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Oral supplementation of the nutraceutical decarboxy carcinine HCl for rhytids and skin rejuvenation

Suplementação oral do nutracêutico decarboxicarnosina HCl para rítides e rejuvenescimento da pele

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ABSTRACT

INTRODUCTION: Advanced glycation end products (AGEs) are stable compounds formed by nonenzymatic reactions between amino groups of biomacromolecules and carbonyl groups of reducing sugars. AGEs are known to play a role in various diseases such as diabetes, cardiovascular diseases, and neurodegenerative disorders, as well as contributing to premature skin aging. Decarboxy carcinine HCl, a stable analogue of carnosine, has demonstrated potential in reducing the effects of glycation.

OBJECTIVE: To evaluate the effects of oral supplementation with Glycoxil®, a patented decarboxy carcinine HCl molecule, on signs of skin aging in participants with mature skin.

METHODS: This randomized, double-blind, placebo-controlled study involved 30 participants aged 30-50 years, with skin phototypes I to IV and clinical signs of skin aging (e.g., rhytids). Participants were divided into two groups: one received Glycoxil® 300 mg daily for 90 days, while the other received a placebo. Standardized skincare products were provided, and participants underwent evaluations using Visia® and Focco® imaging systems at baseline (T0), 45 days (T45), and 90 days (T90). Statistical analysis was conducted using RStudio, with ANOVA and Wilcoxon tests. Significance was set at $p<0.05$.

RESULTS: Of the 30 participants, 18 were analyzed with Focco® and 22 with Visia®. Objective evaluations showed no statistical differences between groups in rhytid improvement at T0, T45, or T90. However, slight improvements were observed in the treatment group at T45 and T90. Blinded dermatologists noted improvements in hydration, firmness, and texture in both groups, with some participants in the treatment group reporting "improved" or "much improved" appearance. No adverse effects were reported.

CONCLUSIONS: Although no statistically significant differences were found between the groups, the findings suggest that Glycoxil® may contribute to minor improvements in skin-aging signs, corroborating existing literature on anti-glycation strategies. Further studies with larger sample sizes, extended follow-up periods, and advanced analytical methods are recommended to confirm these preliminary results.

Keywords: Glycation End Products, Advanced; Antiglycation Agents; Maillard Reaction.

RESUMO

INTRODUÇÃO: Os produtos finais de glicação avançada (AGEs) são compostos estáveis formados por reações não enzimáticas entre grupos amino de biomacromoléculas e grupos carbonila de açúcares redutores. Os AGEs são conhecidos por desempenharem um papel em várias doenças, como diabetes, doenças cardiovasculares e distúrbios neurodegenerativos, além de contribuírem para o envelhecimento precoce da pele. A decarboxicarnosina HCl, um análogo estável da carnosina, demonstrou potencial na redução dos efeitos da glicação.

OBJETIVO: Avaliar os efeitos da suplementação oral com Glycoxil®, uma molécula patenteada de decarboxicarnosina HCl, sobre os sinais de envelhecimento da pele em participantes com pele madura.

MÉTODOS: Este estudo randomizado, duplo-cego e controlado por placebo envolveu 30 participantes com idades entre 30 e 50 anos, com fototipos I a IV e sinais clínicos de envelhecimento cutâneo (por exemplo, rítides). Os participantes foram divididos em dois grupos: um recebeu 300 mg de Glycoxil® diariamente durante 90 dias, enquanto o outro recebeu placebo. Produtos de cuidados com a pele padronizados foram fornecidos, e os participantes passaram por avaliações utilizando os sistemas de imagem Visia® e Focco® nos momentos iniciais (T0), 45 dias (T45) e 90 dias (T90). A análise estatística foi realizada utilizando o RStudio, aplicando os testes de análise de variância (ANOVA) e Wilcoxon, com significância definida em $p < 0,05$.

RESULTADOS: Dos 30 participantes, 18 foram analisados com o Focco® e 22 com o Visia®. As avaliações objetivas não mostraram diferenças estatísticas entre os grupos na melhora das rítides em T0, T45 ou T90. No entanto, pequenas melhorias foram observadas no grupo Glycoxil® em T45 e T90. Dermatologistas cegados observaram melhorias na hidratação, firmeza e textura em ambos os grupos, com alguns participantes do grupo Glycoxil® relatando um resultado "bom" ou "muito bom". Nenhum efeito adverso foi relatado.

CONCLUSÕES: Embora não tenham sido encontradas diferenças estatisticamente significativas entre os grupos, os achados sugerem que o Glycoxil® pode contribuir para pequenas melhorias nos sinais de envelhecimento da pele, em concordância com a literatura existente sobre estratégias antiglicação. Recomenda-se a realização de novos estudos com amostras maiores, períodos de acompanhamento mais longos e métodos analíticos avançados para confirmar esses resultados preliminares.

Palavras-chave: *Reação de Maillard; Agentes Antiglicação; Produtos Finais de Glicação Avançada.*

Original Article

Authors:

Célia Kalil[1]
Luciane Zagonel[2]
Valéria Barreto Campos[2]
Christine Chaves Prato[3]
Clarissa Reinehr[4]
Patrícia França[5]
Pedro Vargas[3]

1 Dermatology Service of the Federal University of Froteira Sul, Passo Fundo (RS), Brazil
2 University of Jundiaí, Jundiaí (SP), Brazil
3 Farmatec Compound Pharmacy, Porto Alegre (RS), Brazil
4 Clinica's Hospital of Porto Alegre, Porto Alegre (RS), Brazil
5 Biotec São Paulo, São Paulo (SP), Brazil

Correspondence:
Pedro Vargas
E-mail: pedro@farmatecrs.com.br / pedro.vargas@acad.pucrs.br

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INTRODUCTION

Advanced glycation end products (AGEs) are a group of structurally different compounds derived from nonenzymatic reactions between reducing sugars and proteins, lipids, or nucleic acids, followed by further chemical modifications that result in stable, irreversible end products. These biochemical molecules can bind to several cell types as well as to receptors for AGEs (RAGEs), with several biological implications.[1]

Cooking methods such as roasting and broiling at high temperatures facilitate chemical reactions between primary and secondary amino groups of amino acids in proteins and the carbonyl groups of reducing sugars, leading to the formation of AGEs. This reaction is commonly referred to as the Maillard reaction.[2] In the last decades, AGEs have garnered significant scientific interest due to mounting evidence of their involvement in several pathophysiological processes and diseases, such as cancer, diabetes, neurodegenerative diseases, cardiovascular events, and even SARS-CoV-2 infection.[3-4]

Several studies have shown that moderate levels of reactive oxygen species (ROS) are important for several physiological functions, as ROS plays an important role in many defense mechanisms. However, with increased consumption of processed foods in Western diet, AGE intake has dramatically increased, leading to the identification of glycosylated hemoglobin (HbC1) as the first glycation biomarker.[5-6] AGE-related cross-linking of structural proteins such as collagen and elastin contributes to the stiffening of the extracellular matrix (ECM) and is frequently involved in organ and vascular dysfunction. These proteins, due to their long half-lives and direct exposure to high extracellular glucose levels, are particularly susceptible to glycation. Protein glycation products can trigger a complex, chronic inflammatory process that involves several cytokines, including NF-κB, interleukin 6, interleukin 2, and tumor necrosis factor. Over time, these repetitive signals can induce subtle but critical epigenetic changes, leading to significant skin-aging effects such as loss of firmness, pigmentation alterations, wrinkle formation, and increased skin stiffness.[7-10]

Carnosine (β-alanyl-L-histidine) is a naturally occurring dipeptide found in many organisms that has demonstrated potential in interfering with AGEs. Although its precise mechanism of action has not been fully elucidated, it is hypothesized that both the free amino group from β-alanine and the imidazole ring of histidine compete with protein amino groups in the presence of reactive dicarbonyl compounds.[11-12] However, carnosine has low bioavailability due to its rapid hydrolysis by carnosinase, an enzyme with two isoforms found in plasma and kidneys. This limitation led to the search for a more stable and bioavailable compound.[13-14] Carcinine, an important analog of carnosine, exhibits remarkable stability compared to other derivate molecules; the depletion of the carboxylic acid group at the β-position increases its stability and bioavailability while making its hydrolysis by carnosinase negligible.[13-14]

Considering the growing body of biological evidence on AGEs and their impact on general health and premature skin aging in Western populations, this study aimed to evaluate how volunteers with signs of mature skin responded to oral treatment with Glycoxil®, a patented decarboxy carcinine HCl molecule.

MATERIAL AND METHODS

This was a 90-day prospective, randomized, double-blind study conducted at two private, independent dermatology clinics. Thirty-two participants aged between 30 and 50 years, with skin phototypes I to IV, presenting clinical sings of skin aging (including rhytids) were selected from the cities of Porto Alegre and Jundiaí, state of Rio Grande do Sul, Brazil. Participants were instructed to use only the products provided by the investigators, including a facial moisturizer formulated by Farmatec (glycerol 5%, dimethicone 3%, Hyaxel 1%, DSH CN® 3% Q.S. Omega Gold Cream), colorless Anthelios Hydraox sunscreen (La Roche-Posay), and a neutral facial soap.

Participants were excluded if they met any of the following criteria: current or previous use of oral retinoids in the last 6 months; use of systemic corticosteroid therapy, immunosuppressants, or immunobiological agents; use of topical medications containing retinoids or hydroquinone; aesthetic procedures, including laser treatments, chemical peels, microneedling, botulinum toxin, or collagen biostimulators, in the last 6 months; facial plastic surgery in the last 12 months; presence of a skin disease that compromises skin structure (e.g., collagenosis); autoimmune diseases or active infections; pregnancy, lactation, or intent to become pregnant during the study period; not using effective contraception; presence of suspected neoplastic lesion on the face; hypersensitivity to any component of the formulation, capsules, or topical products used in the study; use of oral supplements for skin improvement in the last 6 months (e.g., collagen supplements, organic silica, or antioxidants).

The analysis methodology was adapted from Kalil et al.[15] Participants were randomly allocated into two groups: one group received 300 mg of oral decarboxy carcinine HCl (Glycoxil®) daily for 90 days, while the other received a placebo (microcrystalline cellulose) as a negative control. Clinical assessments were performed using Visia® imaging equipment for participants in Jundiaí and Focco® imaging equipment for participants in Porto Alegre. Front and side photographs were taken at baseline, mid-treatment (45 days), and after treatment completion (90 days).

Evaluations consisted of subjective assessments by the participants using the Global Aesthetic Improvement Scale (GAIS) and the Wrinkle Severity Classification (WSRS), as well as objective efficacy assessments using the Visia® equipment and subjective photo evaluations by two dermatologists. Descriptive analysis was conducted for both qualitative and quantitative variables as well as to evaluate quantitative variables in relation to study outcomes.

The study was approved by the Research Ethics Committee under protocol number 53636521.5.1001.5412, dated August 8, 2022. All participants enrolled in the study provided written informed consent.

Objective image evaluation

Objective assessments were conducted using Visia® and Focco®, both of which require precise patient positioning throughout imaging acquisition to ensure adequate quality. Participants had to assume the same position for all follow-up images. The Visia® and Focco® imaging systems provide accurate evaluation of skin rhytids.

Clinical image evaluation

A blinded dermatologist reviewed the paired photos taken at baseline, day 45, and day 90 to conduct the clinical analysis. The evaluation focused on wrinkles, hydration, firmness, texture, and brightness. Based on these parameters, responses were classified into 5 groups: 1) very much improved, 2) much improved, 3) improved, 4) no change, and 5) worse.

Self-reported assessment of improvement

Self-reported assessments were informed by two measures: overall improvement – yes or no; and the GAIS scale: 1) very much improved, 2) much improved, 3) improved, 4) no change, and 5) worse. Patients also assessed treatment tolerability based on the following criteria: 1) gastrointestinal symptoms, 2) skin rash, 3) skin allergy, and 4) UV exposure-induced redness.

Statistical analyses

Data analysis was performed using RStudio software (Posit, Boston, USA). Parametric analysis was conducted using analysis of variance (ANOVA), while nonparametric analysis was conducted using the Wilcoxon test. For the Wilcoxon test, a multiple comparisons post-hoc test was applied to determine the specific differences. For ANOVA with repeated measures, the paired t-test adjusted by the Bonferroni method was used. Statistical significance was set at $p < 0.05\%$, while a trend towards significance was considered for $\#p < 0.07\%$.

RESULTS

The study included 30 participants, of whom 18 were analyzed with Focco® equipment (9 per group) and 22 with Visia® equipment (11 per group). No patient was undergoing isotretinoin treatment or had undergone any recent dermatological procedures.

Objective image evaluation

Objective assessments of rhytids using the Focco® software in both groups are presented in figure 1. The analysis showed no statistically significant difference between groups at baseline, day 45, and day 90. Similar results were found using the Visia® software, as shown in figure 2.

Because Focco® and Visia® are distinct software systems with different methodologies, direct comparisons between their results were not feasible.

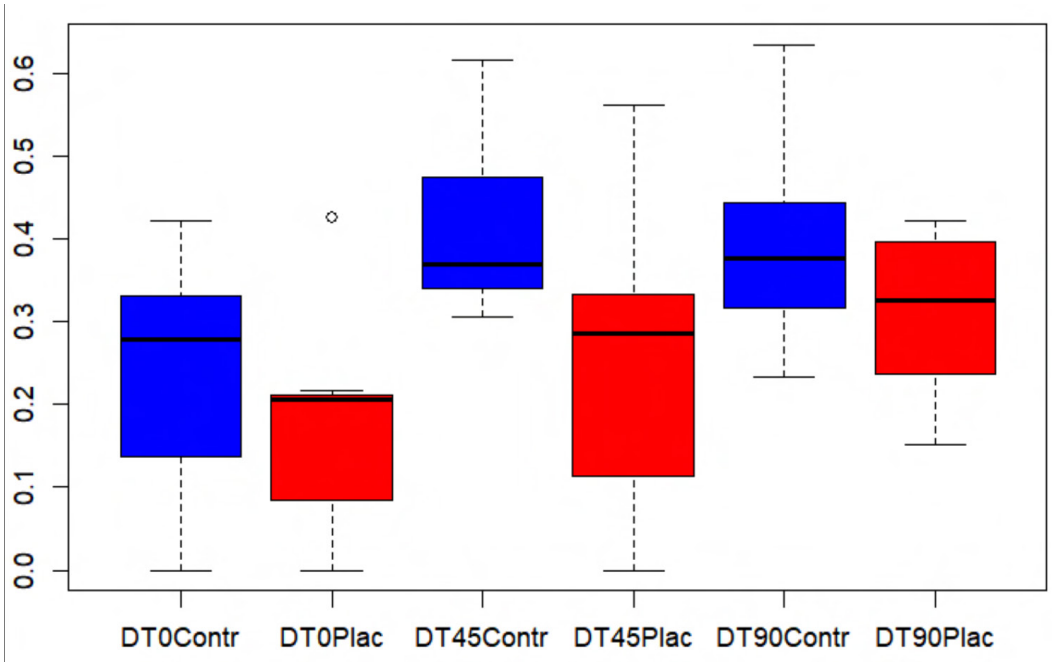

FIGURE 1: Objective analysis of rhytids using Focco® software

Boxplot analyses of rhytides by Focco Software. No statistical diffence between the two groups. p> 0.05

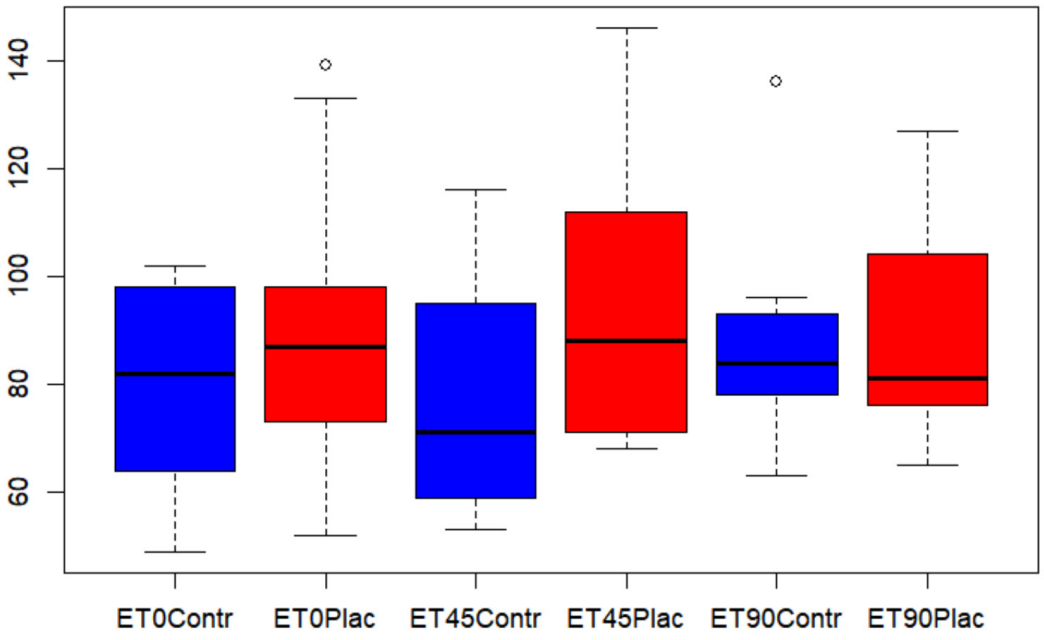

FIGURE 2: Objective Rhytids Analysis by Visia Software

Boxplot analysis of rhytids using Visia® software. No statistical difference was observed between the two groups ($p > 0.05$)

Additionally, dermatologists performed a blind evaluation of images to assess hydration, firmness, texture, and brightness in both groups (placebo vs. decarboxy carcinine HCl). These findings are presented in table 1 (Focco®) and table 2 (Visia®). figure 3 presents a sample of participants who completed the study, showing improvement in rhytid appearance.

DISCUSSION

AGEs are a group of stable compounds formed through nonenzymatic reactions between the amino groups of biomacromolecules and the free carbonyl groups of glucose or other reducing sugars, commonly produced in thermally processed foods.[16] AGEs have been implicated in the pathogenesis of several diseases, including atherosclerosis, diabetes, chronic kidney disease, and neurodegenerative disorders, through its binding to RAGEs in the human body.[17-18]

There is evidence that AGEs may also affect the different structures and physiological functions of the skin.[19] During the aging process, excessive intake of AGEs or highly processed foods that increase internal synthesis of AGEs can trigger a subclinical inflammatory state, leading to premature skin aging.[20] Structural proteins such as collagen and elastin are particularly susceptible to glycation, leading to loss of function, as the Maillard reaction induces collagen crosslinking, compromising its mechanical properties.[21]

The skin-aging process is complex, being influenced by genetic and individual factors as well as external factors such as smoking, pollution, UV exposure, diet, and exercise.[22] The healing process is also compromised in aged skin, affecting recovery from spontaneous injuries or surgical procedures.[22] As ages progresses, the body accumulates a large amount of free radicals and other substances that promote premature skin aging, leading to pronounced wrinkles, loss of firmness, roughness, and dark spots.[23] The decline in the production of structural proteins such as collagen, elastin, and ECM components contributes to the development of rhytids and others skin-aging signs.[24]

According to scientific literature and studies conducted by Exsymol (Monaco), the developer of decarboxy carcinine HCl, this nutraceutical has been shown to reduce collagen glycation induced by malondialdehyde, inhibit lipid peroxidation, and protect DNA from UV-B radiation damage (Exsymol, Monaco). Decarboxy carcinine HCl is a patented molecule, an analog of carnosine.[13-14] In a recent double-blind, placebo-controlled study with 38 overweight volunteers supplemented with 200 mg/day of decarboxy carcinine HCl, the authors reported a significant reduction in key biomarkers, including HbA1c, fructosamine, total cholesterol, and insulin levels.[25]

The present study is the first to investigate the potential benefits of a 90-day treatment with Glycoxil® (decarboxy carcinine HCl). In the Focco® equipment analysis, the control group (treated with decarboxy carcinine HCl) showed a mild improvement between the baseline and day 90. Similarly, the Visia® group presented a slight but significant improvement at day 45, although this improvement did not persist, potentially due to intrinsic factors, a short follow-up period, and technical limitations.

Table 1: Summary of Focco® analysis results

Objective Analysis – Amount of Wrinkles			
Image	**Comparison of groups (placebo vs control) (Paired t-test)**	**Control (Glycoxil®) (Two-way ANOVA and Tukey)**	**Placebo (Two-way ANOVA)**
Right side	T0 – ns (p=0.41) T45 – ns (p=0.06) T90 – ns (p=0.18)	ANOVA:T0/T45/T90 – s (p=0.03★) Tukey:T90/T45 – ns (p=0.95) T0/T45 – s (p=0.03★) T0/T90 – s (p=0.06#)	T0/T45/T90 – ns (p=0.28)
Subjective Analysis			
Item	**Control (Glycoxil®)**	**Placebo**	**Placebo vs control (Wilcoxon test)**
Brightness	Majority reported "no change" (37.5%) and "much improved" (37.5%)	Majority reported "improved" (71.43%)	ns (p=1)
Texture	Majority reported "no change" (37.5%) and " improved" (37.5%)	Majority reported "much improved" (57.14%)	ns (p=0.38)
Firmness	Half reported "no change" (50%) and "improved" (50%)	Majority reported "much improved" (57.14%)	ns (p=0.32)
Hydratation	Majority reported "no change" (37.5%) and " improved" (37.5%)	Majority reported "much improved" (71.43%)	ns (p=0.75)
Overall appearance	Half reported "improved" (50%) and "no change" (50%)	Majority reported "improved" (71.43%)	ns (p=0.45)

 # = statistical trend (p < 0.07); ns = not significant; ★ = statistically significant (p < 0.05).

Table 2: Summary of Visia® analysis results

Objective Analysis – Amount of Wrinkles			
Image	**Comparison of groups (placebo vs control) (Wilcoxon or paired t-test)**	**Control (decarboxy carcinine HCl) (Nonparametric Friedman)**	**Placebo (Nonparametric Friedman)**
Front	T0 – ns (p=0.44) T45 – ns (p=0.10) t test paired T90 – ns (p=0.25) Wilcoxon	T0/45/90 – ns (p=1.0)	T0/45/90 – ns (p=0.24)
Right side	**Paired t-test**	**Two-way ANOVA**	**Two-way ANOVA**
	T0 – ns (p=0.09) T45 – s (p=0.003★) T90 – ns (p=0.11)	T0/45/90 – ns (p=0.77)	T0/45/90 – ns (p=0.43)
Left side	**Paired t-test**	**Two-way ANOVA**	**Two-way ANOVA**
	T0 – ns (p=0.33) T45 – (p=0.09#) T90 – ns (p=0.78)	T0/45/90 – ns (p=0.47)	T0/45/90 – ns (p=0.83)
Subjective Analysis			
Item	**Control (decarboxy carcinine HCl)**	**Placebo**	**Placebo vs control (Wilcoxon test)**
Brightness	Majority reported "no change" (44.44%) or "improved" (44.44%)	Equal distribution between "no change" (33.33%), "improved" (33.33%), and "much improved" (33.33%)	ns (p=0.93)
Texture	Majority reported "no change" (44.44%) or "improved" (44.44%)	Equal distribution between "no change" (33.33%), "improved" (33.33%), and "much improved" (33.33%)	ns (p=0.93)
Firmness	Majority reported "no change" (55.56%)	Equal distribution between "no change" (33.33%), "improved" (33.33%), and "much improved" (33.33%)	ns (p=0.52)
Hydration	Majority reported "no result" (55.56%)	Most reported "no change" (44.44%)	ns (p=0.66)
Overall appearance	Majority reported "no result" (55.56%)	Most reported "no change" (55.56%)	ns (p=1)

 # = statistical trend (p < 0.07); ns = not significant; ★ = statistically significant (p < 0.05).

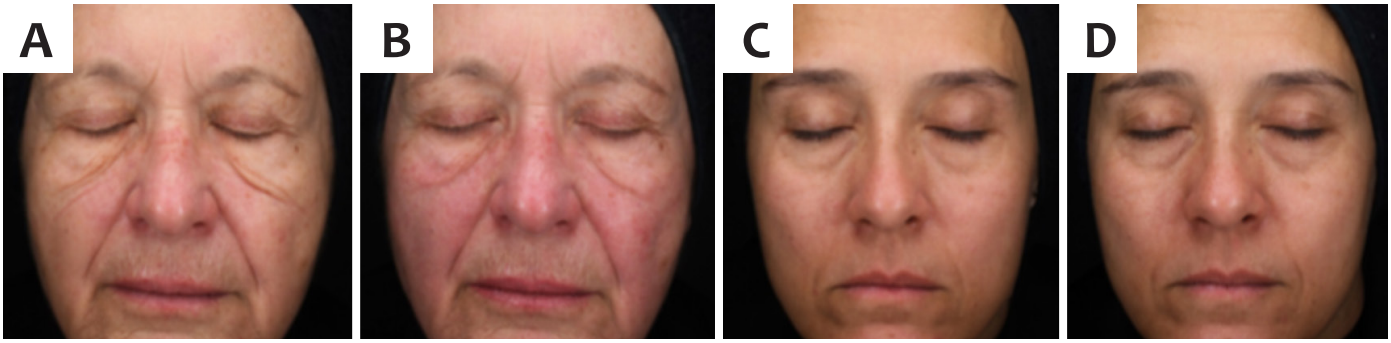

Figure 3: Photos samples of subjects

A/B - Subject representing a sample of the decarboxy carcinine HCl group T0 and T45, respectively. **C/D -** Subject representing the placebo group T0 and T45, respectively

Our results indicate that rhytids improved in both Focco® and Visia® evaluations, supporting the clinical relevance of the data. These findings are also consistent with previous studies using Visia® and Focco® imaging systems. However, further research with larger and more representative populations is necessary to confirm the efficacy of this treatment.

All patients tolerated the treatment well, reported no adverse effects, and expressed willingness to use the product again. Research involving beauty products and procedures is always evolving, with the introduction of new tools and technologies to elucidate mechanisms of action and molecular markers involved in the aging process. Despite this progress, supplements targeting skin aging remain relatively new, with only a few available on the market that have robust scientific backing, such as collagen peptides.[26] Although our study did not find statistical significance between the groups, the detrimental effects of glycation on the skin are well-documented in the literature.[27-31] Our study has some limitations, including a short follow-up time, small size sample, and the absence of histopathological analyses or advanced analytical techniques. Therefore, the authors acknowledge the need for future studies with larger sample sizes, longer follow-up periods, and more comprehensive evaluations. ●

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AUTHOR'S CONTRIBUTION:

Célia Kalil ORCID **0000-0002-1294-547X**
Approval of the final version of the manuscript, Effective participation in research guidance, Intellectual participation in propaedeutic and/or therapeutic conduct of studied cases

Luciane Zagonel ORCID **0000-0002-7687-6557**
Approval of the final version of the manuscript, Study design and planning, Collecting, analyzing, and interpreting data, Effective participation in research guidance, Critical review of the literature, Critical review of the manuscript

Valéria Barreto Campos ORCID **0000-0002-3350-8586**
Approval of the final version of the manuscript, Study design and planning, Collecting, analyzing, and interpreting data, Effective participation in research guidance, Critical review of the manuscript

Christine Chaves Prato ORCID **0000-0001-8861-6499**
Approval of the final version of the manuscript, Effective participation in research guidance, Critical review of the literature, Critical review of the manuscript

Clarissa Reinehr ORCID **0000-0003-1811-4519**
Approval of the final version of the manuscript, Study design and planning, Collecting, analyzing, and interpreting data, Effective participation in research guidance, Critical review of the manuscript

Patrícia França ORCID **0000-0002-2047-4161**
Approval of the final version of the manuscript, Intellectual participation in propaedeutic and/or therapeutic conduct of studied cases, Critical review of the manuscript

Pedro Vargas ORCID **0009-0004-5404-8832**
Statistical analysis, Approval of the final version of the manuscript, Preparation and writing of the manuscript, Critical review of the literature, Critical review of the manuscript