Original Article

Assessment of dermocosmetics containing retinaldehyde, nicotinamide and Vitis vinifera in the cutaneous photoaging of women between 25 and 40 years old

Avaliação de dermocosmético com retinaldeído, nicotinamida e vitis vinifera no fotoenvelhecimento cutâneo de mulheres entre 25 e 40 anos de idade

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ABSTRACT

Introduction: The skin is subject to intrinsic and extrinsic aging processes, which makes treating cutaneous photoaging clinically challenging.

Objective: To use objective and subjective parameters to evaluate the safety, tolerability, and clinical efficacy of a cosmetic product containing 0.05% retinaldehyde, 4% nicotinamide, and 1% Vitis vinifera extract in the treatment of skin aging.

Methods: A monocentric, prospective, open study evaluated 40 female volunteers (25-40 years old) with Fitzpatrick skin types I to IV, who used the dermocosmetic product for 60 consecutive days. Subjective assessments were carried out by the physician and the volunteer patients. In addition, ultrasound examination and objective assessment of photographic records using the Visia® imaging system, skin biopsies, corneometry, pH metry, and sebumetry were conducted.

Results: Thirty-six volunteers completed the study. Subjective evaluations revealed improvements in wrinkles, fine lines, sagging, vitality, and overall appearance. Ultrasound and skin biopsies showed increased collagen (94.4% and 30.6%, respectively). Pictures from the Visia® device demonstrated a reduction in stains, wrinkles, and pores, and improvements in the skin's texture. Sebumetry revealed a decrease in the oiliness and the pH. Measurements taken with the corneometer remained constant.

Conclusions: This dermocosmetic product is effective and safe in the treatment of photoaging.

Keywords: retinoids; rethinaldehyde; niacinamide; skin aging.

RESUMO

Introdução: *A pele está sujeita ao envelhecimento intrínseco e extrínseco. Desse modo, tratar o fotoenvelhecimento cutâneo representa desafio clínico.*

Objetivo: *Avaliar, através de parâmetros objetivos e subjetivos, segurança, tolerabilidade e eficácia clínica de produto cosmético contendo retinaldeído 0,05%, nicotinamina 4% e extrato de Vitis vinifera 1% no tratamento do envelhecimento da pele.*

Métodos: *Estudo monocêntrico, prospectivo, intervencional, aberto que avaliou 40 voluntárias do sexo feminino de 25 a 40 anos, fototipos I a IV de Fitzpatrick, que aplicaram produto dermocosmético durante 60 dias consecutivos. As avaliações foram realizadas de forma subjetiva pelo médico, voluntária e exame ultrassonográfico e de forma objetiva por fotografias pelo Visia®, biópsias cutâneas, corneometria, pHmetria e sebumetria.*

Resultados: *36 voluntárias completaram o estudo. Avaliações subjetivas demonstraram melhora nas rugas, linhas finas, flacidez, viço e aparência geral. Ultrassom e biópsia cutânea evidenciaram aumento de colágeno em 94,4% e 30,6% respectivamente. Fotos do aparelho Visia® demonstraram redução de manchas, rugas, poros e melhora da textura cutânea. Sebumeter revelou diminuição da oleosidade, e houve redução do pH. As medidas do Corneometer mantiveram-se constantes.*

Conclusões: *o produto dermocosmético analisado foi eficaz e seguro para combater o fotoenvelhecimento.*

Palavras-chave: *retinoides; retinaldeido; niacinamida; envelhecimento da pele.*

INTRODUCTION

Environmental and genetic factors are actively involved in the skin's aging process. Exposure to ultraviolet (UV) radiation is the main environmental factor linked to changes in the skin and is a proven cause of premature skin photoaging. UV rays alter mitochondrial DNA and the cell nucleus, and attack keratinocytes and fibroblasts, causing molecular changes that destroy extracellular collagen and decrease new collagen synthesis. [1-5] Aged skin is clinically characterized by mottled pigmentation, xerosis, and thin wrinkles. [1-4] Aging skin is associated with a decrease in microcirculation, elastosis, cellular atypia, preneoplastic dysplasia, and epidermal atrophy.[6]

UV rays are also associated with an increase in free radicals, which play an important role in aging. [7,8] These molecules damage important skin structures such as collagen and elastic fibers, cell membranes, and DNA segments. Proteasome, a multichannel protease, is responsible for the degradation of oxidized products. This protease appears to become less active with aging, leading to the incomplete degradation of oxidized proteins, an increase in protein aggregates, and an acceleration of cellular dysfunction. [7, 8]

Photodamaged skin presents important alterations in the cellular components and the extracellular matrix of the connective tissue. The activation of extracellular matrix metalloproteinases (MMPs) causes the accumulation of disorganized elastin and collagen loss.[9] MMPs mediate the oxidative effects of UV rays; an increase in the expression of MMPs relates to a reduction of collagen and connective tissue synthesis. [5] Given the focus on beauty and looking younger in today's society, the cutaneous aging process has an important psycho-emotional impact, which has prompted the development of many therapies aimed at reducing or preventing this effect.[5]

Topical retinoids – a term used to describe molecules that have a biological action typical of vitamin A – are important for the treatment of photodamaged skin due to their ability to produce molecular and biochemical alterations that lead to visible changes, which improve the skin's appearance.[5, 10] Topical vitamin A inhibits the expression of MMP and stimulates collagen synthesis in both photodamaged and photoprotected skin. [5]

These substances also enhance skin hydration through different suggested mechanisms, including deposition of glycosaminoglycans in the epidermis, stratum corneum compaction, and modifications in the epidermal proliferation and thickening. [5] Retinoid compounds improve skin pigmentation, and their affect on skin dyschromia is achieved through a number of complicated mechanisms including the inhibition of tyrosinase activity, the decrease in the size of cellular organelles linked to melanin synthesis, and the inhibition of melanosomes. [5, 11.12]

Although topical retinoids are effective in treating various skin alterations, some – such as retinoic acid – have local adverse effects, including desquamation, erythema, dryness, and burning and itching, which are mainly observed at the start of treatment. The degree of intolerance varies among patients and is often linked to the vehicle used in the formulation. Irritation can be mitigated by reducing exposure to the sun, avoiding extreme temperatures, and using emollient creams. [13]

Retinaldehyde, derived from vitamin A, is a natural precursor of retinoic acid that exhibits biological action and good tolerance in the treatment of aging skin. It acts similarly to retinoic acid, but causes less irritation. [5, 6.10] In addition to retinoids, other cosmeceutical products have been developed to improve photoaged skin, including vitamins and phytotherapic products.[14]

Vitamins are natural constituents of human skin and are part of the antioxidant system that protects skin from oxidative stress.[15] There is increasing interest in the use of vitamins and natural antioxidants to boost antioxidant action. [15]

Nicotinamide – also known as niacinamide – is a water-soluble vitamin (vitamin B3), which is part of the coenzyme nicotinamide-adenine dinucleotide. [14] Topical nicotinamide reduces transepidermal water loss, improves the stratum corneum's hydration, increases keratin synthesis and stimulates the synthesis of ceramides. It also helps reduce the appearance of wrinkles, hyper and hypopigmented patches, and yellowed skin.[14, 16.17]

Vitamins A and B3 have demonstrated potent anti-inflammatory and antioxidant actions. Products containing these substances have proven effective in treating skin aging and inflammatory skin diseases such as acne, pigmentation alterations, and scarring.[14, 15] There is evidence of additive effects when those substances are used in combination. Nevertheless, they must be prepared and combined appropriately in formulations in order to achieve the desired effects.[15]

Phytotherapic substances are also seen as important ingredients for cosmeceutical products. *Vitis vinifera* extract, which is derived from grape seed, is a flavonoid rich in proanthocyanidins, which are excellent antioxidants that reduce the damage caused by free radicals.[18, 19] In this context, clinical research and incentives for the use of cosmeceuticals have been growing in modern dermatology practice.

METHODS

After being approved by the Committee of Ethics in Human Research (CAAE n. 04450000142-10), a monocentric, open, prospective and intervening clinical study was carried out in accordance with best clinical practices and the principles of Resolution 196/96 of the Brazilian National Health Counsel.

The volunteers signed a term of free and informed consent and underwent a general dermatological evaluation to assess whether they met the inclusion criteria. The study included women (n = 40) aged 25- 40 who were regular users of facial sunscreen, had Fitzpatrick skin types I to IV, and with mild to moderate signs of photoaging (Glogau Scale I and II). They were to be free of conditions that, according to the investigator, could interfere in the evaluation of skin aging; able to follow the visitation schedule and the treatment course; and have no known history of allergic reaction to components of the study product). Exclusion criteria were: the presence of any dermatosis, systemic disease or use of medications that could interfere

with the clinical evaluation of the treatment; intense exposure to the sun during the study and/or in the preceding 60 days; use of illicit drugs; smoking; HIV positive.

The clinical trial consisted of the application of retinaldehyde, nicotinamide, and *Vitis vinifera* extract-based cosmetic products. It lasted 75 days, during which the volunteers attended the research center four times (D-15, D0, D30, D60) and used the study product for 60 days. Volunteers were excluded from the study if they interrupted the use of any product for five consecutive days or an absolute total of ten days, during the 60 days planned in the protocol. In the four planned visits, the volunteers underwent physical examination and their vital signs were evaluated. On visits 1 (D-15) and 4 (D60), skin biopsies were performed with a n.2 punch in the photoexposed area of the face. The following stainings were used in the analysis of the samples taken: Masson's trichrome (collagen fibers), Verhoeff (elastic fibers), Alcian Blue (mucin).

Measurements of corneometry, sebumetry, and pH-metry (Derma Unit SSC3, CK Eletronic GmbHO, Cologne, Germany), ultrasound in the facial regions subjected to biopsy (DUBO-USB®, SkinScanner, Luneburg, Germany), and pictures of the face with a Visia® device (Canfield System®, Fairfield, New Jersey, USA) were taken on visits 2, 3, and 4.

Ultrasound examination was used to map the existing pattern of elastic and collagen fibers. Those results were analyzed by software that rated the data as: "greatly increased," "increased," "unchanged," or "decreased." The pictures obtained using the Visia® equipment analyzed the following variables: "patches," "UV patches," "brown patches," "red area," "wrinkles," "texture," "pores," and "porphyrin." The parameters *count*, *rating* and *percentile* were analyzed for each variable (*count* was defined as the number of elements, *rating* as the total size/area and intensity of those elements, and *percentile* as the comparison between the volunteer and other individuals of the same age, sex, and phototype). In addition, the safety assessment was carried out using an adverse event questionnaire.

On visits 3 and 4, subjectivity, tolerability, and the clinical evaluations were evaluated using subjective questionnaires administered by physician evaluators and a volunteer self-assessment. In the clinical evaluation questionnaire the parameters wrinkles, thin lines, melanoses, other hyperchromies, erythema, skin sagging, hydration, vitality, oiliness, softness to the touch, and overall appearance were evaluated (Tables 1 and 2).

Since the variables did not present normal distribution (bell curve) according to the Anderson-Darling test, nonparametric statistic tests were used throughout the analysis. A significance level of 0.05 ($p < 0.05$), with 95% confidence intervals, was established for this study. Wilcoxon tests were used to analyze the data obtained from corneometry, pH-metry, sebumetry, and Visia®. The test for equality of two proportions was used to analyze answers obtained from the questionnaires, from adverse events, subjective evaluation of tolerability, and ultrasounds.

RESULTS

Of the 40 volunteers, 36 (90%) completed the study. One volunteer was excluded due to an adverse event (burning sensation, redness, and mild desquamation) resulting from the use of the study product; one was excluded due to protocol violation; and two due to withdrawal of consent.

The analysis of the volunteers' self-assessment questionnaires revealed an absence of adverse events in 83.3% of patients. Furthermore, it showed a predominance of the answer "excellent" between D0 and D60 for the parameters of pleasantness with 25% for odor ($p = 0.058$), 58.3% for spreadability ($p = 0.099$), and 33.3% for absorption ($p = ?$). The analysis of tolerability questionnaires (erythema, dryness, desquamation, itching/burning sensation) did not present a statistically significant difference during the visits, suggesting that the product was well tolerated throughout the study. The absence of a statistical difference for erythema indicates that the product did not cause any reddening of the skin.

The volunteers' subjective evaluations showed a progressive increase in the number of volunteers who answered "marked improvement," reaching, on D60, 38.9% for wrinkles ($p = 0.006$), 36.1% for thin lines ($p = 0.029$), 63. 9% for sagging ($p = 0.009$), 66.7% for vitality ($p = 0.018$), 47.2% for melanoses ($p = 0.005$), 47.2% for other hypercromies ($p = 0.005$), and 75% for overall appearance ($p = 0.002$). There was an increase in the number of volunteers who responded "complete improvement" for hydration (11.1% on D60, $p = 0.04$), oiliness (13.9% on D60, $p = 0.088$), and softness to the touch (13.9% on D60, $p = 0.020$). The evaluator physician's subjective assessment revealed an increase in the answer "moderate improvement" in all visits, with the following results on D60: 27.8% for wrinkles ($p = 0.032$), 33.3% for thin lines ($p = 0.009$), 33.3% for sagging ($p = 0.001$), 30.6% for oiliness ($p = 0.017$), 75% for vitality ($p < 0.001$), 72.2% for softness to the touch ($p < 0.001$), 72.2% for hydration ($p = 0.001$), and 80.6% for overall appearance ($p = 0.002$) (Figure 1). There were no statistical differences for other hyperchromies, melanoses, and erythema.

The ultrasound showed increased amounts of collagen, demonstrated by the rating "greatly increased" in 77.8% of the volunteers, between D0 and D30 ($p < 0.001$) and in 94.4% of participants between D0 and D60 ($p < 0.001$) (Graph 1). These data were corroborated by the amount of collagen, which continued to increase up until D60 (Figures 2 and 3).

A skin biopsy revealed an increase of roughly 10% in the

Chart 1: Subjective tolerability evaluation

Excellent	Total absence of adverse events
Good	Adverse events are easily tolerated
Regular	Adverse events are tolerated and do not lead to discontinuation of treatment
Bad	Adverse events require cessation of treatment

Chart 2: Subjective evaluation of efficacy	
Full improvement	Absence of signs of skin aging
Marked improvement	Considerably improved signs of skin aging (50-99% better than baseline, qualitatively)
Moderate improvement	Skin aging signs are present, however noticeably improved (25-50% better than baseline, qualitatively)
Slight improvement	Minimal improvement only, with presence of skin aging signs (up to 25% better than baseline, qualitatively)
Unchanged	Absence of improvement: skin aging signs unaltered or worse compared to initial visit
Slight worsening	Presence of skin aging signs, with minimal worsening only (up to 25% worse than baseline, qualitatively)
Moderate worsening	Skin aging signs present, but noticeably worse (25-50% worse than baseline, qualitatively)
Marked worsening	Skin aging signs considerably worse (50-99% worse than baseline, qualitatively)
Total worsening	Skin aging signs considerably worse (100% worse than baseline, qualitatively)

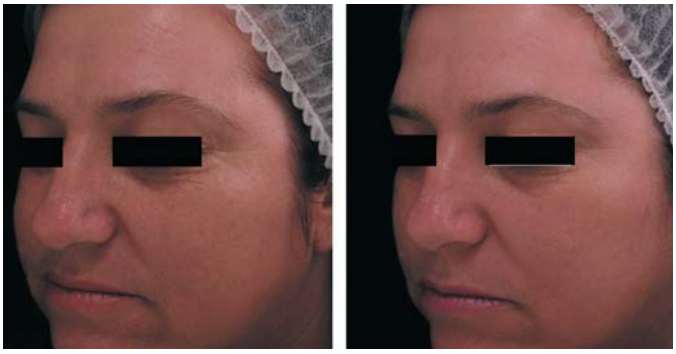
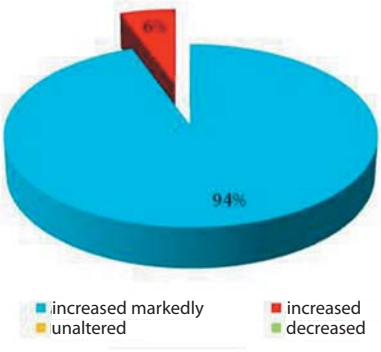


Figure 1: Comparison of overall appearance between D0 and D60



Graph 1: Evaluation of the amount of collagen demonstrated by ultrasound on D60

percentage of collagen fibers compared to the baseline average ($p < 0.001$). No statistical differences were found in the elastic fibers and mucin evaluations: respectively 14% on D-15 to 13.3% on D60, and 19.8% on D-15 and 22.6% on D60. In turn, the subjective analysis demonstrated an increased percentage of collagen fibers in 30.6% of volunteers between the initial (D-15) (Figure 4) and final (D60) (Figure 5) visits. The elastic fibers and mucin evaluations remained unchanged in 61.1% and 94.4% of the volunteers, respectively. The pictures obtained using the Visia® equipment revealed statistically significant differences for count, score, and improvement percentile for the variables "patches," "wrinkles," and "texture." In the evaluation of "patches" there was a reduction in the count to 36,0 (D60) from 41.7 (D0) ($p < 0.001$), in the score to 1.352 (D60) from 1.598 (D0) ($p < 0.001$), and in the improvement percentile to 68.3 (D60) from 60.9 (D0) ($p < 0.001$). For the variable "UV patches" there was a worsening of the parameters count to 25.3 (D60) from 10 (D0) ($p< 0.001$) and score to 0.654 (D60) from 0.25 points (D0) ($p< 0.001$).

No change was verified for the "brown patches" variable.

The "wrinkles" parameter count decreased to 4.7 (D30) from 5.7 (D0) ($p ,<0.041$), which remained stable up until D60. The score presented the same pattern: a reduction to 0.776 (D30) from 0.962 (D0) ($p <0.023$), which remained stable up until D60. Regarding the improvement percentile, there was an increase to 77.3% from 73.4% (D0) ($p <0.014$), which remained stable after D30.

Reductions in the count and score were verified in all visits for the variable "texture." For the count parameter, values ranged from 350.7 on D0, to 295.6 on D30 ($p< 0.012$), and 267.0 on D60 (p 0.088). For the parameter score, values ranged from 2.399 (D0), to 1.915 (D30) ($p = 0.015$), and 1.649 (D60) ($p = 0.043$). The improvement percentile presented a significant increase in all visits (57% on D0, 62.1% on D30, and 65.8% on D60).

Reductions in the count and score parameters were also observed in all visits for the variable "pores." For the count parameter, values ranged from 201.5 (D0), to 184.5 (D30), and 171.7 (D60). For the parameter score, values ranged from 1.556 on D0, to 1.356 on D30, and 1.253 on D60. The variable "porphyrins" increased between visits, both in the count and score parameters, however that difference was statistically significant only on D0 and D60: the count parameter developed from 17.2 on D0 to 43 on D60 ($p <0.035$) and the score parameter from 0.096 on D0 to 0.241 on D60 ($p <0.040$).

Measurements of the "sebumetry" variable demonstrated a reduction in skin oiliness between D0 and D30 (from 72.74 to 58.45, $p = 0.016$); values became stable after 30 days. Statistically significant differences were also observed for the variable "pH-metry." There was a reduction between D0 and D30 (to 4.75 from 4.91, $p = 0.018$), with a return to the initial

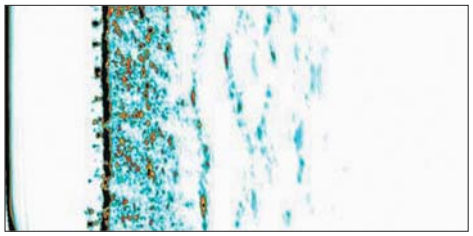


Figure 2: Collagen amount demonstrated by ultrasound on D0 (yellow dots)

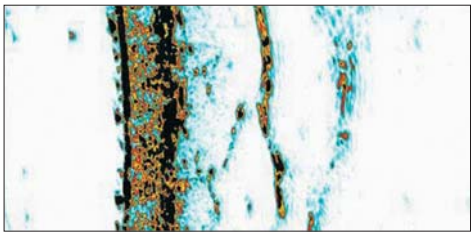


Figure 3: Collagen amount demonstrated by ultrasound on D60 (yellow dots)

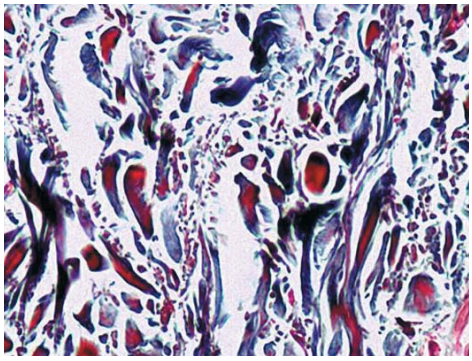


Figure 4: Percentage of collagen fibers on D-15 (Masson trichrome staining)

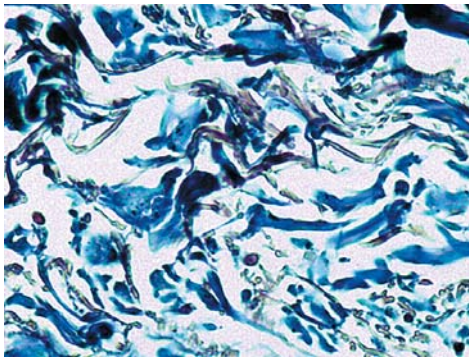


Figure 5: Percentage of collagen fibers on D60 (Masson trichrome staining)

parameters on D60. Measurements of the variable "corneometry" remained constant.

DISCUSSION

In 1986, Kligman and colleagues suggested for the first time that derivatives of vitamin A (retinoic acid or tretinoin) were effective in treating cutaneous photoaging.[20] In 1988, Weiss and others demonstrated in a double-blind controlled study that the use of a cream containing 0.1% isotretinoin reduced the effects of cutaneous photoaging, such as expression lines and wrinkles. Nonetheless, they verified the presence of a number of adverse events, including erythema, xerosis, burning and tingling sensations, and swelling. [21]

Since then, other formulas containing tretinoin have been developed in efforts to find a formulation that is better tolerated.[22] Notwithstanding, it is still common in clinical practice to find patients who do not adhere to long-term use due to the side effects.[23]

Retinaldehyde – a natural precursor of tretinoin – spurred studies that aimed to verify its improvement of skin aging with milder side effects.[24] In 1994, Saurat demonstrated that retinaldehyde's biological effects on human skin were similar to those of tretinoin, and noted that the compound was better tolerated.[25] In 1999, Creidi and colleagues published a series of open controlled studies proving that the regular use of cosmetics containing retinaldehyde improves the effects of photoaging without causing adverse events.[23]

Other vitamins besides vitamin A and its derivatives have been increasingly attracting attention in the cosmeceuticals marketplace – especially vitamin B3 (nicotinamide). [15] As with vitamin A, vitamin B3 has important antioxidant and anti-inflammatory actions, and therefore stands out as effective in improving the clinical effects of photoaging. [14,15] In a double-blind, placebo-controlled trial with 50 women aged 40-60 using products containing 5% nicotinamide only, quantitative analysis and digital imaging demonstrated a reduction of approximately 5.5% in thin lines and wrinkles, and an improvement in the skin's texture and whitening.[17]

Other natural products, including herbal medicines, can also fight the effects of photoaging. Nonetheless, due to their exemption from clinical efficacy and safety evaluation by the Food and Drug Administration, it is impossible to assert the effectiveness of the benefits claimed.[19]

Vitis vinifera had its antioxidant action demonstrated recently in a study by Cornachionne and collegues. That study also revealed that *in vitro*, the extract of *Vitis vinifera* presented a higher antioxidant power than those of vitamins C and E, and is therefore an effective agent to treat skin damage caused by the formation of free radicals. [18, 19]

The analysis of the volunteers' subjective questionnaires in the present study showed an absence of adverse events and good tolerability of the product, similar to the results obtained by Saurat [25] and Creid and others. [23] The prevalence of the answer "excellent" for the parameter "pleasantness" and the lack of statistical difference for erythema stand out. Thus the investigated product was agreeable and did not produce cutaneous irritation that could be translated as a reaction to the presence of erythema.

The same authors also demonstrated that retinaldehyde can improve clinical aspects of photoaging. [23,25] That study's results, obtained from the subjective analysis of the questionnaires administered to physicians and volunteers, corroborated the authors' assertions by demonstrating that the product was capable of improving wrinkles, thin lines, sagging, vitality, and ove-

rall appearance.

Through images obtained using the Visia® device, the present study was also able to objectively demonstrate the product's efficacy in reducing "patches," "wrinkles," "pores," and improving the skin's "texture." There was a significant reduction in the number of elements (count), total size/area and intensity of these elements (score) for "patches." For "wrinkles," in addition to the reduction in count and score, there was an percentile improvement, i.e., the volunteers' clinical improvement when compared to other individuals of the same age, gender, and phototype. "Pores" and "texture" presented the same pattern as "wrinkles," demonstrated a reduction in count and score, and improved in the percentile. In this way, pictures taken using the Visia® equipment demonstrated objective improvement in the general appearance of the skin. The same analysis showed that there was a worsening of the parameters "brown spots" and "UV spots." This finding was not supported by the subjective evaluations, given that the analysis of the volunteers' questionnaires suggested improvement in melanoses and other hyperchromies.

Although doctors and volunteers noticed improvement in the skin's hydration during the subjective evaluations, objective corneometry measurements did not corroborate these findings; there were no significant statistical differences throughout the study.

The measurements obtained through pH-metry demonstrated a decrease between D0 and D30, and returned to baseline on D60. However, this increase in the skin's acidity is relevant for its hydration, given that cutaneous acidity controls the stratum corneum's and epidermis' cohesion and integrity; it is essential to establishing the epidermal barrier's permeability and therefore maintaining the skin's hydration.26 Therefore, although corneometry did not reveal a statistically significant difference, the improvement in clinical hydration may have resulted from the decrease in the skin's pH.

There was a reduction in the skin's oiliness, as assessed by sebumetry between D0 and D30 visits; this finding is in line with other studies in the literature.[27] It is important to note that the studied dermocosmetic formulation was not comedogenic and did not induce the formation of acne, as described in the clinical evaluation.

Also noteworthy are the ultrasound and skin biopsy results, which revealed an increase in the amount of collagen in the skin. Previous studies have suggested that the use of retinaldehyde induces morphological changes in the skin, and have advised that further detailed research should be carried out to assess this finding. [23, 25,28] The increase in the amount of collagen, evidenced by the biopsy and subjectively assessed, was 30.6%, which was higher than that demonstrated in 1999 by Bosnic and colleagues, [28] whose study described an 18.9% increase in the amount of collagen after the administration of a formulation containing 0.05% retinaldehyde. Nevertheless, the present study did not present a statistically significant increase in the number of elastic fibers, whereas Bosnic showed an increase of 3.88%. It should be noted, however, that Bosnic used a smaller sample (n = 8), which may have contributed to the statistical difference found in the study. No studies demonstrating an increased amount of collagen after ultrasound use were found in the researched literature. The present study, however, showed an increase in the amount of collagen in 94.4% of the volunteers during ultrasound measurements.

By demonstrating through skin biopsy and ultrasound that there was an increase in collagen fibers, the present study supports the hypothesis that retinaldehyde, alone or combined with the other two substances, induces morphological changes in the skin.

CONCLUSION

It is possible to assert that the product containing retinaldehyde, nicotinamide, and *Vitis vinifera* extract in its formulation was safe in the treatment of photoaging in women aged 25-40. This dermocosmetic formulation also improved several skin aging parameters such as wrinkles, thin lines, sagging, vitality, and general appearance when subjectively evaluated by physicians and volunteers, and was objectively confirmed using the Visia® equipment analysis. In addition, an increase in the amount of collagen was demonstrated through ultrasound and biopsy. This dermocosmetic formulation has therefore proven itself an effective option in the treatment and prevention of skin disorders caused by photodamage. ●

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