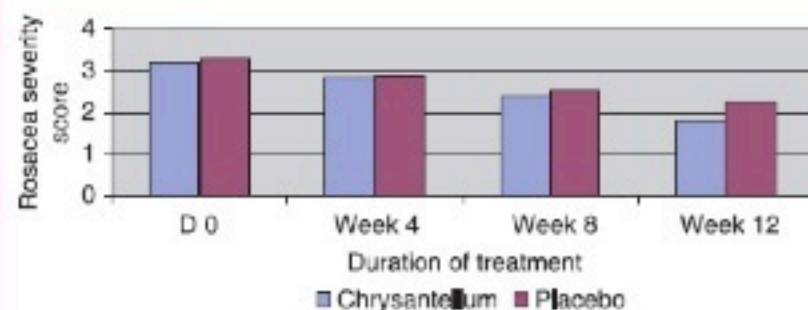


fig. 2 Rosacea overall severity score reduction for *Chrysanthellum indicum* and placebo over a 12-week period.

• CLINICAL RESULTS

Rosacea Severity Evaluation

- 84,4% Improvement of Rosacea Global Assessment
- 43,3% Severity Rosacea Reduction



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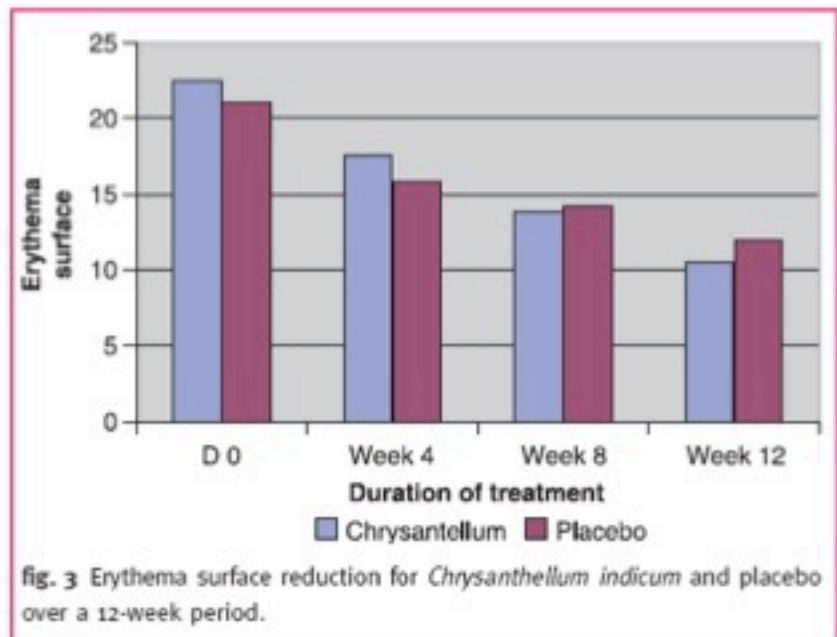
Results (B)

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).

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, $P = 0.031$).



CLINICAL RESULTS

Surface Erythema Evaluation

- 90,8% improvement of erythema surface
- 53,7% global erythema diminution

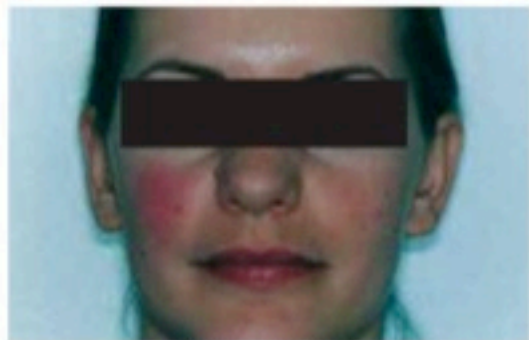
Final Efficiency Assessment:

- Improvement in 67 % of patients (Colorimetric/Clinical Evaluation by Dermatologists)

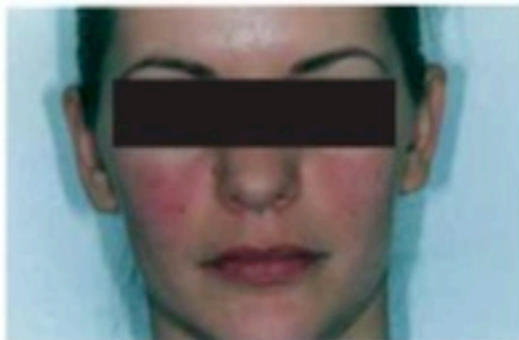
Discussion

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 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.

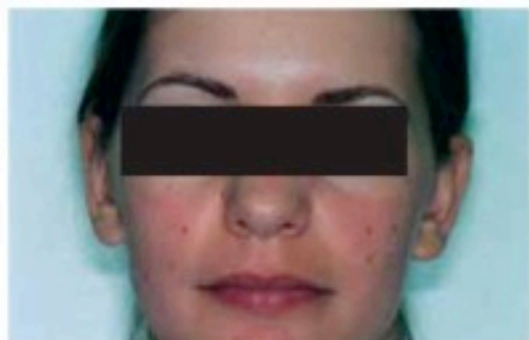
Multicentric Study



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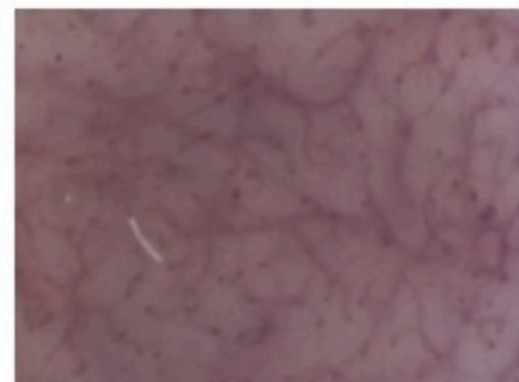
4 semaines



8 semaines



12 semaines



Capillary loop X100



Week 12