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A Clinical Study of Orally Collagen Intake and Evaluation of the Effects on Human Skin Physiological Properties

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Abstract Today, food supplements have become an indispensable part of a healthy and balanced life, and one of them, collagen supplements especially support the healthy skin structure and have many positive effects on it. The present study is aimed that evaluating the effects of PROFIN® Collagen on healthy skin conditions such as skin hydration, wrinkles, and elasticity. With this aim, we conducted a prospective, single-center, double-blind, randomized, placebo-controlled, 2-arm, parallel-design study to evaluate the effect of 12-week consumption of PROFIN® Collagen Hydrolysate on skin health. A total of 72 healthy female adults, aged between 40 and 65 with at least moderate eye wrinkles were randomized to receive 10 g of PROFIN® Collagen or placebo, once daily for 12 weeks. The majority (73(%)) of participants who took 'Profin Collagen Hydrolysate' had a statistical improvement (decrease) ($p<0,05$) in mean wrinkle length at Day 42, this improvement continued at the end of the intervention. Furthermore, compared with the placebo group, in placebo group transepidermal water loss results show that there was a significant increase after 6, and 12 weeks of administration, but not in PROFIN® Collagen group. In conclusion, this study demonstrates that PROFIN® Collagen has a positive effect on skin wrinkles and water loss.

Key Words hydrolysate collagen, skin health, physiological properties

1. Introduction

Nowadays, as people attach more importance to healthy lifestyles, the usage of food supplements in addition to daily diets is increasing day by day. In the global food supplement market reports it is stated that supplements are used especially for maintaining skin, bone, and joint health. People of all ages especially use food supplements both to support tissue regeneration and as a precaution against possible functional disorders. Collagen hydrolyzate peptide food supplements are one of the most commonly used supplements in this field [1], [2]. Collagen protein, which constitutes approximately 30-35 (%) of the total protein structure of the human body, plays a very important role in the healthy functioning of skin and cartilage tissue. The collagen composition of the dermis influences skin health, appearance, and firmness. As individuals age, the structural integrity of the dermis is impacted, resulting in drier skin, reduced tension, decreased elasticity, and the formation of wrinkles. In order to improve skin health, nowadays a wide range of dietary supplements are present to the market and are consumed by people. Collagen hydrolysates are used as a bioactive ingredient in nutricosmetic products and have been shown in preclinical studies to improve skin barrier function, induce the synthesis of collagen and hyaluronic acid, and promote fibroblast growth and migration [3].

Collagen hydrolysates present as a mix of specific peptides of different lengths with a high abundance of the amino acids hydroxyproline, glycine, and proline produced by enzymatic hydrolysis of native collagen extracted from animal connective tissues. During digestion, collagen hydrolysates are efficiently broken down into di- and tripeptides, which resist further intracellular hydrolysis [4]. These peptides are transported across the intestinal mucosa via the PEPT-1 transporter. In humans, hydroxyproline-containing di- and tripeptides have been observed in the bloodstream at nanomolar concentrations, as early as one hour after the ingestion of collagen peptides. Furthermore, experiments utilizing radioactively labeled collagen hydrolysates have shown that these collagen peptides can reach the skin and remain for up to two weeks [4]. To investigate the positive effects of collagen hydrolysate on skin tissue, there are many studies have been conducted over the years. In these studies, it was

presented that daily intake of collagen hydrolysate could support the skin's properties and reduce the aging effect. For instance, Modinger et al. (2021) evaluated the effects of a food supplement containing collagen hydrolysate and micronutrients on skin appearance and beauty [5]. Over 12 weeks, 72 healthy women aged 40-65 years with mild to moderate wrinkle depth ingested either the test product Doppelherz system KOLLAGEN BEAUTY or a placebo. Skin roughness, hydration, and collagen structure were measured at baseline, after 4 weeks, and after 12 weeks. The intake of collagen peptides reduced wrinkle depth, particularly in older women, with noticeable effects observed after 4 weeks [5]. Additionally, the consumption of collagen peptides slightly promoted skin hydration in middle-aged females [6]. Also, another study was conducted using bioactive Collagen peptides from porcine skin Type I Collagen and achieved a decrease in the degree of cellulite and skin waviness and an increase in nail growth results [7]. Duteil L et al. (2016) investigated specific natural fish bioactive Type 1 collagen peptides via oral intake to reverse skin aging signs in mature women. For this purpose, 60 women aged 46-69 years who have skin aging signs were randomized to receive a once-daily 5 g dose for 8 weeks. As a result, testing type I Collagen hydrolysates have beneficial effects on skin quality, including improving skin biomechanics and decreasing wrinkles [8].

Therefore, it was aimed to investigate the effects of oral supplementation with specific Profin Collagen Hydrolysate on skin structure and microbiome in a clinical setting. A randomized, placebo-controlled, double-blind clinical trial was conducted to investigate the cosmetic effects of a food supplement containing collagen hydrolysates on skin quality in healthy women over a 12-week period, compared to a placebo. Specifically, the study evaluated the supplement's ability to reduce periorbital lines (wrinkles around the eyes), improve skin roughness and hydration, enhance collagen structure, and investigate alterations in the skin microbiome. The study included 72 healthy female participants aged 40-65 years and employed bovine-derived collagen peptides (PROFIN®) with an average molecular weight of 2000-5000 Da and a collagen content of 90 (%).

2. Materials and Methods

A. Test Product and Dose Adjustment

This clinical study, bovine hide dervied type I-III collagen hydrolysate which produceb by specific enzymatic hydrolisation process was used. The product was provided by PROFIN® Collagen (Halavet Food, Turkey). In this study, as an active compound 10 g collagen hydrolysate per sachet was used while 10 g per sachet of Maltodextrin (100 (%)) was used as a placebo. Participants will be instructed to consume 1 sachet dissolved in 200 ml water or orange juice in the evening 1-2 hours before sleeping for the 12 week intervention period. It was instructed that the participants consume 10 g of hydrolyzed collagen or placebo powder daily, in the morning for 12 weeks. The 3 measurement time points were determined to carry out the skin physiological analysis immediately before starting the collagen intake (t0), after 6 (t1) and 12 weeks (t2) of daily product intake.

B. Clinic Study Design

Collagen forms approximately 30 (%) of the total protein in our body and is essential for maintaining skin, joint, and bone health. It is well known that hydrolyzed collagen supplementation can reduce signs of aging and improve skin quality, including reducing wrinkle size, improving skin hydration, and improving texture [1], [3]. However, not all collagen products will work in the same way, it certainly depends on the properties of the products. Their mechanism of action will depend on their protein composition. PROFIN® collagen is a pure collagen peptide product containing 90 (%) protein and 10 (%) moisture. Produced through a specific hydrolyzing process, the small peptides and free amino acids that makeup PROFIN® are easily digestible and well absorbed, making them an ideal supplemental ingredient for functional foods and multi-supplement products. To investigate the clinical effect of consuming PROFIN® on skin health, a clinical study was planned and conducted by the principles of ICH-GMP. The clinical study was performed according to the Declaration of Helsinki (2008) and complied with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines and Good Clinical Practice. The clinical trial registration number is AFCRO-157.

This study was a prospective, single-center, double-blind, randomized, placebo-controlled, 2-arm, parallel-design study to evaluate the effect of 12-week consumption of PROFIN® Collagen Hydrolysate on skin health. Participants were instructed to follow their habitual diet, and level of physical activity and to not consume any disallowed medications or dietary supplements that could interfere with the study objectives. They were asked to provide blood samples on-site/provide skin swabs and urine samples as outlined in the schedule of assessments. The study included the following 2 phases: screening period/run-in and intervention. There were 4 onsite clinic visits over a 12-week period, with a screening period of up to 14 days, and a treatment period of 12 weeks. A total of 72 healthy female adults, aged between 40 and 65 with at least moderate eye wrinkles who meet study eligibility criteria were enrolled. Eligible participants were randomised in a 1:1 ratio to PROFIN® Collagen Hydrolysate or placebo according to a randomization scheme. This study used an unstratified, restricted randomization list based on a set block size specified outside the protocol and SAP in the randomization list and procedure. The randomization list and procedure were prepared by an independent statistician and applied by the science team.

C. Physiological Measurements of the Skin

1) Skin Hydration Measurements

In order to determine the effect of the use of the collagen hydrolysate on the moisture values of the skin, the Corneometer ® CM 825 (Courage & Khazaka) device was used and the

moisture content of the stratum corneum layer was quantified. The Corneometer was used to assess skin hydration at baseline and after 42 days and 84 days. The Corneometer is the world's bestselling hydration measurement device and it operates by measuring the capacitance of a dielectric medium in this case skin. In this measurement, the changes in the water content of the stratum Corneum are translated to arbitrary hydration units. Notably, the measurement time is kept short, lasting only 1 second, to minimize occlusion effects. Furthermore, the depth of the measurement is restricted to 10-20 μm, specifically targeting the stratum corneum, thereby avoiding potential influences from deeper skin layers.

2) Trans-Epidermal Water Loss (TEWL) Measurements

The Tewameter was used to assess Trans-Epidermal Water Loss at certain time points. Trans-epidermal water loss (TEWL) refers to the water that permeates through the skin and evaporates from its surface to maintain adequate moisture in the outer cell layers. The rate of evaporation is measured in gm-2h-1 and serves as an indicator of skin functionality, specifically the barrier function.

3) Skin Wrinkling Measurements

In order to evaluate the efficacy of a 12-week supplementation of Profin Collagen Hydrolysate at reducing the number of periorbital lines Antera 3D skin analysis system was used and size (depth, length, and width) and the number of wrinkles were measured. The Antera 3D system can provide evaluation scores for wrinkles and roughness, number of wrinkles, depth of wrinkles, length of wrinkles, the width of wrinkles, skin pigmentation, the concentration of melanin, distribution (heterogeneity) of melanin, superficial vascular component, the concentration of hemoglobin, distribution (heterogeneity) of hemoglobin, facial furrows analysis, nasogenian furrow analysis, and roughness. Both the left and the right sides of the face were analyzed. All measurements about the size and the count of the wrinkles were performed and analyzed statistically separately.

4) Skin Elasticity Measurements

The elasticity of the skin was measured using The Cutometer and skin elasticity was assessed at baseline, after 42 and 84 days. Cutometer has been recognized as a standard for the measurement of elasticity and other biomechanical skin properties for many years. The device operates based on a suction-based measurement method. The device's pump creates negative pressure, drawing the skin into the aperture of the probe. A non-contact optical measuring system is present within the probe, consisting of a light source projected across the aperture to a light receiver. This system measures the distance that the skin travels into the aperture. The resistance of the skin to being drawn into the aperture indicates its firmness, whereas the ability of the skin to return to its original position reflects its elasticity. The measurement of each test area was repeated 3 times for all time points.

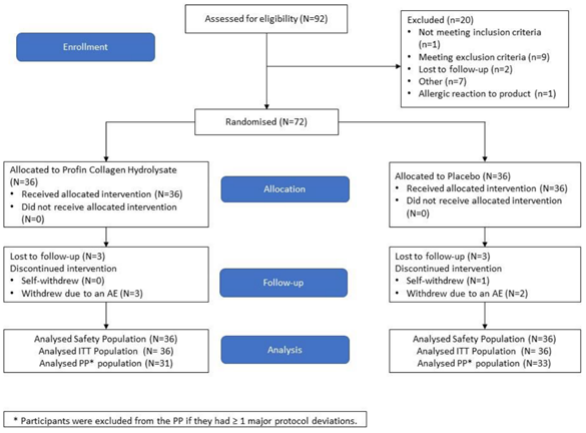

Figure 1: The clinical study flow diagram (Abbreviation, AE: Adverse event, ITT: Intent-To-Treat Population, PP: Per-Protocol Population)

D. Statistical Analysis

All statistical analyses were conducted using SPSS IBM V28.0, and graphics were prepared using the R Project for Statistical Computing Version 4.2.3, using validated and tested analysis scripts or, as appropriate. Primary and secondary objectives were analyzed using both the ITT population and the PP population. Safety objectives were analyzed using the safety population. All analyses requiring significance testing were two-sided at a 5 (%) significance level. Results were viewed as statistically significant if the p-value was less than or equal to 0.05. P-values were rounded to three decimal places. P-values less than 0.001 were reported as <0.001 in tables. For primary and secondary endpoints, the change in outcome was compared using an independent-sample t-test. The non-parametric Mann-Whitney test was used if the parametric assumptions were in doubt. Missing endpoints were handled statistically using the available case analysis method. All measurements are presented as the mean standard error, and $P < 0.05$ was considered to indicate statistical significance.

3. Results

A. Participant Baseline and Dropout

A total of 64 participants (Profin Collagen group = 36; placebo group = 36) completed the clinical study, and their data were entered into the analyses. There were 6 dropouts while the clinical trial was carried out. One participant in the placebo group quit for personal reasons and all the other 5 participants from both groups were excluded because of the adverse event. Continuing participants came to the clinic on certain time points and underwent the necessary tests, analyses, and evaluations, and the study was concluded by statistically examining the data received. The participant diagram is presented in detail in Figure 1.

	Day 0	Day 42	Day 84
Placebo Group	39.70±4.47	38.00±8.01	42.02±13.32
Trial Group	41.09±8.58	37.87±8.40	39.17±9.30

Table 1: Skin hydration measurement of the placebo and treatment group up to 84 days

	Day 0	Day 42	Day 84
Placebo Group	8.89±2.81	12.02±11.43	14.43±13.12
Trial Group	9.88±7.27	9.80±4.39	10.00±6.11

Table 2: TEWL measurement of the placebo and treatment group up to 84 days

B. Skin Hydration

The level of skin hydration was about 39.70±4.47 and 41.09±8.58 AU at the baseline with no statistical difference between placebo and trial groups. All measured values are presented in Table 1. In the inter-day change, a decrease was observed on the 42nd day compared to the baseline in both groups and then skin moisture values increased again on the 84th day compared to the 42nd day. But these changes are not statistically significant.

C. Trans-Epidermal Water Loss

TEWL can be summarized as water loss from the stratum corneum, the barrier layer of the skin. It is an important parameter for the integrity and healthy appearance of the skin barrier. The TEWL values were measured at baseline (Day 0), midpoint (Day 42), and end of intervention (Day 84) and analysed statistically. According to the results of the trial, although the difference of the TEWL results against the days measured in the participants receiving Profin collagen hydrolyzate are not statistically significant, it can be said that it has a positive effect on the formation of water loss when looking at the measured values. The TEWL results of participants who took Profin collagen hydrolysate were 9.88±7.27, 9.80±4.39, and 10.00±6.1 g/m2/h for measurement points respectively. When looking at the placebo group, the TEWL measurements were 8.89±2.81, 12.02±11.43, and 14.43±13.12 g/m2/h, it was determined that there was a significant increase in TEWL values in the 84th-day measurements. All TEWL measurement results were given in Table 2. As seen from Figure 2 this difference in changes between the baseline and after 84 days of treatment was statistically significant, z= -2.42, p= 0.015. In contrast to Profin collagen-receiving participants, the participants who took the placebo had an increase in mean TEWL at days 42 and 84, and these results indicate that profin collagen hydrolysate supports the skin to maintain the transepidermal water content.

D. Skin Wrinkling

The wrinkles parameters of the skin were measured via Antera 3D skin analysis system, the number of the length and count were calculated and statically analyzed. According to wrinkles measurement, the Profin collagen hydrolysate

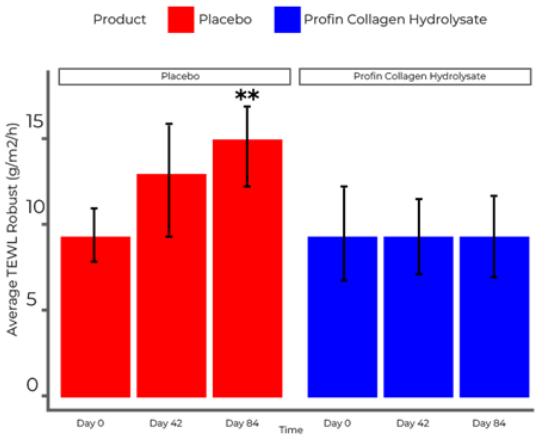

Figure 2: The changes in transepidermal water loss (TEWL) in the placebo and treatment group up to 84 days. Data are expressed as the mean ± S.D. * indicates significant differences between the placebo and treatment group

group showed significant improvements compared to the placebo group at 12 weeks. The images of the recovery of the wrinkles were taken from different participants at certain time points and are presented in Figure 3. The mean wrinkle length data had statistically significant results ($p<0.05$) for the Shapiro-Wilks test. Mean wrinkle length was measured at baseline (Day 0), midpoint (Day 42) and end of intervention (Day 84). The majority (73(%)) of participants who took the Profin Collagen Hydrolysate had an improvement (decrease) in mean wrinkle length at day 42, and this improvement continued at the end of the intervention. In contrast, only 36 (%) of participants who took the placebo product had an improvement at Day 42, and 42 (%) by day 84. When participants took Profin Collagen Hydrolysate, there was a median decrease (improvement) in Mean Wrinkle Length from baseline (Mdn = 73.5) to Day 42 (Mdn =60.04). This improvement continued at the end of the intervention where there was a median decrease (improvement) in Mean Wrinkle Length from baseline (Mdn = 73.5) to Day 84 (Mdn = 56.44). In contrast, when participants took the placebo product, there was a median increase from baseline (Mdn = 74.95) to Day 42 (Mdn = 79.62) and Day 84 (Mdn = 80.41).

A Wilcoxon signed-rank test was conducted to determine the effect of Profin Collagen Hydrolysate on Mean Wrinkle Length and the graph of this test was presented in Figure 4. Mean Wrinkle Length was measured at baseline (Day 0), midpoint (Day 42) and end of intervention (Day 84). When participants took Profin Collagen Hydrolysate, there was a statistically significant median decrease (improvement) in Mean Wrinkle Length from baseline (Mdn = 73.5) to Day 42 (Mdn =60.04), z = 2.01, p = 0.044. This improvement continued at the end of the intervention where there was a statistically significant median decrease (improvement) in Mean Wrinkle Length from baseline (Mdn = 73.5) to Day

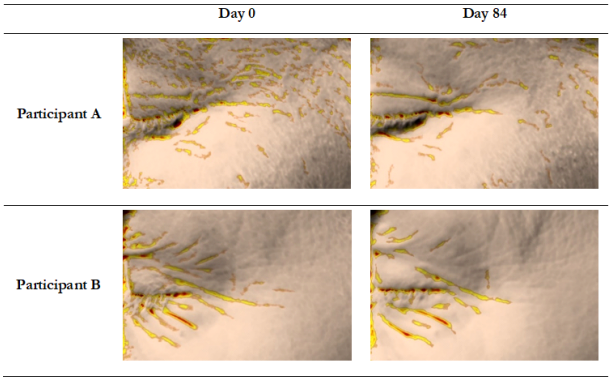

Figure 3: Effect of Profin collagen hdyrolysate on skin wrinkles on two different paticipants in the trial group

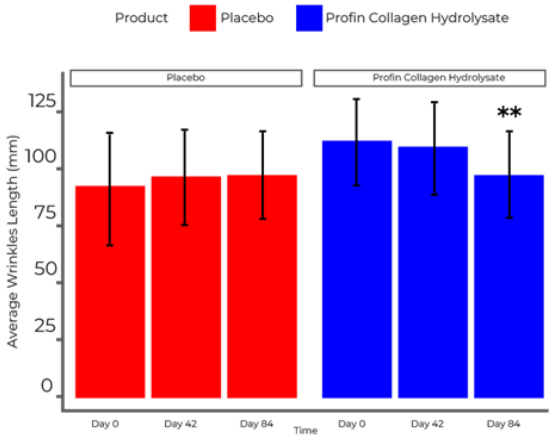

Figure 4: The changes in wrinkle length in the placebo and treatment group up to 84 days. Data are expressed as the mean ± S.D. * indicates significant differences between the placebo and treatment group

84 (Mdn = 56.44), z = 2.31, p = <0.001. In contrast, when participants took the placebo product, there was a median increase from baseline (Mdn = 74.95) to Day 42 (Mdn = 79.62) and Day 84 (Mdn = 80.41) but these changes were not statistically significant (z =-1.26, p = 208, Day 42), (z = -1.09, p = 198, Day 84).

The wrinkle numbers also were measured and statistically analyzed and all results were presented in Figure 5. According to the analysis results, the average number of wrinkles data gave statistically significant results for the Shapiro-Wilks test (p<0.05). During the trial, mean wrinkle count was measured at baseline (Day 0), midpoint (Day 42) and end of intervention (Day 84). The majority (73 (%)) of participants who took the active product 'Profin Collagen Hydrolysate' had an improvement (decrease) in mean wrinkle count at Day 42, this improvement continued at the end of the intervention (76 (%)). In contrast, only 39 (%) of participants who took the placebo product had an improvement at Day 42, and

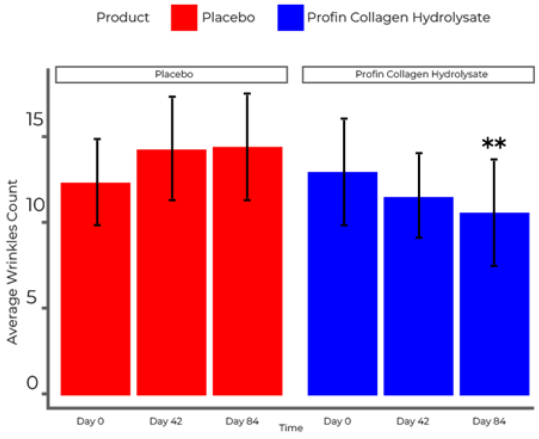

Figure 5: The changes in wrinkles count in the placebo and treatment group up to 84 days. Data are expressed as the mean ± S.D. * indicates significant differences between the placebo and treatment group

33 (%) by day 84. When participants took Profin Collagen Hydrolysate, there was a median decrease (improvement) in Mean Wrinkle Count from baseline (Mdn = 13.70) to Day 42 (Mdn =11.12). This improvement continued at the end of the intervention where there was a median decrease (improvement) in Mean Wrinkle Count from baseline (Mdn = 13.70) to Day 84 (Mdn = 10.64). In contrast, when participants took the placebo product, there was a median increase from baseline (Mdn = 11.71) to Day 42 (Mdn = 13.87) and Day 84 (Mdn = 14.09).

A Wilcoxon signed-rank test was conducted to determine the effect of Profin Collagen Hydrolysate on Mean Wrinkle Count. Mean Wrinkle Count was measured at baseline (Day 0), midpoint (Day 42) and end of intervention (Day 84). When participants took Profin Collagen Hydrolysate, there was a statistically significant median decrease (improvement) in Mean Wrinkle Count from baseline (Mdn = 13.70) to Day 42 (Mdn =11.12), z = 2.71, p = 0.038. This improvement continued at the end of the intervention where there was a statistically significant median decrease (improvement) in Mean Wrinkle Count from baseline (Mdn = 13.70) to Day 84 (Mdn = 10.64), z = 2.87, p = 0.004. In contrast, when participants took the placebo product, there was a median increase from baseline (Mdn = 12.17) to Day 42 (Mdn = 13,87), but this change was not statistically significant (z =-0.85, p = 0.396). Also in Day 84 there was a median increasing from baseline (Mdn = 11.71) to Day 84 (Mdn = 14.09), but these changes were not statistically significant (z = -0,91, p = 0.386).

E. Skin Elasticity

Skin elasticity (R2) results are given in Figure 6. There was not a significant difference detected in skin elasticity levels between the trial group and the placebo group following the

	Day 0	Day 42	Day 84
Placebo Group	78.16±5.59	79.07±7.05	79.50±6.59
Trial Group	79.11±5.81	80.51±6.64	80.99±7.32

Table 3: Skin elasticity measurement of the placebo and treatment group up to 84 days

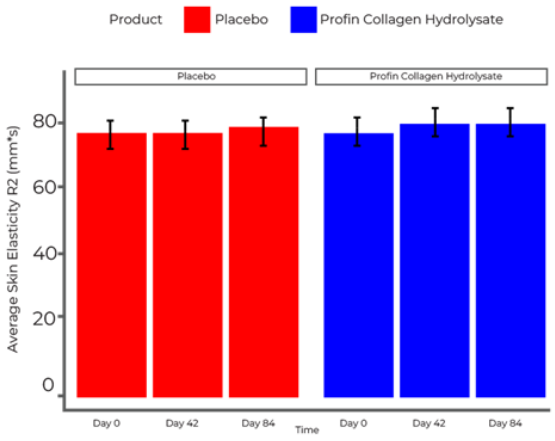

Figure 6: The changes in skin elasticity in the placebo and treatment group up to 84 days. Data are expressed as the mean ± S.D. * indicates significant differences between the placebo and treatment group

12-week application. When comparing the placebo group data with the trial group data, presented in Table 3, it was not found a statistically significant difference in skin hydration levels after 42 and 84 days of daily collagen hydrolysate intake.

4. Discussion

Digestion and absorption of consumed healthy food items are important for skin health, just like all parts of our body. The most critical factor for healthy skin is complete and balanced nutritional habits. Unwanted changes in the skin, such as the decrease in skin elasticity and moisture and wrinkle formation, which develop over time due to daily habits and aging, cause aesthetic problems, especially for women [9], [10]. As the demand for applications to eliminate visible signs of aging increases, interest in the development of supplements and functional food products for skin health has also increased. Nowadays, food supplements specially formulated for skin beauty are also defined as nutricosmetics [11].

Collagen hydrolyzate products, which have been frequently used in the field of food supplements lately, are known to have positive effects on bones, joints, skin and connective tissue [12]–[14]. In particular, the effect of collagen hydrolyzate supplements on the physiological properties of the skin has been examined by many researchers and demonstrated in clinical studies. While experimental studies have examined the development and proliferation of fibroblast cells, increased dermal extracellular matrix synthesis, antioxidative protection and reduction of skin wrinkle formation, clinical studies have examined the effects on many different factors such as skin moisture, elasticity, and reduction in the number and structure of wrinkles [15], [16].

There are many studies on the positive effects of collagen hydrolysates on the skin. In these studies, the effects of collagen hydrolysate intake at different doses on different skin characteristics such as skin moisture, elasticity, wrinkle formation, and skin color were investigated. This single-center, double-blind, randomized, placebo-controlled, 2-arm, parallel-design clinical study is conducted to evaluate the effect of 12-week consumption of PROFIN® Collagen Hydrolysate on skin health. At the end of the study oral usage of PROFIN® Collagen Hydrolysate significantly improved wrinkles lengths and counts after 84 days of intake, while no changes from baseline were observed in the placebo group at 42nd and 84th days. Similar results on the improvement of the skin were obtained in a study by S. Oesser et al in 45–65 years old 57 women by the bioactive collagen peptide. It was recorded that after 4 and 8 weeks of bioactive collagen hydrolysate intake promoted a statistically significant reduction of eye wrinkle volume in comparison to the placebo group [17].

In the another study conducted by S. Oesser et al., the skin characteristics of the participants receiving collagen hydrolyzate for 8 weeks were evaluated in 69 women in the 35-55 age group. At the end of the study, there was a statistical improvement in skin elasticity results. It has also been revealed that collagen hydrolyzate supplements contribute positively to skin moisture, although it is not statistically significant [16]. However, there was not a significant difference in skin hydration and skin elasticity measurement between the trial and placebo groups in this study. It could be related to ages and race of the participants.

Considering the results of transepidermal water loss, a statistically significant increase was observed in the placebo group on the 84th day compared to the baseline, while there was no significant change in the trial group. At the end of the 84th day, it was considered that the skin maintained its transepidermal water content in participants taking collagen hydrolyzate supplements. Similar results were seen in the study conducted by Tak et al. on 84 women between the ages of 40 and 60 who take collagen tripeptide hydrolyzate supplements, showing that collagen hydrolyzate intake reduced the TEWL value and was well tolerated among middle-aged women [18]. Despite all these good results of the study, the dosage and the effects on skin elasticity can also be re-investigated more comprehensively.

5. Conclusion

The presented study investigated to the widespread use of collagen hydrolyzate products as food supplements and their effects on skin health. Based on the results of the conducted study, it can be concluded that the oral ingestion of 12-week consumption of PROFIN® Collagen Hydrolysate has been effective on skin health. It was demonstrated a statistically

significant reduction of eye wrinkle length. Also, on day 84th it was observed that significant decrease in the skin wrinkles count. Moreover with the collagen consumption TEWL content of the skin was protected while there was a significant increase in the placebo group. This was attributed to daily collagen intake can enhance the absorption rate of water content in the SC. When the positive effects of hydrolyzed collagen supplements on the skin are examined, it is seen that their consumption for both cosmetic and health purposes is effective. In this context, supplementary collagen hydrolyzate products can be used as a safe, economical, and effective solution to support human health.

Conflict of interest

The authors declare no conflict of interests. All authors read and approved final version of the paper.

Authors Contribution

All authors contributed equally in this paper.

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