Original Contribution

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Clinical efficacy of a serum integrating multiple cosmetic ingredients in the management of erythema of the face in aging skin

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Summary

Background Skin redness is a common cosmetic concern affecting predominantly fair-skin individuals and often leading to rosacea. On the basis of the current scientific knowledge of the physiological mechanisms underlying the problem, a complex and integral skin care serum (100RXED2025) was developed and tested clinically for efficacy.

Method Forty-five healthy men and women volunteers, age 30–65, were recruited. All subjects had fair skin (phototype I, II, or III) and presented some degree of skin redness with telangiectasia on the cheeks, the nose, or the nose sides, at baseline. In the course of this open label study, subjects applied the test product on their face, twice daily for 56 days. For each subject, skin redness was evaluated through colorimetric and visual analysis of photographs taken under cross-polarized light at T = 28 (week 4) and T = 56 (week 8), then compared to baseline measurements obtained at day 0.

Results Forty-four volunteers completed the study. On visual evaluation, skin redness had decreased in average by 32.2% at T = 28 ($P < 0.001$) and by 48.0% at T = 56 ($P < 0.001$). Importantly, 91% of the subjects showed improvement of skin redness at T = 28, reaching 100% at T = 56. Colorimetric analysis gave an average reduction in redness of 11.6% at T = 28 ($P < 0.001$) and 13.7% at T = 56 ($P < 0.001$).

Conclusion The anti-redness efficacy of the test product was demonstrated after 28 days with further increase following 56 days of application.

Keywords: clinical trial, cosmeceutical, rosacea, sensitive skin, telangiectasia, topical

Introduction

Chronic facial redness is a motif of embarrassment and discomfort affecting both genders. Most commonly the underlying condition is rosacea, a chronic and progressive inflammatory disease of the skin preferentially affecting the cheeks, nose, chin, and forehead.[1] Facial erythema comes with a variety of etiological causes and precipitating factors in predisposed individuals,[2,3] but no matter the cause, abnormalities in the vasculature homeostasis seem to be a common denominator.[4,5]

The cutaneous microvasculature plays a major role in the maintenance of a healthy looking skin. Microvessels in the dermis deliver oxygen and nutritive elements to the upper skin layers and assure that cellular metabolic byproducts are evacuated properly.[6] The cutaneous vessels in normal skin are characterized by relatively resistant walls, well adapted to a rather fluctuating and active blood flow.

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As illustrated in Figure 1, aging[5,7] and other factors such as exposure to UV radiation, chemicals, climate changes, stress, hormone fluctuations, and sometimes even nutritional factors[3] tend to activate mediators that team up to fragilize the cutaneous microvasculature. These reactions are exacerbated in predisposed sensitive skin. Indeed, chronic facial erythema is associated with the overactivation of metalloproteinases (MMPs) and the release of reactive oxygen species (ROS), angiogenic factors (VEGF), and inflammatory cytokines.[8–10] ROS and MMPs directly attack and weaken vessel walls and the surrounding extracellular matrix (ECM), while VEGF dilates vessels and induces their permeability.[8] Increased leakiness allows inflammatory cells, such as neutrophils and macrophages, to crawl out of vessels, their migration being facilitated by cytokines acting as chemoattractants.[11] Inflammatory cells get activated in the process, liberating additional cytokines, VEGF, ROS, and MMPs to create a state of chronic inflammation favorable to the development of telangiectasia.[12] What started as intermittent flushing progressively develops into a more permanent state marked by the apparition of spider veins and red plaques on the face.[13]

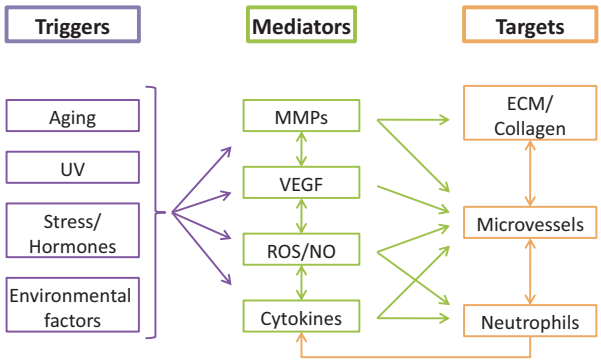

Figure 1 Molecular mechanisms in rosacea.

Chronic facial erythema is a complex condition with yet no simple solution. But as we better understand the pathophysiology behind it, the development of pertinent cosmetic cares becomes possible. One such product has recently been developed to address the specific needs of sensitive aging skin. The present study evaluates the clinical efficacy of this complex integral skin care serum, in reducing facial erythema in affected human volunteers.

Materials and methods

Test product

The test product (100RXED2025) was supplied as a serum. The commercially available formulation contains several cosmetic ingredients (listed in Table 1), including a patented technology aiming at reducing the signs of skin aging as described elsewhere,[14] to which additional

Table 1 List of cosmetic ingredients by alphabetic order (INCI names)

1	Acetyl octapeptide-3	26	Glycosaminoglycans
2	Acetyl tetrapeptide-2	27	Hesperidin methyl chalcone
3	Ahnfeltia concinna extract	28	Hyaluronic acid
4	Alteromonas ferment extract	29	Hydrolyzed rice bran protein
5	Ascophyllum nodosum extract (depolymerised fucans)	30	Hydrolyzed soy protein
6	Ascophyllum nodosum extract (crude extract)	31	Hydrolyzed wheat protein
7	Ascorbic acid	32	Imperata cylindrica (red baron) extract
8	Asparagopsis armata extract	33	Iris florentina extract
9	a-Bisabolol (vegetal extract)	34	Oxido reductases
10	Cantella asiatica (gotu kola) extract	35	Palmitoyl oligopeptide
11	Carica papaya extract	36	Palmitoyl tetrapeptide-7
12	Ceramide 1	37	Palmitoyl tripeptide-8
13	Ceramide 3	38	Phytosphingosine
14	Ceramide 6 II	39	Pseudoalteromonas ferment extract
15	Cholesterol	40	Retinol
16	Creatine	41	Rumex occidentalis (western dock) extract
17	Dimethylmethoxy chromanol	42	Salix nigra (willow) bark extract
18	Dipalmitoyl hydroxyproline	43	Sesame seed oil
19	Dipeptide-2	44	Sodium DNA
20	Dipotassium glycyrrhizate (licorice extract)	45	Squalane (vegetal)
21	Esculin (horse chestnut bark extract)	46	Tocopheryl acetate
22	Ethylbisiminomethylguaiacol manganese chloride	47	Tripeptide-1
23	Fucus serratus extract	48	Tripeptide-10 citrulline
24	Glycerine	49	Triticum vulgare (wheat) germ oil
25	Glycine soja protein	50	Ubiquinone

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cosmetic ingredients were added on the basis of their documented potential to address the specific needs of sensitive aging skin, with a tendency to redness. The total concentration of ingredients (excluding excipients) in the formulation reaches 40% (w/w).

Study protocol

The study was an open label, noncomparative study. Forty-five healthy volunteers, five men and 40 women, aged 30–65 (mean age 50 years), were recruited. All subjects had fair skin (phototype I, II, or III) and presented some degree of skin redness with telangiectasia on the cheeks, the nose, or the nose sides, at baseline. For the duration of the study, subjects were requested to refrain from using oral anti-inflammatory medications (except Tylenol) and food supplements that can alter skin pigmentation or cause skin redness. All volunteers gave their informed consent to the study protocol.

In the course of this study, subjects were instructed to apply the test product on their face, once in the morning and once at night, on a clean and dry skin, until complete penetration, except on assessment days when no product was to be applied prior to measurements.

Clinical evaluation was performed by an independent contract testing laboratory specialized in claim validation for cosmetic products. The study took place in Montréal, Canada, during the fall, spreading from the end of September to the end of November, for a total of 56 consecutive days following the first application of the product. Clinical evaluation was performed at T = 0 (baseline), T = 28 days (week 4), and T = 56 days (week 8). The subjects served as their own reference and results obtained at T28 and T56 were compared with those obtained at T0.

Clinical evaluation

Cross-polarized photographs of the face were taken for each volunteer, at T = 0 (baseline), T = 28 days (week 4), and T = 56 days (week 8). From these photographs, visual evaluation and colorimetric analysis were performed on one side of the face, randomly assigned for evaluation at T = 0.

Visual evaluation

For each time point, (T0, T28, and T56), visual evaluation of skin redness from cross-polarized photographs was accomplished by two experts using a well-defined grading scale for erythema, on the area assigned for evaluation at T = 0. The score was expressed on a 5-point scale (with possibility of half-grades), as follows:

- Grade 0: Very small telangiectasia on the sides of the nose
- Grade 0.5: Very small telangiectasia on the nose and cheekbones
- Grade 1: Small telangiectasia on the nose, cheekbones and chin
- Grade 1.5: Small telangiectasia on the nose, cheekbones and slight erythrosis
- Grade 2: Visible erythrosis and slight local telangiectasia
- Grade 2.5: Visible erythrosis and visible telangiectasia on the roots of the nose and cheekbones, or chin
- Grade 3: Medium erythrosis and telangiectasia
- Grade 3.5: Medium erythrosis and local visible telangiectasia
- Grade 4: Strong erythrosis and severe local telangiectasia
- Grade 4.5: Generalized erythrosis and severe generalized telangiectasia
- Grade 5: Extreme erythrosis and telangiectasia

Colorimetric analysis

For each time point (T0, T28, and T56 days), colorimetric analysis of skin redness was also performed on cross-polarized photographs. Using a dedicated software, the L*, a*, and b* parameters from the RGB components of the digital images were determined for each volunteer on the area assigned for evaluation at T = 0. The same area was analyzed throughout the study for each volunteer.

The L*a*b*, parameters are such that:

- L* represents the relative brightness from total black (L* = 0) to total white (L* = 100)
- a* represents the balance between red and green
- b* represents the balance between yellow and blue

The a* parameter is the most relevant to assess the redness of skin. The evolution of this parameter with time can be used to document the anti-erythema effect of a given product.[15]

Data analysis and statistics

Visual evaluation from cross-polarized photographs

A verification of the normality of the distribution using the Shapiro–Wilk test, threshold at 1%, was performed. Statistical analysis of the results obtained in the course of the study was performed using the Student's *t*-test (normality of distributions checked) or the Wilcoxon test (normality of the distributions rejected). The significance threshold was fixed at 5% ($P < 0.05$). The number and percentage of subjects presenting an improvement at T28 and T56 was also calculated.

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Colorimetric analysis from cross-polarized photographs
From the raw values of the a* parameter, differences in relation to T0 were calculated at T28 and T56 for each subject. For the entire panel as a group, means, medians, maximum, minimum, standard deviation, and the difference at T28 and T56 in relation to T0, that is (T*n* − T0)/T0, were calculated. Statistical analysis was performed using the Student's *t*-test. The significance threshold was fixed at 5% ($P < 0.05$).

Results

Adherence to the study protocol

Of the 45 volunteers, 44 completed the study. Two subjects were absents at T28 evaluation but showed up at T56, and one subject was not seen at T56.

Expert evaluation of results from cross-polarized photographs

At baseline, all volunteers ($n = 45$) presented erythema of the face, ranging from grade 0.5 (lowest) to 4.5 (highest) on a scale of 5. The mean grade of redness went from 2.0 at T0, down to 1.4 at T28, and further down to 1.0 at T56 (Table 2). Concretely, this means going from ''visible erythrosis and slight local telangiectasia'' (grade 2) to ''small telangiectasia on the nose, cheekbones, and chin'' (grade 1). At T28 of treatment, redness had decreased 0.6 grade of 5 in average, or 32.2% ($P < 0.001$), then continued to regress reaching 1.0 grade of 5 in average at T56, or 48% ($P < 0.001$) (Fig. 2), compared to baseline. Noteworthy, 91% of the subjects presented a reduction in erythema grade at T28, up to 100% at T56 (Table 3). This means that all volunteers were experiencing some degree of erythema reduction by the end of the study. The level of clinical response was independent of the severity of the condition at baseline.

Colorimetric analysis of results from cross-polarized photographs

On colorimetric analysis, a significant and progressive decrease in the a* parameter, representing the balance between red and green tones, was documented throughout the study. A decrease in the a* parameter is an indication that skin redness is improving.[15] The mean value for this parameter went from 19.446 at T0, down to 17.132 at T28, and further down to 16.847 at T56 (results not shown). Results were validated through statistical analysis using the Student's *t*-test from which a *P*-value of 2.27E-09 and 4.35E-10 were obtained at T28 and T56, respectively (results not shown). When these variations were converted in terms of percentage of mean erythema improvement from baseline, the reduction in erythema reached 11.6% ($P < 0.001$) at T28 and 13.7% ($P < 0.001$) at T56 (Fig. 3).

A selection of photographs, representative of the results that were achieved by the volunteers at the end

Table 2 Mean grade and dispersion of the mean grade of erythema, on visual evaluation

	T0	Week 4	Week 8
Mean (5 pts scale)	2.0	1.4	1.0
Standard deviation	1.0	0.9	0.9
Wicoxon test, *P* value		<0.001	<0.001

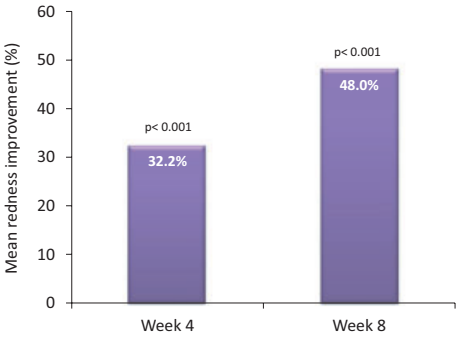

Figure 2 Visual evaluation of mean erythema improvement relative to baseline.

Table 3 Percentage of subjects presenting erythema improvement on visual evaluation, relative to baseline

	Week 4	Week 8
Subjects with improvement	91%	100%

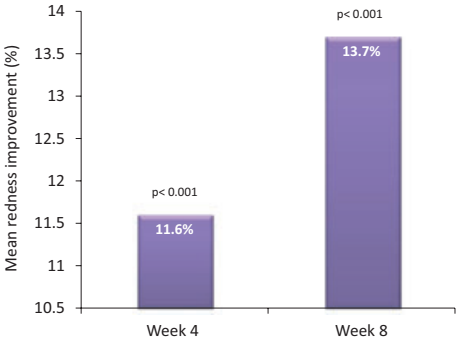

Figure 3 Colorimetric evaluation of mean erythema improvement relative to baseline.

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of the study (T56/week 8) compared to baseline (T0), is presented in Figure 4a–f.

Discussion

Facial skin redness is a common problem often associated with rosacea. Fair skin is a vulnerability factor, while aging, stress, and exposure to the sun and other environmental elements may be aggravating.[3,4] Although facial skin redness is not a life-threatening condition, it has a social impact and often leads to lower self-esteem.[16,17] It is thus important to address this cosmetic concern. As many physiological mechanisms appear to be involved in the condition, an integral approach is highly desirable.

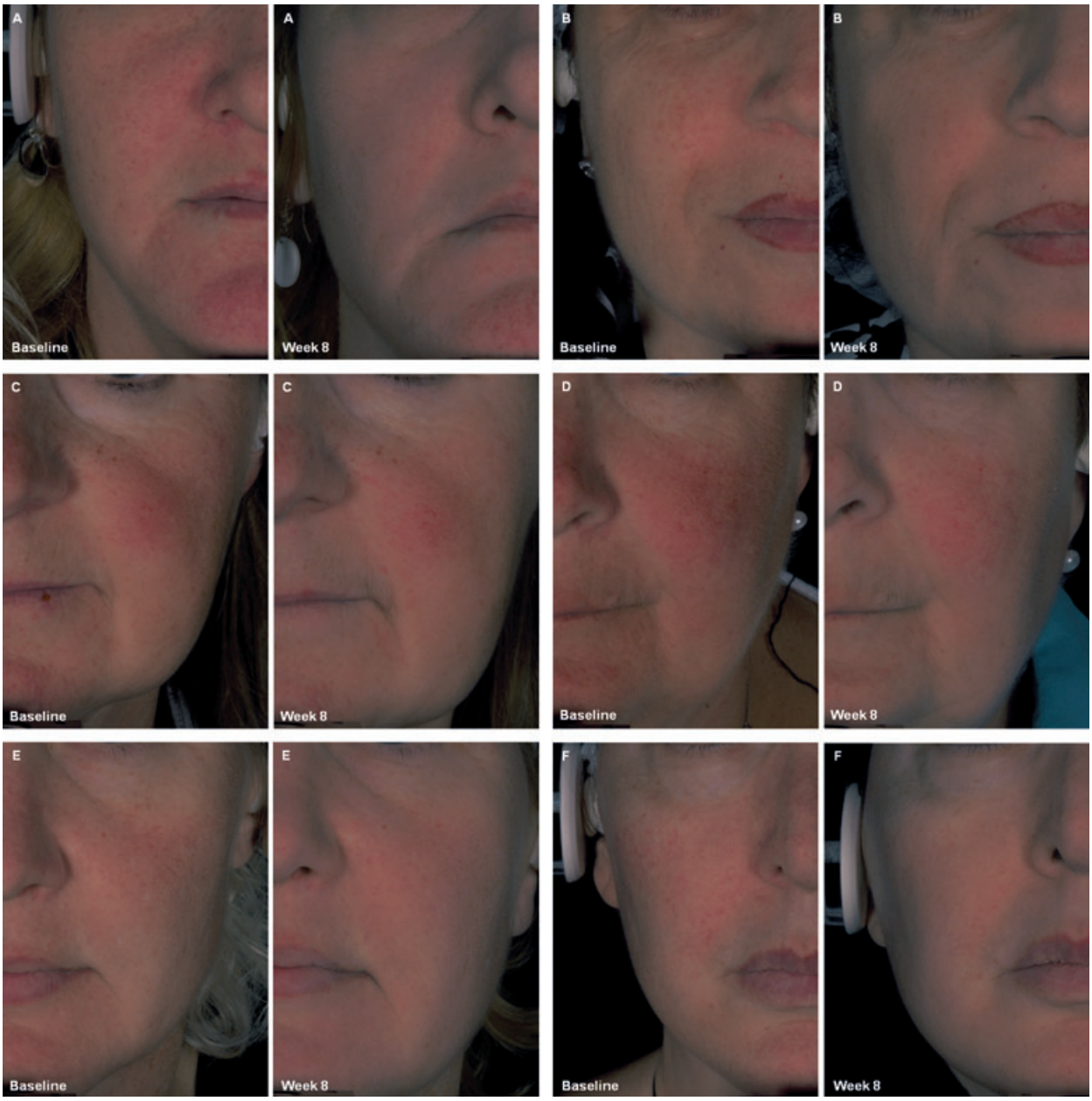

Figure 4 (a–f) Selection of before and after photographs showing improvement in signs of skin redness on the cheeks and chin, following 2 months of twice daily treatment with 100RXED2025. These are representative of results obtained for the whole panel of volunteers.

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The serum (100RXED2025) described here has been formulated with various cosmetic ingredients selected for their potential to synergize in improving skin redness in the context of skin aging. The total concentration of cosmetic ingredients (excluding excipients) in the serum is unusually high, reaching 40% w/w. The skin benefits related to either anti-aging or anti-redness properties of these ingredients are individually supported by *in vitro*, and in many cases, clinical data provided by their manufacturer. Nevertheless, it was mandatory to document the clinical efficacy and safety of the final product.

Serum safety was successfully addressed prior to the clinical trial (data not shown). The serum also appeared to be well tolerated in the course of the study, as reflected by the surprisingly high level of adhesion to the study protocol; of the 45 volunteers only 1 late dropout was registered. No adverse reactions were reported.

Significant signs of improvement in skin redness are evident when comparing the results obtained on cross-polarized photographs at T28 and T56 to baseline. Visual evaluation by experts documented a significant decrease in erythema grading scores at T28, still improving at T56 although less dramatically, suggesting a tendency toward a plateau effect. Women as well as men responded to the treatment and the level of clinical response was independent of the severity of the condition at baseline. By the end of the study (T56), all volunteers (100%) were experiencing some level of improvement, supporting that addressing simultaneously multiple facets of skin redness and aging may maximize cosmetic outcome.

The positive results obtained on visual evaluation were corroborated by the colorimetric analysis. Again, a significant improvement was seen at T28 and benefits were still increasing at T56.

On the basis of the results obtained using colorimetric analysis and visual evaluation, it is concluded that the test product (100RXED2025), a serum containing multiple cosmetic ingredients aimed at addressing skin erythema in aging skin, significantly improves skin tone in individuals presenting sensitive skin. Favorable results may be expected within 1 month of daily application, with further improvement over time.

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