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Original Article

Rheological behavior and clinical efficacy of photoprotective cosmetic formulations with *Spirulina*

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Abstract

Background: The search for treatments of cutaneous alterations caused by the aging process has motivated the cosmetic area to develop innovative products, which led to intense research for new active ingredients with the potential to bring unique benefits to the skin. Using natural active substances to develop cosmetic products with proven stability and clinical efficacy is an essential topic for the cosmetic area today. The objective of this study was to develop and evaluate the stability, sensorial properties, and clinical efficacy of photoprotective cosmetic formulations containing *Spirulin*a dry extract using advanced biophysical and skin imaging techniques.

Materials and Methods: After developing photoprotective formulations added or not 0.1% of *Spirulina*, the rheological behavior, sensory properties, and short and long term clinical studies were carried out. The efficacy studies evaluated transepidermal water loss (TEWL), stratum corneum water content, sebum content, skin micro-relief, dermis echogenicity and thickness, and structural and morphological analysis of the epidermis parameters in the face region before and after the application of the formulations.

Results: The rheological behavior and sensory properties were adequate to the objective of the study. Furthermore, there was an increase in hydration and control of sebum content after the short time of clinical evaluation. Improvements in skin hydration, barrier function, microrelief, dermis thickness, and depth of papillae were noted in the long-term clinical studies.

Conclusions: The present study highlights the importance of stable development, with proper sensory properties and clinically proven efficacy photoprotective cosmetic formulations containing natural ingredients, like *Spirulina*, which can bring multiple benefits to the skin, being a complete treatment to the consumer.

Keywords: Spirulina, Rheological behavior, Cosmetic Formulations, Clinical study

Background

The search for treatments of cutaneous alterations caused by the aging process has motivated the cosmetic area to develop innovative products, which led to intense research for new active ingredients to bring unique benefits to the skin.

In this context, considering that skin aging can result from intrinsic and extrinsic agents that act on different pathways, causing skin damage, innovative approaches to improve and prevent these characteristics are necessary.[1] It is important to note that intrinsic aging is mainly regulated by genetic factors, while extrinsic aging can be originated by ultraviolet (UV) rays exposure.[2]

In general, UV rays are known to cause a great biological impact on the skin, also having a significant impact on skin photodamage and photoaging.[1,3] This way, the association of natural active ingredients with UV filters to the development of multifunctional cosmetic products, with proven clinical efficacy, for maintaining and restoring skin integrity can be considered essential for improving both types of aging.

Active ingredients from natural sources are also a trend in the cosmetic field. Among them, the unicellular blue-green algae, *Spirulina* presents potential benefits to be added to skin care formulations. Its composition is rich in vitamins, minerals, pigments, proteins, polysaccharides, fatty acids, amino acids such as methionine, glycine, lysine, and gamma-linolenic acid, and polysaccharides. These act on the prevention of changes from the aging process and for skin protection.[4]

The development and clinical efficacy studies of cosmetic formulations added with the dry extract of *Spirulina*, obtained through the biotechnological process, by applying biophysical and skin imaging techniques is fundamental to evaluate the proposed effects of cosmetic surgery formulations containing new active ingredients.

Before the clinical efficacy of a cosmetic formulation, it is important to determine the rheological behavior of the product. Rheology, the study of how materials deform and the flow response to mechanical stresses, determine

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the shear strain, shear rate, or shear stress applied to the product under analysis. Furthermore, the rheological measurements can be used to rationalize consumer acceptance of the product under study, according to how the skin feels the cosmetic product.[5]

The sensorial analysis of a product is also fundamental, as an unpleasant sensorial can influence the formulation's efficacy, as the consumers will not maintain the frequency of use and may cause differences in the treatment efficacy.[6]

Considering that the skin aging process has a complex mechanism, the conventional techniques may present limitations to evaluate different parameters practically and efficiently. In this context, many current studies are now performed using non-invasive techniques, as the VivaScope® imaging system, which is a non-invasive reflectance confocal microscopy (RCM) that is designed to evaluate cutaneous characteristics, as the thickness of the different layers of the epidermis, the morphology of keratinocytes and dermal papillae and others. Furthermore, the stratum corneum water content, sebum content, transepidermal water loss (TEWL), and skin microrelief are also very important parameters to be analyzed once they provide information on the interaction of the product and its active substances with the skin itself.[7,8] These techniques allow the analysis of the effects of the formulations understudies in real conditions of use, through different physical or physicochemical principles on skin.[9]

Thus, the objective of this study was to develop and evaluate the stability, sensorial properties, and clinical efficacy of photoprotective cosmetic formulations containing *Spirulina* dry extract using advanced biophysical and skin imaging techniques.

Materials and Methods

Developed Formulations

A formulation based on mineral oil (and) paraffinum liquidum (and) cetearyl alcohol (and) Ceteth-20 (and) glyceryl stearate (and) PEG-40 hydrogenated castor oil (and) polyacrylic acid (and) sodium hydroxide (and) xylitol (and) caprylic acid, C12-15 alkyl benzoate, methylphenyl polysiloxane, glycerin, cyclomethicone and dimethicone crosspolymer and cyclomethicone was developed (vehicle) and added with 0.1% of *Spirulina* dry extract and a combination of sunscreens (F1), 0,1% of *Spirulina* dry extract alone (F2) or only the combination of sunscreens (F3). The combination of sunscreens was calculated in the BASF Sunscreen Simulator to obtain FPS 30 and contained bis-ethylhexyloxyphenol methoxyphenyl triazine, bisoctrizole, diethylamino hydroxybenzoyl hexyl benzoate, ethylhexyl triazone, ethylhexyl methoxycinnamate, and octyl methoxycinnamate.

Study of the Rheological Behavior

Samples of the formulations under study were evaluated using a controlled voltage Rotational Rheometer (TA Instruments, DHR-2, USA), with parallel plate geometries (steel), 40 mm, and fixed gap of 750 µm. The temperature was controlled using a Peltier system. Data were analyzed by statistical software (TRIOS, USA). Standard silicone oils (Cannon Instrument Company, State College, PA) were used for calibration of the equipment. Rotational and oscillatory tests evaluated the rheological properties of the sample emulsions.[10]

Sensory Analysis

Sensory analysis was performed through a questionnaire with consumers of cosmetics. A total of 20 healthy women, aged 18-35, participated in this stage after the application of the free and informed consent form. The tested formulations could be added or not (vehicle) of the active ingredient understudy and applied in the face's frontal region. The subjects had to answer a questionnaire that was formed to evaluate six formulation parameters consisting of stickiness, spreadability, skin smoothness, oily residue, absorption sensation, and hydration sensation. They were asked to evaluate the parameters on a scale of excellent, very good, good, regular, and bad scores (24-25).

Clinical Study

After the approval by the ethics committee (CEP/FCFRP nº315), the short-term (immediate effects) and long-term clinical studies were performed.

The experiments were carried out at the School of Pharmaceutical. Sciences of Ribeirão Preto, University of São Paulo, Ribeirão Preto, São Paulo, Brazil (21°100 S, 47°480 W) in a room set at 21 ± 2°C and 45%- 55% relative humidity. The participants were acclimatized in the room for at least 15 minutes before measurements were taken to allow full adaptation of their skin.

In the short-term study, 20 healthy female subjects between 18-35 years old were recruited, and the amount of 2 mg/cm^2 of the formulation was applied on a delimited area on the frontal region of the face in a randomized way. Measures in stratum corneum water and sebum content were performed before (baseline) and after 2 hours of application, utilizing the equipment Corneometer® CM 825 and Sebumeter® SM810, respectively.[11]

For the long-term clinical study, 25 healthy female subjects were recruited between 39-55 years old. F1 was applied twice daily in the face region, and the frontal and periorbital regions were analyzed. The formulations F2 and F3 were applied on the volar forearm (with sides randomly chosen) for 30 days.

Both baseline (T0) and after 30-days period (T30) measures were made using the following non-invasive biophysical and skin imaging techniques: The sebum content was evaluated in the frontal region of the subjects' face using the Sebumeter® SM810 equipment. A remarkable 64 mm^2 opaque tape was pressed onto the skin for the 30s with a slight pressure to collect the surface

sebum.[12]

The stratum corneum water content was measured by skin capacitance equipment (Corneometer™ CM 825, Courage & Khazaka Electronic GmbH, Germany). The device determines the water content of the superficial epidermal layers down to a depth of about 0.1 mm and expresses the values in arbitrary units.[3]

TEWL was measured with an evaporimeter (Tewameter® TM210, Courage & Khazaka Electronic GmbH), and registered in g/m²h after probe equilibration on the skin for 20 seconds.[3]

Skin microrelief parameters were evaluated by the Visioscan VC 98 (Courage & Khazaka Electronic GmbH, Germany), which is a high-resolution UV-A light video camera developed to analyze skin surface directly and by the Surface Evaluation of the Living Skin (SELS) method.[4]

To the evaluation of the dermis echogenicity and thickness, 20 MHz ultrasound equipment (Dermascan® C, Cortex Technology, Denmark) was utilized. The ultrasonic wave (speed of 1580 m/s) is partially reflected by the skin structure, giving rise to echoes of different amplitudes. This parameter is related to the water retention between collagen fibers and skin intrinsic and photoaging.[13,14]

Morphological and Structural characteristics of the epidermis were analyzed using an RCM (Vivascope® 1500; Lucid, USA). Microscopic images were produced in triplicate using Vivastack® method, which takes multiple confocal images of successive depths within a given tissue region. This parameter presents the epidermis characteristics as its thickness, dermal papillae depth, and its structures.[7]

Statistical Analysis

Data were analyzed statistically with tests chosen according to the sampling distribution detected in preliminary tests of normality distribution and variance homogeneity. Analysis of variance (ANOVA) was applied to parametric results, and the Friedman test was applied to nonparametric results. All statistical tests were performed using the Prism 6 software.

Results and Discussion

Study of the Rheological Behavior

The rheological behavior of cosmetic products is important beyond the technical characteristics of the study formulation, as it also provides information about the aesthetics of the product, helping in the sensory properties that will make the customer enjoy using the product and creating the experience overall.[1,15]

After the development of the study formulations, the rheological analysis was performed in continuous (flow curves) and oscillatory (frequency sweep) flow conditions.[16]

In the flow curves, the determination of the relation between shear stress and shear rate,[17] it was possible to observe a thixotropic effect (Figure 1), which suggests a good spreadability of both formulations vehicle and F2. The thixotropy effect is indicated by the hysteresis area between the up and down curves indicated by the space between the curves.

When added with the combination of sunscreens, F1, it was possible to note a difference in this parameter that now presents lower values, suggesting that UV protection to this product acts in the decrease of the thixotropy effect but still with acceptable values (Figure 2).

The determination of viscosity in a formulation can also be performed through the elastic modulus G' (elastic response), and viscous modulus G" (viscous behavior), which are measurements done by a study of the oscillatory (frequency sweep) flow conditions.[16]

In the developed formulations, when comparing the vehicle and formulation added *Spirulina – F2* (Figure 3) and F1 and vehicle added with the combination of sunscreens only (Figure 4), it was possible to note that the addition of *Spirulina* in the product does not seem to alter its stability, even when in presence with sunscreen.

When comparing F2 and F1 (Figure 5), it is possible to note that the addition of sunscreens significantly increased the solid character of the formulations, indicating more

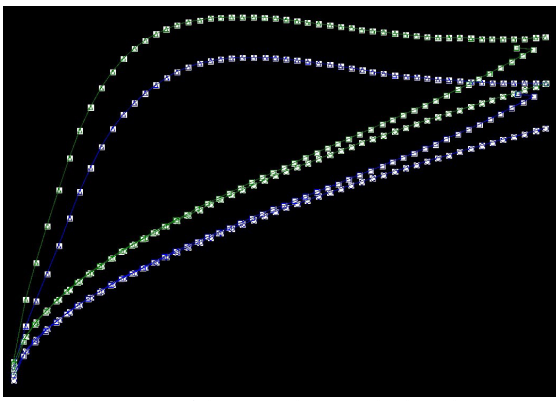

Figure 1. Flow Curve of the Formulation Vehicle only (Green) and Formulation Vehicle (Blue) Added *Spirulina – F2*.

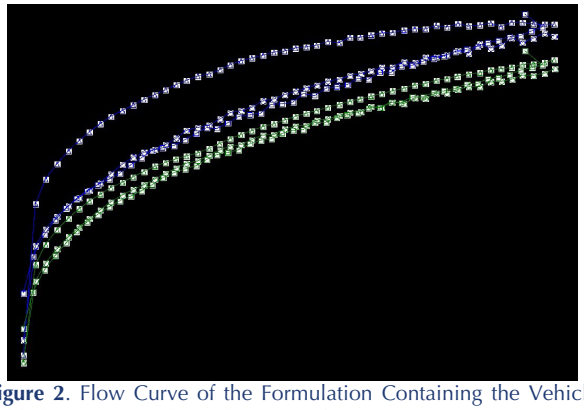

Figure 2. Flow Curve of the Formulation Containing the Vehicle Added *Spirulina* and Combination of Sunscreens – F1 (Green) and Vehicle Added With the Combination of Sunscreens Only - F3 (blue).

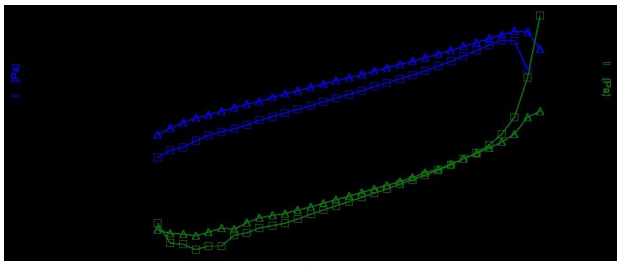

Figure 3. Frequency Sweep of the Formulation Vehicle Only (Triangles) and Vehicle Added *Spirulina* – *F2* (Squares), Being G′ Blue and G″ Green.

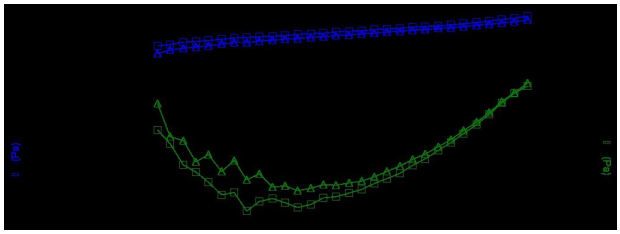

Figure 4. Frequency Sweep of the Formulation Containing the Vehicle Added *Spirulina* and Combination of Sunscreens – F1 (Triangles) and Vehicle Added With the Combination of Sunscreens Only - F3 (Squares), Being G′ Blue and G″ Green.

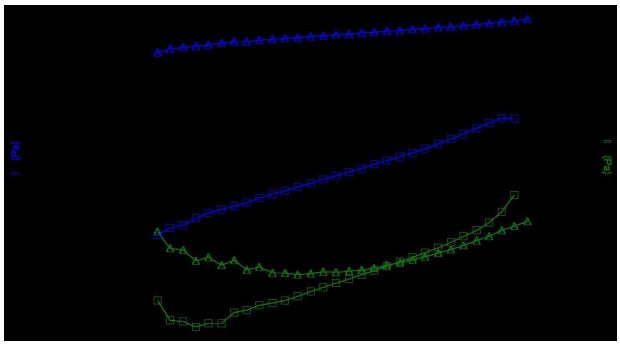

Figure 5. Frequency Sweep of the Vehicle Added *Spirulina* – *F2* (Squares), and the Formulation Containing the Vehicle Added *Spirulina* and a Combination of Sunscreens – F1 (Triangles), Being G′ Blue and G″ Green.

excellent stability of the emulsion when compared to versions without filters. This effect is also shown in other studies in the literature.[15]

In general, we can consider that all flow curves and frequency sweeps indicate good stability of all evaluated formulations, with the expected changes when added with the combination of sunscreens.

Sensory Analysis

As previously mentioned, the sensory properties can be correlated with the results obtained in the rheological analysis. In this study, the results showed that vehicle formulations containing only *Spirulina* have a better spreadability (Figure 6), and the formulations containing the combination of sunscreens, the formulation was characterized with higher stickiness (Figure 7), which also matches the rheological results. This way, the rheology

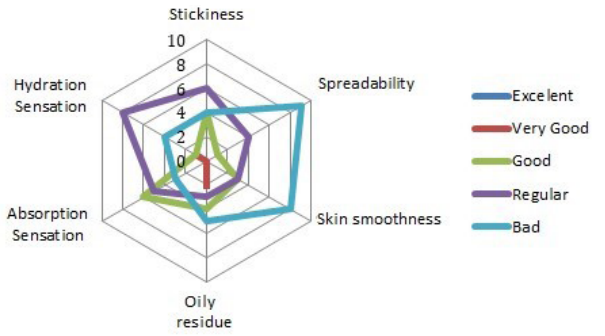

Figure 6. Sensory Analysis of the Formulation Vehicle Added *Spirulina*.

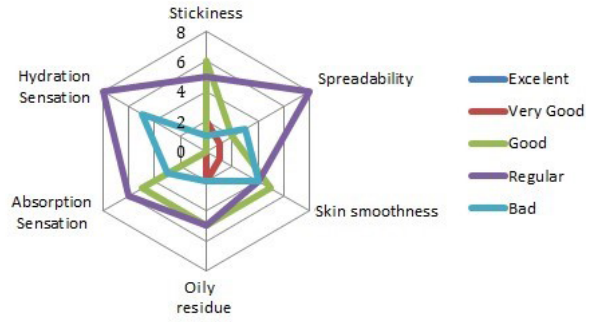

Figure 7. Sensory Analysis of the Added Formulation of *Spirulina* and Sunscreens.

results show significant influence in the sensory of the formulations with UV protection, especially in the spreadability, viscosity, and consistency parameters.[18]

In addition, it was possible to observe that both formulations were well accepted by the subjects, presenting a good sensation of hydration, absorption, and softness in the skin, which are important cosmetic parameters and that demonstrate the intention of purchase by the consumers.

Clinical Efficacy Studies

Short Term Clinical Efficacy

In the clinical study by biophysical and skin imaging techniques, after 2 hours of application of the formulations understudy, only the formulation F1 with *Spirulina* and sunscreens provoked a significant increase in the stratum corneum water content (Figure 8).

In addition, when compared to the control region, *Spirulina*-containing formulations did not interfere with the sebum content of the skin, indicating that the formulation does not lead to increased skin oil conditions (Figure 9).

The non-significant increase in the skin sebum amount is important for the good acceptance of the product since in young skins it is a decisive effect to purchase a cosmetic and for mature skins indicates that the formulation is compatible with the skin, not causing undesirable effects such as significant increase of oiliness, even in the presence of sunscreens.[19]

Similar results in the stratum corneum water content increase and skin oiliness control were observed in cosmetic formulations without sun protection,[20] which shows that these photoprotective ingredients do not alter the benefits of *Spirulina* can be applied in formulations with multiple functions.

Thus, the clinical evaluation of short-term effects demonstrated that multifunctional formulations containing *Spirulina* have great applicability in cosmetics since it unites their stability with good sensory properties and brings benefits in skin hydro lipids characteristics after 2 hours of application.

Long Term Clinical Efficacy

For the long-term clinical efficacy study, after 30 days of application on the face region, the formulation containing *Spirulina* extract added (F1) or not (F2) with the sunscreen combination, showed a significant increase in the stratum corneum water content (Figure 10) and decrease of TEWL (Figure 11), acting on the improvement of skin barrier function, when compared to baseline values. The decrease of TEWL was also observed on the formulation added with the combination of sunscreens only, which could be related to the fact that the UV light increases stress and reduces cohesion of stratum corneum, impairing the barrier function and increasing TEWL.[21]

The improvement of the skin barrier function has great importance to the maintenance of the cutaneous physiology, being a great benefit to be considered on multifunctional formulations. In our previous study, a reduction of the TEWL was also observed in a mature skin group with the application of a gel cream containing 0.1% of *Spirulina*.[4] This information is relevant to our study as it shows that even in the presence of a different vehicle and sunscreen, the addition of Spirulina is beneficial to the skin barrier function health.

The photoprotective formulation added with *Spirulina* (F1) also acted in the improvement of skin microrelief, dermal thickness and increased the depth of dermal papillae. These effects were not observed in the formulation containing only sunscreens, relating the improvements of skin conditions due to *Spirulina* in the formulation composition.

In the microrelief analysis, which allows a qualitative and quantitative evaluation of the skin surface under physiologic conditions, significant changes after a 30-days period of treatment were observed on the number and

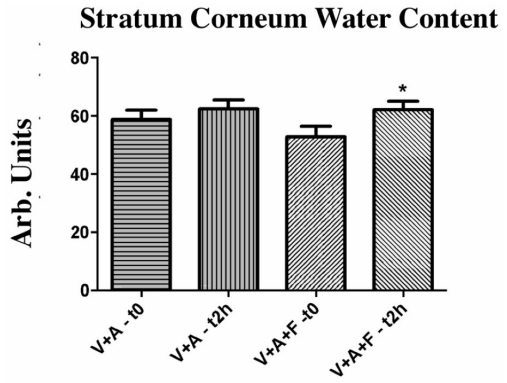

Figure 8. Stratum Corneum Water Content in the Frontal Region of the Formulations Added *Spirulina* (V + A - F2) and Added With *Spirulina* and Combination of Solar Filters (V + A + F - F1) Before and After 2 h of Application. * Significant difference from baseline ($P<0.05$).

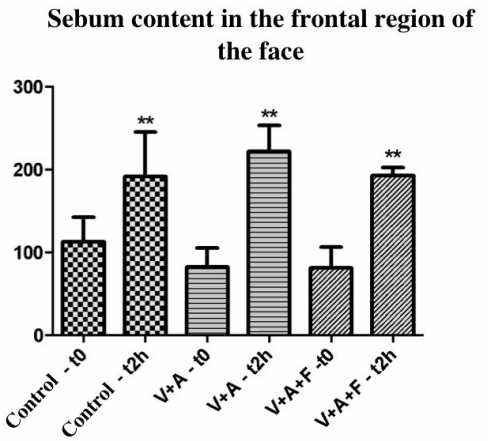

Figure 9. Sebum Content in the Frontal Region of Vehicle Formulations Added *Spirulina* (V + A - F2) and Added With *Spirulina* and Combination of Sunscreens (V + A + F - F1) before (baseline) and After 2 h of Application. * Significant difference from baseline ($P<0.001$).

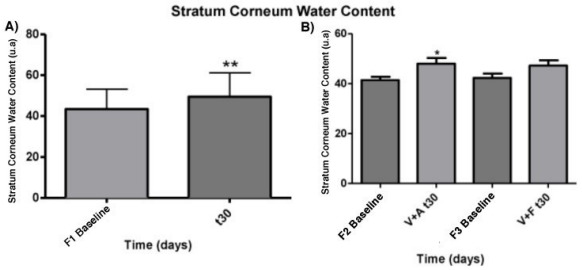

Figure 10. Stratum corneum water content after 30 days-period of application the formulation F1 (added with UV filters and 0,1% *Spirulina)* on the face (A) and after application on the forearm region (B) of the formulations F2 (with 0.1% of *Spirulina)* and F3 (with the sunscreens combination). ** Significantly different from baseline values ($P<0.002$); * Significantly different from baseline values ($P<0.05$).

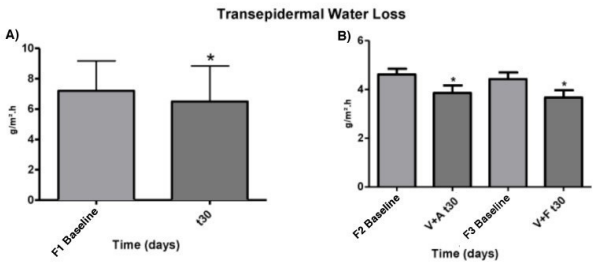

Figure 11. Transepidermal Water Loss After 30 Days-Period of Application the Formulation F1 (Added With UV Filters and 0.1% *Spirulina)* on the Face (A) and After Application on the Forearm Region (B) of the Formulations F2 (With 0.1% of *Spirulina)* and F3 (with the sunscreens combination). * Significantly different from baseline values ($P<0.05$).

width of wrinkles (Sew parameter) and on skin roughness (Ser parameter) (Figure 12), indicating an improvement on skin appearance on the face region. On the forearm region, a significant difference from baseline values was observed on the skin roughness parameter (Ser) only on the formulation added with 0.1% of *Spirulina* (Figure 13).

A significant increase in the dermis thickness was observed on the face region after 30 days-period of treatment with the photoprotective formulation added with 0.1% of *Spirulina* (Figure 14). This could indicate an improvement in the skin conditions once a reduction on this parameter can be observed during skin aging, but its increase can also be related to a higher water content.[22] No significant result was observed in the skin echogenicity study.

The epidermis structural and morphological analysis showed a significant increase in the depth of dermal papillae (Figure 15), which is an important parameter to characterize skin aging, as this skin structure increases the contact area between the epidermis and dermis, benefiting this connection and increasing the availability of nutrients to the epidermis. Also, during the aging process, the papillae (Figure 16) suffer a flattening process, so an increase of their depth is related to improving this phenomenon.[7]

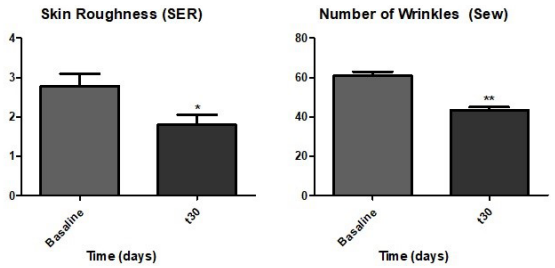

Figure 12. Number and Width of Wrinkles (Sew) After 30 Days-Period of Application the Formulation F1 (Added With UV Filters and 0.1% *Spirulina)* on the Face Region. ** Significantly different from baseline values ($P<0.002$). * Significantly different from baseline values ($P<0.05$).

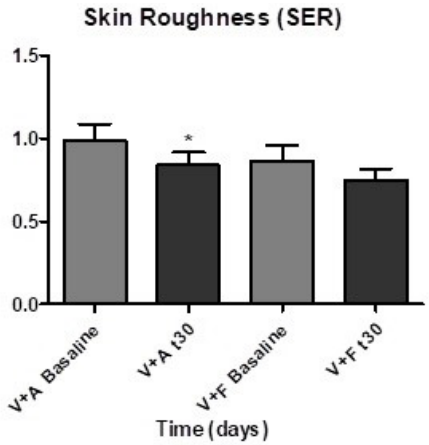

Figure 13. Skin Roughness (Ser) After 30 Days-Period of Application the Formulations F2 (With 0.1% of *Spirulina)* and F3 (With the Sunscreens Combination) on the Forearm Region. * Significantly different from baseline values ($P<0.05$).

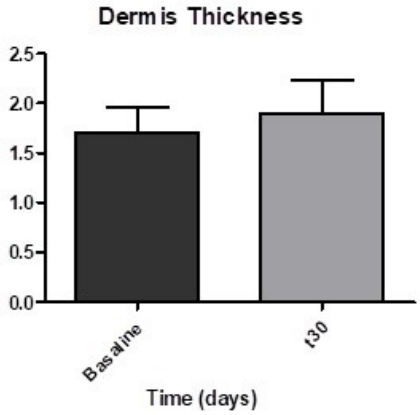

Figure 14. Dermis Thickness After 30 Days-Period of Application the Formulation F1 (Added With UV Filters and 0.1% *Spirulina)* on the Face Region. * Significantly Different From Baseline Values ($P<0.05$).

Conclusion

The present study highlights the importance of the development of cosmetic formulations containing the dry extract of *Spirulina*, as it brings relevant benefits

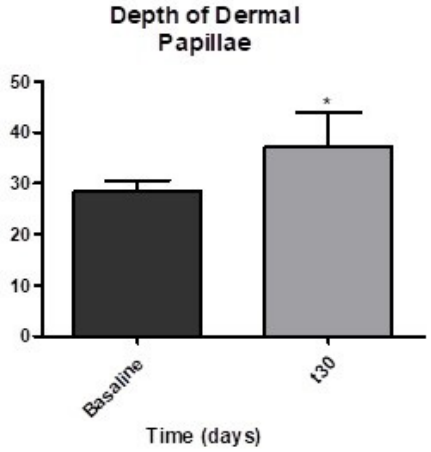

Figure 15. Depth of Dermal Papillae After 30 Days-Period of Application the Formulation F1 (Added With UV Filters and 0.1% *Spirulina)* on the Face Region. *Significantly different from baseline values ($P<0.05$).

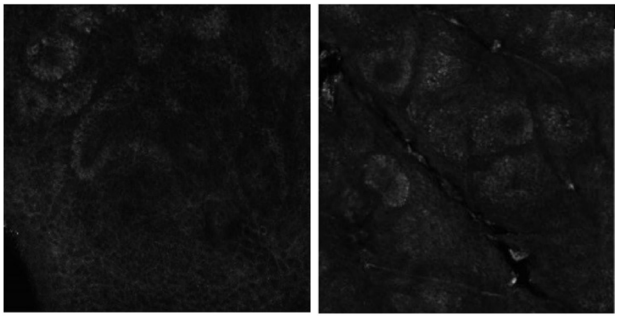

Figure 16. Structural differences in the dermal papillae obtained before and after 30 days of use of the formulation containing 0.1% of *Spirulina* dry extract and combination of sunscreens in the periorbital region.

to general skin conditions. A significant increase in the stratum corneum water content, dermis thickness, TEWL reduction, microrelief, and skin morphological characteristics improved the epidermis. Finally, because of its multiple benefits to the skin, the development of multifunctional formulations containing *Spirulina* has led to a stable, skin-friendly sensorial product with the clinical effectiveness of its proven functions.

Competing Interests

No conflict of interest is noted.

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