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Original Research

Evaluation of the Oral Use of Pycnogenol and Polypodium Leucotomos as Prophylactic Therapy for Post-Inflammatory Hyperpigmentation after Skin Sublimation by Plasma

Avaliação do Uso Oral de Pycnogenol e Polypodium Leucotomos como Terapia Profilática para Hiperpigmentação Pós-Inflamatória após Sublimação da Pele por Plasma

Evaluación del Uso Oral de Picogenol y Polypodium Leucotomos como Terapia Profiláctica para la Hiperpigmentación Posinflamatoria después de la Sublimación de la Piel Mediante Plasma

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Abstract
Post-inflammatory hyperpigmentation (PIH) is a common reaction observed in various cosmetic procedures, such as plasma energy skin resurfacing treatments, which aim to reduce excess skin in the periorbital region of the eyes. For the treatment of PIH, the use of nutraceuticals such as oral photoprotectors Pycnogenol and Polypodium Leucotomos is prescribed, which promise antioxidant actions, but their mechanism of action and clinical efficacy are not scientifically proven. In view of this, this randomized, controlled, triple-blind clinical study evaluated the effect of the isolated and/or combined use of Pycnogenol and Polypodium Leucotomos in the prevention of post-inflammatory hyperpigmentation resulting from plasma skin sublimation on the upper and lower eyelids. Fifty-five participants were recruited and randomly divided into four groups: G1 (n=13) – control/placebo; G2 (n=14) – 50 mg of Pycnogenol; G3 (n=15) - 250 mg of Polypodium Leucotomos; and G4 (n=13) - 50 mg of Pycnogenol + 250 mg of Polypodium Leucotomos. The experiment was monitored at three evaluation times: baseline (T0) – start of nutraceutical use; T1 – evaluation at 30 days and plasma sublimation on the eyelids; and T2 – evaluation at 60 days after the start of the experiment. The results were evaluated by photographs, topography by Antera® 3D, evaluating skin pigmentation and small wrinkles, and by the validated Face-QTM questionnaire for skin satisfaction, psychosocial disorders related to appearance, and adverse events related to the skin. The data were statistically analyzed considering a significance level of p = 0.05. The photographic evaluation was performed by 10 blind professionals specializing in the field, who indicated that only groups G3 and G4 had the best scores ($p < 0.001$), indicating excellent improvement in skin blemishes. In the topographic analysis, no differences were found between the mean pigmentation values between the groups (p = 0.837), regardless of the time and duration of evaluation (p = 0.630), as well as in the relative variation in pigmentation (p = 0.511). However, a significant increase in pigmentation variation was observed at 60 days (T2) only in group G2 – Pycnogenol (p = 0.040), when compared to the initial value. For the small wrinkle parameters, there was no significant difference between the groups and times evaluated T0 (p = 0.472), T1 (p = 0.484), and T2 (p = 0.641). Finally, after 60 days ($p < 0.001$), according to Face-Q(TM)for skin satisfaction, participants' perception was higher than at T0, with no change in psychosocial disorders related to appearance and adverse skin events. The conclusion indicates that oral intake of Pycnogenol and Polypodium Leucotomos did not affect the prevention of post-inflammatory hyperpigmentation caused by plasma skin sublimation on the upper and lower eyelids.
Descriptors: Nutraceuticals; Skin; Post-Inflammatory Hyperpigmentation; Cosmetic Procedures.

Resumo
A hiperpigmentação pós-inflamatória (PIH) é uma reação comum observada em vários procedimentos cosméticos, como tratamentos de rejuvenescimento da pele com energia de plasma, que visam reduzir o excesso de pele na região periorbital dos olhos. Para o tratamento da PIH, é prescrito o uso de nutracêuticos, como os fotoprotetores orais Pycnogenol e Polypodium Leucotomos, que prometem ações antioxidantes, mas seu mecanismo de ação e eficácia clínica não são comprovados cientificamente. Diante disso, este estudo clínico randomizado, controlado e triplo-cego avaliou o efeito do uso isolado e/ou combinado de Pycnogenol e Polypodium Leucotomos na prevenção da hiperpigmentação pós-inflamatória resultante da sublimação da pele com plasma nas pálpebras superiores e inferiores. Cinquenta e cinco participantes foram recrutados e divididos aleatoriamente em quatro grupos: G1 (n=13) – controle/placebo; G2 (n=14) – 50 mg de Pycnogenol; G3 (n=15) – 250 mg de Polypodium Leucotomos; e G4 (n=13) – 50 mg de Pycnogenol + 250 mg de Polypodium Leucotomos. O experimento foi monitorado em três momentos de avaliação: linha de base (T0) – início do uso do nutracêutico; T1 – avaliação aos 30 dias e sublimação plasmática nas pálpebras; e T2 – avaliação aos 60 dias após o início do experimento. Os resultados foram avaliados por fotografias, topografia por Antera® 3D, avaliando a pigmentação da pele e pequenas rugas, e pelo questionário validado Face-QTM para satisfação com a pele, distúrbios psicossociais relacionados à aparência e eventos adversos relacionados à pele. Os dados foram analisados estatisticamente considerando um nível de significância de p = 0,05. A avaliação fotográfica foi realizada por 10 profissionais cegos especializados na área, que indicaram que apenas os grupos G3 e G4 tiveram as melhores pontuações ($p < 0,001$), indicando excelente melhora nas manchas da pele. Na análise topográfica, não foram encontradas diferenças entre os valores médios de pigmentação entre os grupos (p = 0,837), independentemente do tempo e da duração da avaliação (p = 0,630), bem como na variação relativa da pigmentação (p = 0,511). No entanto, observou-se um aumento significativo na variação da pigmentação aos 60 dias (T2) apenas no grupo G2 – Picnogenol (p = 0,040), quando comparado ao valor inicial. Para os parâmetros de pequenas rugas, não houve diferença significativa entre os grupos e os tempos avaliados T0 (p = 0,472), T1 (p = 0,484) e T2 (p = 0,641). Finalmente, após 60 dias ($p < 0,001$), de acordo com o Face-Q(TM) para satisfação com a pele, a percepção dos participantes foi maior do que em T0, sem alteração nos distúrbios psicossociais relacionados à aparência e eventos adversos da pele. A conclusão indica que a ingestão oral de Pycnogenol e Polypodium Leucotomos não afetou a prevenção da hiperpigmentação pós-inflamatória causada pela sublimação da pele com plasma nas pálpebras superiores e inferiores.
Descritores:Nutracêuticos; Pele; Hiperpigmentação Pós-Inflamatória; Procedimentos Cosméticos.

Resumen
La hiperpigmentación posinflamatoria (PIH) es una reacción común observada en diversos procedimientos cosméticos, como los tratamientos de rejuvenecimiento cutáneo con energía plasmática, cuyo objetivo es reducir el exceso de piel en la región periorbital de los ojos. Para el tratamiento de la PIH, se prescribe el uso de nutracéuticos como los fotoprotectores orales Pycnogenol y Polypodium Leucotomos, que prometen acciones antioxidantes, pero su mecanismo de acción y eficacia clínica no están científicamente probados. En vista de ello, este estudio clínico aleatorizado, controlado y triple ciego evaluó el efecto del uso aislado y/o combinado de Pycnogenol y Polypodium Leucotomos en la prevención de la hiperpigmentación posinflamatoria resultante de la sublimación cutánea con plasma en los párpados superiores e inferiores. Se reclutó a 55 participantes y se dividieron aleatoriamente en cuatro grupos: G1 (n = 13): control/placebo; G2 (n = 14): 50 mg de picnogenol; G3 (n = 15): 250 mg de Polypodium leucotomos; y G4 (n = 13): 50 mg de picnogenol + 250 mg de Polypodium leucotomos. El experimento se supervisó en tres momentos de evaluación: línea de base (T0): inicio del uso del nutracéutico; T1: evaluación a los 30 días y sublimación plasmática en los párpados; y T2: evaluación a los 60 días del inicio del experimento. Los resultados se evaluaron mediante fotografías, topografía con Antera® 3D, evaluación de la pigmentación de la piel y las arrugas pequeñas, y mediante el cuestionario validado Face-QTM para la satisfacción con la piel, los trastornos psicosociales relacionados con la apariencia y los eventos adversos relacionados con la piel. Los datos se analizaron estadísticamente considerando un nivel de significación de p = 0,05. La evaluación fotográfica fue realizada por 10 profesionales ciegos especializados en el campo, quienes indicaron que solo los grupos G3 y G4 obtuvieron las mejores puntuaciones ($p < 0,001$), lo que indica una excelente mejora en las imperfecciones de la piel. En el análisis topográfico, no se encontraron diferencias entre los valores medios de pigmentación entre los grupos (p = 0,837), independientemente del momento y la duración de la evaluación (p = 0,630), así como en la variación relativa de la pigmentación (p = 0,511). Sin embargo, se observó un aumento significativo en la variación de la pigmentación a los 60 días (T2) solo en el grupo G2 - Pycnogenol (p = 0,040), en comparación con el valor inicial. En cuanto a los parámetros de arrugas pequeñas, no hubo diferencias significativas entre los grupos y los momentos evaluados T0 (p = 0,472), T1 (p = 0,484) y T2 (p = 0,641). Finalmente, después de 60 días ($p < 0,001$), según Face-Q(TM) para la satisfacción con la piel, la percepción de los participantes fue mayor que en T0, sin cambios en los trastornos psicosociales relacionados con la apariencia y los eventos adversos de la piel. La conclusión indica que la ingesta oral de Pycnogenol y Polypodium Leucotomos no afectó a la prevención de la hiperpigmentación posinflamatoria causada por la sublimación plasmática de la piel en los párpados superiores e inferiores.
Descriptores: Nutracéuticos; Piel; Hiperpigmentación Postinflamatoria; Procedimientos Cosméticos.

INTRODUCTION

Currently, there are several procedures to correct the shape, function, and aesthetics of the periorbicular region of the eyes, aiming to improve the patient's appearance and self-esteem. In 2005, plasma skin regeneration (PSR) technology was licensed by the Food and Drug Administration (FDA)[1] and considered safe and effective for reducing excess skin in this region[2,3].

The mechanism of action of PSR creates an ultra-high radiofrequency energy pulse from the device's generator, which then converts nitrogen gas into plasma inside the handpiece. The plasma emerges from the distal end of the handpiece, immediately transferring thermal energy to the skin surface. Unlike ablative lasers such as CO_2[2], PSR leaves an intact, desiccated layer of epidermis that acts as a natural biological dressing and promotes faster recovery than would be seen with ablative treatments. First, immediate tissue contraction is achieved through thermal denaturation of dermal collagen. Second, thermal damage causes interruption of solar elastosis and activation of fibroblasts, stimulating a cascade of wound healing necessary for neocollagenesis[4]. However, as with any aesthetic procedure, immediate responses to thermal energy treatments may occur on the skin, such as erythema, edema, and changes in pigmentation[5].

In this context, post-inflammatory hyperpigmentation (PIH) is defined as reactive hypermelanosis secondary to a wide range of stimuli, including dermatoses, trauma, skin procedures, ultraviolet radiation, and medications, among others. In its transient phase, it can occur in up to 4% of patients treated with plasma[5]. However, it is a condition that disappears spontaneously or can take months to years to resolve and, in some cases, can be permanent[6].

In orofacial harmonization, hyperpigmentation is found because of various procedures, making it customary to prescribe nutraceuticals to control the onset of HPIs, even though their mechanisms of action and efficacy are not clear and scientifically proven. These nutraceuticals are dietary supplements used to improve health, delay senescence, prevent disease, and support the proper functioning of the human body[7].

They are natural bioactive or chemical compounds that, in addition to their nutritional function, have health-promoting, healing, or disease-preventing properties. Nutraceuticals contain lipids, vitamins, carbohydrates, proteins, minerals, or other necessary nutrients. They can be classified according to their chemical composition into antioxidants, dietary fibers, inorganic mineral supplements, phytochemicals, prebiotics, probiotics, and herbs as functional foods[7].

Among nutraceuticals, a class of oral photoprotectors stands out for containing one or more main active ingredients that modulate different photoprotection mechanisms, mainly those related to their antioxidant actions[8,9]. One such nutraceutical is the extract of Polypodium Leucotomos (PL), a fern of the Polypodiaceae family, native to Central and South America, which was developed by Gonzalez in 1996 and commercially named Fernblock®. Some authors argue that this extract has potential as a specific antioxidant active ingredient for the skin, offering protection against damage caused by solar radiation, including aging, hyperpigmentation, and DNA damage[10].

In vitro studies have shown that Fernblock® (Polypodium leucotomos 240 mg) is an effective scavenger of various reactive oxygen species—specifically superoxide anion (O_2^-), hydroxyl radicals (OH), singlet oxygen ($^1O_2$), and hydrogen peroxide (H_2O_2). Like nonsteroidal anti-inflammatory drugs, oral administration of Fernblock® has been shown to reduce the levels of inflammatory markers in the liver and spleen[11], and hydrogen peroxide (H_2O_2)[11]. Similar to nonsteroidal anti-inflammatory drugs, oral administration of Fernblock® prevents the release of prostaglandins by inhibiting cyclooxygenase-2 in mice[12]. Based on its potential action, it is possible that this product may play an adjuvant role in the treatment of HPI[13].

A human study conducted by Martins et al. in 2012[14] demonstrated the efficacy of treating melasma in 12 randomized participants who used Polypodium Leucotomos extract or a placebo. The group of patients treated with PL had a significant decrease in the mean Melasma Area and Severity Index after 12 weeks of treatment, while the placebo group did not. Another clinical study also using Polypodium Leucotomos extract evaluated 9 participants irradiated with UV light, in which there was a significant decrease in erythema in the skin treated with PL, concluding that it is a nutraceutical with effective systemic action that leads to significant protection of the skin against UV radiation[15].

Another nutraceutical with similar potential to PL is Pycnogenol. This active ingredient has been widely used as a nutritional supplement for numerous diseases, from chronic inflammation to circulatory diseases[16]. Pycnogenol is a compound obtained from the bark of the Pinus Maritima pine tree, rich in flavonoids that could play an important role in cell protection against oxidative stress induced by reactive nitrogen species such as nitric oxide and peroxynitrite[17]. Pycnogenol also appears to reduce melanin production in vitro by downregulating tyrosinase and pigmentation-related mediators, contributing to the inhibition of pathways associated with skin hyperpigmentation[18].

Another study also indicated that oral intake of Pycnogenol (2 x 50 mg/day for a total of 12 weeks) benefited the skin of outdoor workers under considerable environmental stress. From spring to fall, these workers were constantly exposed to increased levels of particulate matter, as well as seasonal changes in humidity and temperature. Despite this environmental stress, Pycnogenol intake prevented a decrease in skin hydration, transepidermal water loss, and skin darkening during dry fall season[19].

Given this, some studies suggest benefits in the oral use of Pycnogenol or Fernblock® (Polipodium Leucotomos 240mg) in relation to HPI[20,21]. Generally, these nutraceuticals are used individually in these studies[14,19,22], leaving gaps as to whether the combination of these active ingredients would add to the results they provide. Thus, the objective of this randomized, controlled, triple-blind clinical study was to evaluate the effect of the isolated and/or combined use of Pycnogenol and Polypodium Leucotomos in the prevention of post-inflammatory hyperpigmentation resulting from plasma skin sublimation on the upper and lower eyelids.

MATERIAL AND METHOD

This study was designed in accordance with the recommendations of the Consort 2010 Statement, part of the Equator Network (Enhancing the Quality and Transparency of Health Research), for conducting and reporting randomized controlled clinical trials[23].

- *Study Design*

This randomized, controlled, triple-blind clinical trial was designed to compare the prophylactic efficacy of oral photoprotectors (Pycnogenol and Polypodium Leucotomos), alone and in combination, in skin preparation for plasma skin sublimation in the periorbital region. The investigation was evaluated at three distinct moments: baseline (T0), beginning of nutraceutical use; T1 – evaluation at 30 days and plasma skin sublimation on the eyelids; and T2 – evaluation at 60 days after the start of the experiment. The methodological design followed the flowchart presented in Figure 1.

Ethical aspects

The study was approved by the research ethics committee of São Leopoldo Mandic College, São Paulo, Brazil, under opinion n°. 6,834,160. All participants received detailed guidance and explanations about the study, its objectives, and procedures, and signed the Free and Informed Consent Form (FICF), in accordance with Resolution 466/2012 of the National Health Council.

- *Sample Size and Population Calculation*

The sample calculation was based on a related study that evaluated the effect of Pycnogenol on skin parameters[22], which identified a Cohen's average effect size of 0.25 (Cohen's f = 0.25). Using G*Power 3.1.9.4 software, with 80% statistical power and a 95% confidence level, the minimum requirement was determined to be 36 participants, with 9 individuals per group. Considering possible follow-up losses, i.e., 20% losses, an expanded sample of 60 individuals (15 per group) was established to ensure balance and robustness in intergroup comparisons.

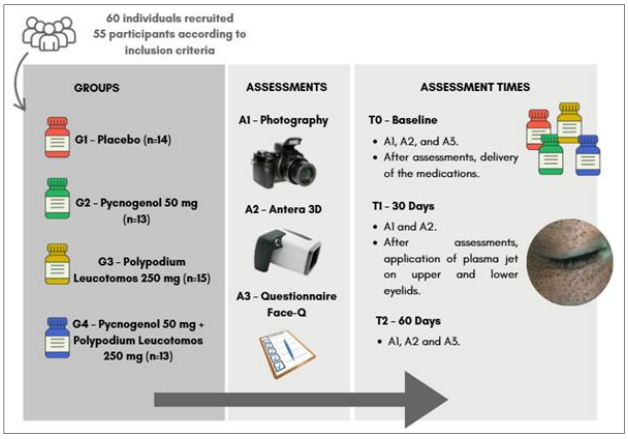

Figure 1. Flowchart of experimental design (Source: own work).

Participants were recruited from clinics in the Department of Dental Prosthetics at the Araçatuba School of Dentistry – UNESP during the years the study was conducted, according to the following inclusion criteria: individuals of both sexes, aged between 22 and 68 years, with photoaging identified by the Glogau scale types I to III, phototype I to IV by the Fitzpatrick scale, good general health, skin prone to blemishes, and those who signed the informed consent form. On the other hand, individuals with autoimmune diseases, users of anti-inflammatory drugs or medications for prolonged use in the last three months preceding the start of the study, those using prior supplementation with Pycnogenol or Polypodium Leucotomos in the 30 days preceding the start of the study, individuals with melasma, pregnant and lactating women, with allergies to any component of the product formula, smokers, users of retinoic acid on the face, with artificial tanning or facial cosmetic procedures in the 30 days before the start of the study. Given this, only 55 participants in total remained in the study and were monitored during the 60 days of the experiment.

- *Interventions*

Participants were randomized into four groups of up to 15 individuals each using a digital application. Each bottle of nutraceuticals was labeled numerically and separated by color-coded groups. Bottles 1.01 to 1.15 were assigned to the yellow group; bottles 1.16 to 1.30 to the green group; bottles 1.31 to 1.45 to the red group; and bottles 1.46 to 1.60 to the blue group. The 60 numbers were randomly drawn once, and the resulting sequence was recorded in a spreadsheet

so that, based on the screening and selection of patients, the bottles could be distributed in chronological order of care.

Therefore, participants were allocated to receive the nutraceuticals orally for 60 consecutive days, as follows:

- G1 – Control, microcrystalline cellulose placebo (n = 14).
- G2 – Use of Pycnogenol 50 mg/day (n = 13).
- G3 – Use of Polypodium Leucotomos 250 mg/day (n = 15).
- G4 – Combined use of Pycnogenol 50 mg plus Polypodium Leucotomos 250 mg per day (n = 13).

The capsules for each product were compounded in a compounding pharmacy following strict compounding protocols, accompanied by purity and traceability reports. The use of nutraceuticals was monitored by counting capsules and weekly records.

At baseline (T0), after completing a medical history questionnaire containing the study eligibility criteria, participants responded to the validated Face-Q™ questionnaire ("Copyright© 2013 Memorial Sloan Kettering Cancer Center, New York, USA, all rights reserved") for skin satisfaction, psychosocial disorders related to appearance, and adverse skin-related events. At follow-up, all faces were photographed according to the protocol of Lobo et al.[24] in frontal, 45° lateral (bilateral), and 90° lateral (bilateral) perspectives, in front of a black background, with hair tied back, wearing a black cape, without accessories, and with the face cleaned with 2% chlorhexidine surfactant solution. The camera used was a Canon EOS R100, coupled with a macro lens (Canon RF100mm F2.8 USM), a Youngnuo flash (Yn 24ex Ttl Macro Twin), and a diffuser. The camera settings were standardized for all patients (ISO 3200, autofocus, F32, speed 1/125), as were the location and ambient lighting, to minimize interference between photos.

Finally, the skin surface was captured with the Antera® 3D three-dimensional topographer (Miravex, Dublin) in the periorbicular region of the eyes. For this, a horizontal line was marked on each participant's face connecting the tragus to the wing of the nose bilaterally, as a reference line to position the base of the device (Figure 2), and another reference point was the inner corner of the eye tangent to the lateral end of the device (Figure 3). With their eyes closed, three consecutive captures were made for each eye, and the parameters of pigmentation (melanin) and small wrinkles were evaluated.

After collecting this data at baseline (T0), each participant received a kit containing neutral facial cleansing soap (sodium lauryl ether sulfate 23%, coconut fatty acid diethanolamine 4%, cocoamidopropyl betaine 3%, 1% sodium chloride thickener, distilled water qsp), sunscreen (SPF 50 PPD17), and a bottle containing 60 capsules of the nutraceutical according to their previously randomized group. The kit was used continuously for 60 days from the day of delivery, without interruption.

Figure 2. Marking the reference line to position the base of the Antera® 3D device (Source: own work).

Figure 3. Positioning of the Antera® 3D with reference point at the inner corner of the eye (Source: own work).

Thirty days after starting to use the nutraceuticals (T1), participants underwent plasma skin sublimation procedures (Plasma IQ™, NEAUVIA) on the upper and lower eyelids, after photographic and topographical evaluation. The clinical protocol followed standardization of asepsis, topical anesthesia, and controlled shots, as directed by the manufacturer (Figure 4).

Figure 4. Sublimation points on the upper and lower eyelids (Source: own work).

Skin asepsis was performed with 2% chlorhexidine and sterile saline, followed by the application of anesthetic ointment containing 23% lidocaine and 7% tetracaine. After 40 minutes, the ointment was removed, leaving the skin dry. Sublimation points were marked in the periorbicular region of the eyes, limited to 3 mm from the upper and lower lash lines, distributed in a non-linear zigzag pattern. With Plasma IQ™ and parameters for eyelid sagging in LOW mode, a curved disposable electrode, and spacing of 1 mm per point for all participants, the shots were fired from the inside out, in the direction of the patient's midline, and from the bottom up, with the possibility of adding interspersed end points for anchoring, always starting at the upper mobile eyelid and consecutively at the lower eyelid, ending at the lateral region of the orbicularis oculi. Immediately after completion of the procedure, 0.5 mg/g desonide corticosteroid ointment (Adinos®, Aché) was applied, as instructed by the manufacturer.

At this stage of the experiment, all participants received a post-plasma kit with one bottle of 0.5 mg/g desonide ointment (Adinos®, Aché) and one bottle of facial moisturizer (Cicaplast® Baume B5+, La Roche Posay). They were instructed to use topical corticosteroid (Adinos®, Aché) twice a day for three days; use the moisturizer (Cicaplast® Baume B5+, La Roche-Posay) twice a day for 7 days; apply sunscreen to the face after 24 hours; avoid hot baths for the first 72 hours, drink plenty of water to aid hydration, and avoid sun exposure for two weeks.

At 60 days (T2) from baseline, a photographic and topographical evaluation was performed, and the validated Face-Q™ questionnaires were completed following the same protocol as at T0.

- *Assessment Phase*
  - Photographic evaluation:

The images of each participant were presented in paired format (T0 and T2), in frontal and 45° bilateral angles, to ten specialists in orofacial harmonization with clinical experience and no connection to the study. These specialists were blinded to the allocation of the groups and performed the analysis of the photographs in a standardized environment, using the same display equipment and monitor calibration to ensure visual consistency and minimize external interference.

Improvements in skin tone and uniformity, i.e., discoloration of the periorbicular region of the eyes, were evaluated using a five-point ordinal rating scale adapted by Carvalho et al. (2023)[22], organized as follows 0 - Worsened (skin appeared more discolored); 1 - No noticeable change in skin tone; 2 - Slight improvement (slight reduction in discoloration); 3 - Good improvement (noticeable improvement in skin uniformity); and 4 - Excellent improvement (evident and homogeneous lightening). The responses were collected and subsequently analyzed for inter-rater agreement and variation between the intervention and control groups.

- Topographic evaluation:

At each evaluation time point (T0, T1, and T2), three images were acquired from each side of the periorbicular region of the participants' eyes, totaling six captures per time point. The acquisitions were performed in an environment with controlled and standardized lighting, distance, and head positioning, according to the equipment calibration protocol. Each image obtained was analyzed using the software option that identifies melanin in the skin (pigmentation) and quantifies it in three parameters: mean, variation, and relative variation, as well as the evaluation of the small wrinkle parameter. All data were obtained in triplicate and analyzed by the principal investigator of the study (Figure 5).

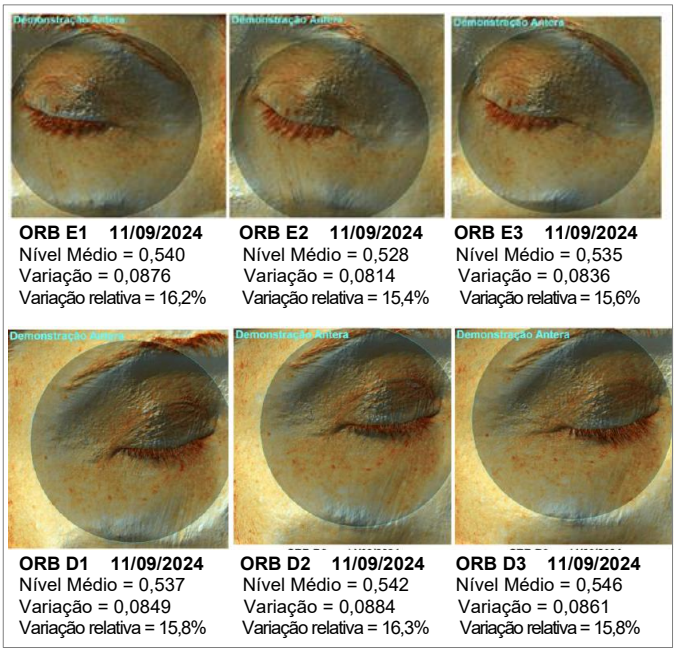

Figure 5. Example of an Antera® 3D report (Source: own work).
Legend: ORB E1, ORB E2, and ORB E3 (left orbicularis), ORB D1, ORB D2, ORB D3 (right orbicularis). Source: own work.

- Subjective evaluation of the Face-Q™ questionnaires

Face-Q™ is a validated patient-reported outcome measure (PROM) instrument widely used in research on facial aesthetic procedures (Klassen et al., 2010)[25]. Its structure allows for objective quantification of subjective perceptions, standardizing intra- and interindividual comparisons over time. Thus, the following modules were applied: (i) Skin satisfaction, (ii) Psychosocial distress related to appearance, and (iii) Skin-related adverse events.

The questionnaires were applied at times T0 and T2, and the scores were calculated according to the instrument's application and interpretation manual, allowing for a comparative analysis of the results according to the criteria of Otternhof et al. (2022)[25].

Statistical Analysis

The data were organized and analyzed using SPSS 23.0 (IBM, USA) and BioEstat 5.0 (Mamirauá Foundation, Brazil) software, where continuous variables were described by mean ± standard deviation, and normality was verified using the Shapiro-Wilk test. Data with normal distribution were submitted to ANOVA for repeated measures of two factors (time × group). In case of normality violation, nonparametric tests (Kruskal-Wallis, Wilcoxon, and Friedman) were applied. Inter-examiner photographic assessments were verified by Kendall's coefficient of agreement (W), according to the criteria of Landis and Koch (1977) (27). The level of significance adopted was $p < 0.05$.

RESULTS

- *Characterization of participants*

Of a total of 60 participants, five were excluded due to discontinuation of treatment, leaving only 55 participants, mostly women (47, 85.5%) and a minority of men (8, 14.5%). There was no statistically significant difference between the four groups in terms of the proportion of women or men ($p = 0.822$). The mean age of the participants was 47.7 ± 12.9 years, with no difference between the groups ($p = 0.973$).

- *Results of the photographic analysis*

In the descriptive analysis and distribution of absolute and relative frequencies of scores ranging from 0 (zero) to 4 (four) in the photographic evaluations. Consistency among experts was classified as reasonable for the Pycnogenol ($W = 0.217$), Polypodium Leucotomos ($W = 0.211$), and Pycnogenol/Polypodium Leucotomos ($W = 0.203$) groups, and poor for the placebo group ($W = 0.136$).

Based on the median scores assigned by the ten experts to the 55 participants, no differences were observed between the four groups ($p = 0.386$). However, when analyzing the frequencies of responses for each score, the chi-square indicated a difference between the groups ($p < 0.001$), albeit under the influence of reasonable or weak inter-examiner agreement.

However, the groups that received only Polypodium Leucotomos and the combination of Pycnogenol/Polypodium Leucotomos had higher proportions of participants with a score of four, indicating excellent improvement in discoloration and marked skin lightening. However, the placebo group (G1) had a lower frequency of this score. A similar trend was observed for score 3, which represented moderate improvement in skin tone. Score 2, associated with a slight improvement, was more prevalent in the Pycnogenol group (G2). Score 1, which reflects no noticeable change in skin tone, was more frequent in the Polypodium Leucotomos (G3) and placebo (G1) groups (Table 1).

Finally, score 0 (zero), which indicates worsening hyperpigmentation (increased skin blemishes), was observed more frequently in the placebo group (G1) and to a lesser extent in the Polypodium Leucotomos group (G3), followed by the Pycnogenol (G2) and Pycnogenol/Polypodium Leucotomos (G4) groups (Table 1).

Table 1. Absolute (n) and relative (%) frequencies of responses to the photographic evaluation by examiners, according to score and group.

Group	Score				
	0	1	2	3	4
Placebo	20 (15.4%)	49 (37.7%)	34 (26.2%)	22 (16.9%)	5 (3.8%)
Pycnogenol	12 (8.6%)	33 (23.6%)	57 (40.7%)	30 (21.4%)	8 (5.7%)
Polypodium leucotomos	5 (3.3%)	48 (32.0%)	39 (26.0%)	44 (29.3%)	14 (9.3%)
Pycnogenol/Polypodium Leucotomos	11 (8.5%)	32 (24.6%)	39 (30.0%)	37 (28.5%)	11 (8.5%)

Legend: (0) Worsened (more blemished); (1) No change (no change in skin tone); (2) Slight improvement (slight lightning); (3) Good improvement (moderate lightning); (4) Excellent improvement (significant lightning). Source: Own work.

- *Topographic results*

In the topographic analysis performed by Antera® 3D, no differences were found between the mean pigmentation values between the groups ($p = 0.837$), regardless of the time of evaluation. Within each group, there was also no significant variation between the measurements taken at T0, T1, and T2 ($p = 0.630$). That said, these results indicate that the single Plasma IQ(™)session did not cause post-inflammatory hyperpigmentation over the 60 days of the experiment (Table 2).

Similarly, pigmentation variations did not show significant differences between groups at the three assessment times: T0 ($p = 0.921$), T1 ($p = 0.902$), and T2 ($p = 0.768$). However, a significant increase in pigmentation variation was observed at 60 days (T2) only in the G2 – Pycnogenol group ($p = 0.040$) when compared to the initial value. For the other groups – placebo ($p = 0.584$), Polypodium Leucotomos ($p = 0.449$), and association between Pycnogenol/Polypodium Leucotomos ($p = 0.118$) – there were no significant differences between the periods analyzed (Table 2).

Table 2. Means and standard deviations of quantitative topographic analyses by Antera 3D, according to group and time of evaluation.

Quantitative evaluation (Antera 3D)	Groups	Evaluation times		
		Initial	30 days	60 days
Average pigmentation level*	Placebo	0.568 (0.061) Aa	0.556 (0.056) Aa	0.561 (0.054) Aa
	Pycnogenol	0.558 (0.052) Aa	0.550 (0.051) Aa	0.556 (0.054) Aa
	Polypodium leucotomos	0.561 (0.058) Aa	0.546 (0.047) Aa	0.547 (0.055) Aa
	Pycnogenol/ Polypodium Leucotomos	0.558 (0.038) Aa	0.558 (0.037) Aa	0.554 (0.046) Aa
Pigmentation variation**	Placebo	0.094 (0.014) Aa	0.098 (0.013) Aa	0.099 (0.012) Aa
	Pycnogenol	0.095 (0.021) Aa	0.096 (0.020) Aab	0.100 (0.024) Ab
	Polypodium Leucotomos	0.092 (0.023) Aa	0.093 (0.017) Aa	0.093 (0.018) Aa
	Pycnogenol/ Polypodium Leucotomos	0.091 (0.014) Aa	0.092 (0.014) Aa	0.094 (0.014) Aa
Relative variation in pigmentation (%)*	Placebo	16.74 (3.55) Aa	17.76 (3.47) Aa	17.73 (2.82) Aa
	Pycnogenol	16.92 (2.85) Aa	17.37 (2.95) Aa	17.83 (3.08) Aa
	Polypodium Leucotomos	16.34 (2.78) Aa	16.91 (2.26) Aa	17.02 (2.49) Aa
	Pycnogenol/ Polypodium Leucotomos	16.37 (2.73) Aa	17.16 (2.77) Aa	17.04 (2.43) Aa

Legend: * = data compared by analysis of variance; ** = data compared by Kruskal-Wallis and Friedman tests. Considering each assessment, groups identified by the same capital letters do not differ significantly from each other (comparisons within each column). Considering each assessment, groups identified by different lowercase letters have moments with values that differ significantly from each other (comparisons within each row).Source: own work.

Regardless of the time of evaluation, no significant differences were observed between the four groups in relation to the relative variation in pigmentation (p = 0.511). Similarly, the follow-up time did not influence this parameter (p = 0.309) (Table 2).

Regarding the parameters for small wrinkles, there was no statistically significant difference between the placebo, Pycnogenol, Polypodium Leucotomos, and Pycnogenol/Polypodium Leucotomos combination groups at the three time points analyzed T0 (p = 0.472), T1 (p = 0.484), and T2 (p = 0.641). Within each group, no significant changes were observed between the evaluation periods (placebo, p = 0.584; Pycnogenol, p = 0.526; Polypodium Leucotomos, p = 0.247; Pycnogenol/Polypodium Leucotomos combination, p = 0.232) (Table 3).

Table 3. Means and standard deviations of small wrinkles, according to group and time of evaluation.

Groups	Evaluation times		
	Initial	30 days	60 days
Placebo	20,281 (4,262) Aa	20,249 (4,227) Aa	20,269 (4,002) Aa
Pycnogenol	19,453 (4,469) Aa	20,360 (5,116) Aa	20,063 (4,976) Aa
Polypodium Leucotomos	19,323 (2,976) Aa	19,523 (2,678) Aa	19,926 (3,031) Aa
Pycnogenol/ Polypodium Leucomotomus	17,915 (2,376) Aa	18,416 (1,584) Aa	18,804 (2,167) Aa

Legend: Data compared to Kruskal-Wallis and Friedman tests. Groups identified by the same capital letters do not differ significantly from each other (comparisons within each column). Groups identified by the same lowercase letters do not have moments with values that differ significantly from each other (comparisons within each row). Source: Own work.

Subjective results of the Face-Q™ questionnaires

In the evaluation of Face-Q™ results - skin satisfaction, for any of the groups, at the end of 60 days (T2), skin satisfaction was higher than at T0 (p < 0.001) (Table 4).

For Face-Q™– psychosocial disorder related to appearance, no differences were found between the groups at either T0 (p = 0.845) or T2 (p = 0.202). That said, it should be noted that regardless of the participants in the groups that used Pycnogenol (p = 0.300), Polypodium Leucotomos (p = 0.307) nutraceuticals or a combination of these (p = 0.056), there was no statistically significant difference when comparing the values indicated at T0 and T2. However, for G1 - the control group that received the microcrystalline cellulose placebo - there was a significant reduction at T2 (p = 0.019) for the same factor (Table 4).

Regarding Face-Q™ – adverse effects on the skin, no significant differences were found between the groups at T0 (p = 0.539) or after 60 days (T2, p = 0.543). In none of the groups, G1 – placebo (p = 0.814), G2 – Pycnogenol (p = 0.583), G3 – Polypodium Leucotomos (p = 0.660); and G4 – Pycnogenol/Polypodium Leucotomos (p = 0.213) – were found to have differences in adverse effects between the values at T0 and T2 (Table 4).

Table 4. Means and standard deviations of qualitative analyses using the Face-Q™ questionnaire, according to group and time of assessment.

Qualitative assessment (FaceQ)	Groups	Evaluation times	
		Initial	60 days
Skin satisfaction*	Placebo	27 (6) Aa	40 (8) Ab
	Pycnogenol	29 (6) Aa	37 (6) Ab
	Polypodium Leucotomos	27 (5) Aa	35 (8) Ab
	Pycnogenol/ Polypodium Leucotomos	27 (5) Aa	36 (3) Ab
Psychosocial related to appearance**	Placebo	15 (6) Ab	12 (5) Aa
	Pycnogenol	14 (3) Aa	15 (5) Aa
	Polypodium Leucotomos	15 (5) Aa	13 (5) Aa
	Pycnogenol/ Polypodium Leucotomos	14 (5) Aa	11 (4) Aa
Adverse effect on the skin**	Placebo	15 (4) Aa	15 (6) Aa
	Pycnogenol	17 (4) Aa	17 (5) Aa
	Polypodium leucotomos	17 (4) Aa	17 (4) Aa
	Pycnogenol/ Polypodium Leucotomos	17 (4) Aa	16 (5) Aa

Legend: * = data compared by analysis of variance; ** = data compared by Kruskal-Wallis and Wilcoxon tests. Considering each assessment, groups identified by the same capital letters do not differ significantly from each other (comparisons within each column). Considering each assessment, groups identified by different lowercase letters have moments with values that differ significantly from each other (comparisons within each row). Source: own work.

DISCUSSION

This study represents an important contribution to the scientific literature by investigating, in a randomized, controlled, triple-blind manner, the effect of the isolated and combined oral use of nutraceuticals such as Pycnogenol and Polypodium Leucotomos in the prevention of post-inflammatory hyperpigmentation (PIH) resulting from skin sublimation by Plasma IQ™ in the periorbicular region of the eyes. To date, no previous studies have explored this association in human models with rigorous protocols, which gives scientific and translational relevance to the research.

Given this, the results found in the present study indicated no significant difference between the groups (G1, G2, G3, and G4) in relation to the average level of pigmentation, as well as the variation and relative variation in pigmentation, at all evaluation times (T0, T1, and T2). Therefore, these findings suggest that a single session of dermal sublimation with Plasma IQ™ was not sufficient to induce post-inflammatory hyperpigmentation in any of the groups, indicating a possible limited intensity

of the equipment, which reduced the opportunity for clinical manifestation of pigmentary disorders, regardless of the use or non-use of oral photoprotectors. In addition, the 60-day follow-up possibly restricted the manifestation of medium- and long-term biological responses, particularly those related to melanogenesis and dermal remodeling. The post-inflammatory pigmentation process depends on a melanocyte cycle that can exceed 90 days, suggesting that a longer observation period could reveal variations not detected in the present investigation.

It is also worth noting that participants were instructed to use topical corticosteroids after the plasma procedure, twice a day for three days, according to the manufacturer's instructions, which may have attenuated the local inflammatory cascade, limiting the expression of pro-inflammatory mediators such as IL-6, IL-1β, and TNF-α, and consequently, the activation of tyrosinase—a key enzyme in melanogenesis. Thus, early suppression of inflammation may have reduced the demand for systemic antioxidant mechanisms induced by Pycnogenol or Polypodium Leucotomos. That said, this approach may have influenced the efficacy of the treatment by promoting a low physicochemical stimulus so that the anti-inflammatory and antioxidant role of the tested polyphenols was not necessary in that cellular environment.

This hypothesis is consistent with the findings of Hossain et al. (2021)[28] and Tomita et al. (1989)[29], who demonstrated a direct relationship between inflammatory mediators derived from arachidonic acid and increased tyrosinase expression and melanocytic dendrite number. Therefore, the absence of hyperpigmentation observed in this study can be understood more as a consequence of low activation of the primary inflammatory pathway than as a prophylactic effect of the nutraceuticals tested. Another relevant aspect was the mandatory use of topical photoprotection (SPF 50) throughout the experiment. Thus, exposure to ultraviolet radiation was substantially reduced, minimizing the production of reactive oxygen species (ROS) and, therefore, the need for systemic antioxidant action. This methodological condition, although ethically necessary, introduces a bias of underestimating the efficacy of the compounds under conditions of greater environmental challenge.

In addition, to shed light on the physiological mechanism of action of plasma equipment, Plasma IQ™ has ionized gas electrical properties that are used to transmit a radiofrequency electrical current into the skin to cause tissue heating. Precisely this type of plasma is an operator-dependent device, and this technology has a lesser impact on skin architecture than skin regeneration with purified nitrogen plasma or dermal regeneration with helium plasma[30]. This information is crucial, since the depth of the wound is directly related to the intensity of inflammation at the site and the ability of the treatment to cause complications such as scarring or post-inflammatory hyperpigmentation in susceptible patients[28].

Therefore, based on the physical stimulus produced by the equipment, inflammatory mediators are produced after the activation of intracellular signaling pathways in the injured tissue. These play an important role in melanogenesis[28]. Arachidonic acid metabolites such as prostaglandin (PG) E2, thromboxane (TX) B2, leukotriene (LT) C4, and LTD4 are produced from cell membrane components at inflamed sites. They have been found to increase the amount of immunoreactive tyrosinase, a melanin-forming enzyme, and cell size, as well as the number of melanocyte dendrites[29].

When it comes to nutraceuticals, such as Pycnogenol and Polypodium Leucotomos, previous studies show promising results in photoprotection and control of hyperpigmentation associated with aging and chronic inflammatory diseases. Saliou et al. (2001)[31] observed that Pycnogenol exerted significant photoprotective action against damage induced by ultraviolet radiation, while Middelkamp et al. (2004)[15] reported a reduction in skin erythema and inflammatory markers in individuals treated with Polypodium Leucotomos, confirming its systemic antioxidant effect.

Subsequent studies reinforced the therapeutic potential of these compounds, such as that by Lima et al. (2021)[32], who demonstrated that Pycnogenol associated with sunscreen and triple topical formulation reduced the severity of melasma, and Martins et al. (2012)[14] identified a decrease in melasma after 12 weeks of using Polypodium Leucotomos. Similarly, Furumura et al. (2012)[33] observed a reduction in age spots and signs of photoaging in women supplemented with Flavangenol®, although without an overall change in skin tone, suggesting that the depigmenting effect of polyphenols is limited to specific pigmentary lesions. The present study presented experimental conditions different from those of previous studies, indicating that, under conditions of low thermal and inflammatory injury, the role of these nutraceuticals in the prevention of post-inflammatory hyperpigmentation seems discreet, albeit safe, opening space for new investigations with more challenging protocols and longer follow-up times.

The results obtained by Antera® 3D showed that the group using Pycnogenol alone had a slight increase in pigmentation variation at 60 days ($p = 0.040$), which, although statistically significant, was not clinically relevant. This finding may reflect an adaptive response of the epidermal

melanocytic unit, a concept described by Papa and Kligman (1965)[34], in which keratinocytes modulate the redistribution of melanin as a local protective mechanism. This specific response, therefore, should not be interpreted as an adverse effect but as evidence of the dynamic complexity of the melanocytic system in the face of discrete thermal stimuli.

In parallel, the data on small wrinkles did not show significant changes between times or groups, suggesting that the thermal stimulus generated by Plasma IQ™ was insufficient to promote noticeable tissue remodeling in the short term. This limitation is consistent with the studies by Holcomb et al. (2022)[35] and Foster et al. (2008)[4], which highlight that the structural effects of atmospheric plasma are dependent on the applied energy, the number of sessions, and the tissue regeneration time. Thus, the present study reinforces the need for multiple applications or optimized energy parameters to observe a significant clinical effect on skin microtexture.

In turn, photographic analysis revealed noticeable differences in the subjective assessment of experts, with emphasis on the Polypodium Leucotomos and Pycnogenol/Polypodium Leucotomos groups, which obtained a higher frequency of improvement scores (3 and 4), corresponding to visible skin lightening. Although these differences were not confirmed by objective instrumental analysis, the positive clinical perception suggests that the synergistic effect of the compounds may influence subtle parameters of skin color and uniformity that are not captured quantitatively. This discrepancy between objective and subjective measures is a recognized phenomenon in the literature on facial aesthetics and should be interpreted in light of the ecological validity of clinical assessments, that is, how improvement is perceived in the actual context of observation.

Inter-examiner consistency, considered reasonable (W between 0.203 and 0.217), indicated that perceptual variability among evaluators was moderate but still within acceptable limits for visual assessment studies. This heterogeneity may reflect individual differences in sensitivity to color variation, but it also suggests that, even under controlled conditions, the perception of whitening is multifactorial and may be associated with micro-variations in texture, brightness, and surface homogeneity—aspects not isolated by software analysis.

Additionally, the Face-Q™ questionnaire demonstrated significant improvement in skin satisfaction in all groups ($p < 0.001$), including the placebo group, which reinforces the role of psychosocial and perceptual components in the outcome of aesthetic procedures. It is plausible that this subjective improvement stems both from daily facial care with mild soap and sunscreen and from the experience of receiving free aesthetic treatment, a phenomenon commonly described as the Hawthorne effect or therapeutic gratitude response[35]. This positive psychological influence, although not invalidating, should be considered when interpreting subjective outcomes in aesthetic clinical research.

Methodologically, it is noteworthy that the study used validated and highly accurate instruments, such as Antera® 3D and Face-Q™, ensuring quality in the measurement of outcomes. However, the relatively small sample size (n=55) and short follow-up period are limitations that reduce the statistical power to detect subtle effects. Future studies should incorporate larger samples, multiple plasma sessions, and prolonged monitoring to explore the temporal dynamics of pigmentation and dermal regeneration, as well as evaluate biochemical markers of inflammation and oxidative stress, which would allow for a translational correlation between physiological mechanisms and clinical responses.

Finally, this study plays an important role in establishing a solid empirical basis for future research on the use of oral photoprotectors as adjuvants in thermal energy aesthetic procedures. The absence of adverse effects, good acceptance by participants, and observed pigment stability reinforce the safety profile of the compounds and the method used. However, the prophylactic efficacy of nutraceuticals against post-inflammatory hyperpigmentation remains inconclusive, and it is necessary to expand the types of evaluation to more challenging conditions and more intense therapeutic protocols.

CONCLUSION

Based on the integrated analysis of the findings, it can be inferred that the nutraceuticals Pycnogenol and/or Polypodium Leucotomos, when administered for 60 days, did not promote a measurable prophylactic effect on post-inflammatory hyperpigmentation caused by plasma skin sublimation on the upper and lower eyelids, but presented subjective aesthetic benefits according to experts and participants.

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REGULATORY STATEMENT

This pilot study was conducted in accordance with Resolutions 466/12 and 510/16 of the National Health Council of the Brazilian Ministry of Health, published on December 11, 2012, and the Brazilian Dental Professional Code of Ethics, as per CFO Resolution 179/93. The project was approved by the Ethics Committee of São Leopoldo Mandic College (Opinion No. 6,834,160). All subjects signed an informed consent form.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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