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Communication

Photoprotective Efficacy of the Association of Rosmarinic Acid 0.1% with Ethylhexyl Methoxycinnamate and Avobenzone

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Abstract: Innovative prototype sunscreens with reduced ultraviolet (UV) filters are required to achieve safer, more effective, and more environmentally friendly formulations. Rosmarinic acid (RA) is a phenolic antioxidant and potential candidate for multifunctional sunscreens. We used RA (0.1% *w*/*w*) in combination with avobenzone (2.5% and 5.0% *w*/*w*), a UVA filter, and ethylhexyl methoxycinnamate (10.0% *w*/*w*), a UVB filter, to evaluate in vitro sun protection factor (SPF) and critical wavelength, photostability, and the in vivo SPF. RA, in vitro, improved the SPF of F2 (ethylhexyl methoxycinnamate 10.0% *w*/*w* + avobenzone 2.5% *w*/*w* + RA 0.1% *w*/*w*) and F3 (ethylhexyl methoxycinnamate 10.0% *w*/*w* + avobenzone 5.0% *w*/*w* + RA 0.1% *w*/*w*), which also presented broad-spectrum profiles; however, no expressive effects were observed for the critical wavelength (nm). By the in vivo trial, RA showed an increment in the F3 SPF value and maintained the F2 effectiveness, even when avobenzone was at 2.5%. Nonetheless, no increase in photostability was observed. Our findings suggest that incorporating natural molecules with antioxidant activities into sunscreens could decrease the proportion of conventional UV filters in the final product, with the advantage of providing other functional properties. Further investigation of higher RA concentrations, even from other sources, and other UV filter combinations could reveal important data for the development of multifunctional sunscreens.

Keywords: critical wavelength; rosmarinic acid; sun protection factor; sunscreen

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1. Introduction

Great attention has been given to the harmful effects of sunlight overexposure on the unprotected skin, such as photoaging, oxidative stress, and skin carcinogenesis [1,2]. The use of sunscreens is known as a viable and good strategy to prevent or to overcome those effects. These topical formulations contain molecules or molecular complexes that reduce the ultraviolet (UV) effects over the skin by absorbing, reflecting, or dispersing the incident light. Organic filters absorb UV radiation, while inorganic filters reflect or disperse the radiation, and may also absorb a part of it [3,4]. The increased use of combinations of such filters in sunscreens had been evaluated along with environmental and safety concerns [5,6]. The deposition of synthetic UV filters into the sea [7,8] and the safety of them regarding photoallergy and photoinstability are continuously under regulatory review among the agencies worldwide [9]. Thus, lower concentrations of UV filters to achieve a broad-spectrum sunscreen is very beneficial for formulation approval during safety assessment.

Different exogenous molecules can provide efficient multifunctional effects in sunscreens [10,11]. Polyphenols are probably one of the most efficient classes of compounds

against oxidative stress, having an important role in the adsorption and neutralization of free radicals [12]. In fact, sunscreens associated with antioxidants have shown an increment in skin protection, thus reducing the damage caused by the UV radiation [6,13,14] and acting as a safer environmental alternative [15,16]. For instance, Afonso and coworkers observed that ubiquinone and vitamin E improved, by an in vitro test, the sun protection factor (SPF) of avobenzone, a UVA filter [17].

Rosmarinic acid (RA), a phenolic compound [18], is an ester of caffeic acid (Figure 1). Studies have shown that RA is an efficient antagonist in lipid peroxidation, being able to insert itself spontaneously in lipid membranes with greater affinity for unsaturated lipids, as well as its use in the treatment of atopic dermatitis and in aid of photoprotection [19,20]. It has several biologic activities such as antioxidant, antiviral, and anticancer, among others [21–23]. Considering its topical application, it is a compound that can penetrate the cutaneous tissue. Moreover, it was reported RA increased the survival of keratinocytes exposed to UVB radiation, inhibiting the generation of intracellular reactive oxygen species (ROS) with a concomitant decrease in DNA damage [24]. Furthermore, it is a compound of great interest to the pharmaceutical, food, and cosmetic industries, with beneficial health-promoting effects.

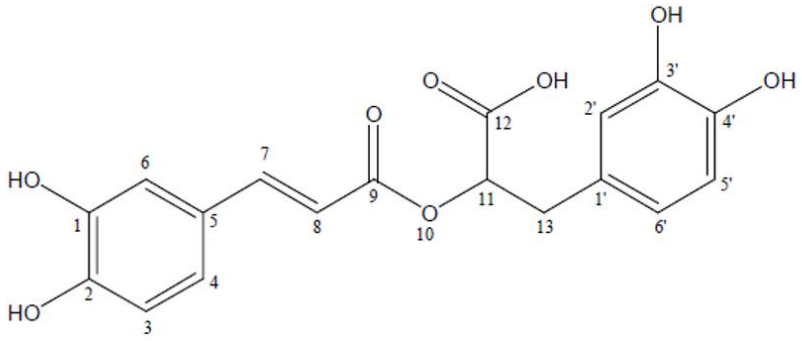

Figure 1. Chemical structure of the rosmarinic acid.

Our research group has been working with natural compounds as photoprotection enhancers for over a decade [12] and, in this research work, we evaluated the effect of the presence of rosmarinic acid in sunscreen system by in vitro and in vivo tests aiming to establish the samples' efficacy profiles.

2. Materials and Methods

2.1. Samples

The qualitative and quantitative (% *w*/*w*) composition of our three emulsions is described in Table 1.

Table 1. Qualitative and quantitative (% *w*/*w*) composition of sunscreens.

Composition	Phase	Concentration (% *w*/*w*)		
		F1	F2	F3
Cetearyl alcohol (and) dicetyl phosphate (and) ceteareth-10 phosphate	O	4.0	4.0	4.0
Isopropyl myristate	O	5.0	5.0	5.0
Ethylhexyl methoxycinnamate	O	10.0	10.0	10.0
Butil methoxydibenzoylmethane (avobenzone)	O	5.0	2.5	5.0
Rosmarinic acid	F	-	0.1	0.1
Glycerin	A	5.0	5.0	5.0
Phenoxyethanol (and) methylparaben (and) butylparaben (and) ethylparaben (and) propylparaben (and) isobutylparaben	A	0.75	0.75	0.75
Ammoniumacryloyldimethyltaurate/VPcopolymer	A	1.0	1.0	1.0
Ethanol	F	5.0	5.0	5.0
Purified water	A	q.s. 100.0	q.s. 100.0	q.s. 100.0

O—oily phase; A—aqueous phase; F—final phase; q.s.—enough quantity to.

The batch size was standardized at 20.00 g of each formulation. The oily phase was heated to 55 °C and the water phase up to 60 °C. The oily phase was added to the water phase to obtain the emulsion using mechanical stirring. The mixture was cooled to 35 °C to add the final phase. The formulations' pH values were adjusted between 5.0–6.0 with triethanolamine or citric acid at 22 ± 2 °C. The samples were stored at room temperature in glass containers. After 48 h, organoleptic characteristics (appearance, color, and odor) were observed.

2.2. In Vitro Photoprotective Efficacy and Photostability Assay

Samples had the sun protection factor (SPF) and the critical wavelength (nm) measured to establish the in vitro photoprotective efficacy using a Labsphere UV2000S Ultraviolet Transmittance Analyzer [25]. An amount of 1.3 mg/cm^2 of each sample was uniformly applied on polymethylmethacrylate plates (n = 3) (Helioplate HD 6, Helioscreen, North Sutton, NH, USA). Then, the plates were left for 30 min under light protection to dry [26]. The test was performed according to Cândido and coworkers. The in vitro SPF and critical wavelength (nm) were calculated by the UV-2000 software [27,28]. Photostability was carried out right after obtaining the in vitro efficacy parameters. The same substrates containing the samples were irradiated for up to 2 h with UV artificial irradiation from the CPS + Atlas Suntest simulator equipped with a xenon lamp. The photostability test was based on previous works from Scalia and Mezzena, Cândido and coworkers, and Pereira and coworkers [28–30]. After the UV stress, the post-irradiation values of the in vitro SPF and critical wavelength (nm) were calculated as mentioned before.

2.3. In Vivo Sun Protection Factor (SPF)

The in vivo trial to evaluate the photoprotective efficacy of the sunscreen samples was previously approved by the local committee on human experimentation, according to ethical standards and the Helsinki Declaration. The pertinent information and clarifications regarding the trial were provided to each subject who expressed the interest to participate [31]. The in vivo SPF assessment was performed according to guidelines and the specialized literature [32–34]. Ten subjects were dermatologically evaluated and selected in this trial. Aliquots of 2.0 mg/cm^2 of each sample were applied to the back of the subjects, after proper cleaning with dry cotton. After 15 min for product drying, the defined areas were irradiated with a Multiport 601 UV Solar Simulator. After 20 ± 4 h of exposure, the areas were visually evaluated under a standard lighting source and the SPF was calculated by DEMp/DEMnp (DEMp is the minimal erythematous dose on the skin protected by the reference product and DEMnp was the minimal erythematous dose on unprotected skin) [34].

2.4. Statistical Analyses

Results were treated by the Minitab® program, version 19. Tests were performed in n = 3, with a significance level of 5.0% ($p \leq 0.05$). One-way ANOVA followed by Tukey tests were applied for the comparisons among the samples.

3. Results and Discussion

All emulsified systems were macroscopically homogeneous, stable after centrifugation and thermal stress tests [35], and they showed pH values biocompatible with human skin (5.2–5.9) (data not shown) [36]. The in vitro efficacy test showed that samples F1 and F2 had equal SPF values, as well as F2 and F3. However, F1 and F3 were dissimilar for this parameter. Regarding the critical wavelength (nm), F1 and F3 developed the highest values, equivalent between them. F2 generated an inferior and different value (Table 2).

Formulations could be considered sunscreens, since they achieved SPF ≥ 6 [31,37]. The critical wavelength was about 380 nm for all samples, this parameter being the section that covers 90% of the area under the integrated optical density curve of the UV from 290 to 400 nm. Formulations with critical wavelength values equal or above 370.0 nm

are classified as broad-spectrum sunscreens, having protection throughout the UVA and UVB ranges for a specific limit of SPF value [33,38,39]. Therefore, statistically, F2 and F3, both with SPF > 15, were classified as broad-spectrum sunscreens. We expected an overall performance increase of the formulations in the presence of RA, since polyphenol molecules show absorbance between 250 and 270 nm (UV region) [3]. We observed an elevation of the in vitro SPF for F2 and F3 and no robust improvements for the critical wavelength of the samples that could be attributed to UVA filter concentration and/or limitation of the spectrophotometric method, for example [40,41]. Accordingly, we observed that RA exerted a more pronounced interaction with the ethylhexyl methoxycinnamate, the UVB filter, contributing with the SPF elevation. Since the critical wavelength is a parameter associated with the broad-spectrum protection of a sunscreen, our results indicated that avobenzone (UVA filter) at the lowest used concentration (2.5% *w*/*w*) in F2 was responsible for the critical wavelength reduction, albeit without interfering with the protection in the UVB region.

Table 2. In vitro sun protection factor (SPF) values and critical wavelength (nm) of sunscreens (F1, F2, and F3).

Samples	In Vitro SPF	Critical Wavelength (nm)
F1	12.00 ± 1.73^{A}	382.67 ± 0.58^{C}
F2	15.67 ± 3.51^{AB}	379.34 ± 0.58^{D}
F3	17.33 ± 0.58^{B}	381.67 ± 0.58^{C}

F1—ethylhexyl methoxycinnamate 10.0% *w*/*w* + avobenzone 5.0% *w*/*w*; F2—ethylhexyl methoxycinnamate 10.0% *w*/*w* + avobenzone 2.5% *w*/*w* + rosmarinic acid 0.1% *w*/*w*; F3—ethylhexyl methoxycinnamate 10.0% *w*/*w* + avobenzone 5.0% *w*/*w* + rosmarinic acid 0.1% *w*/*w*. Samples that share a letter are statistically equal (Tukey test: $p \leq 0.05$).

The photostability test showed that RA at 0.1% was not enough to avoid the instability of the mixture of the UV filters. After 30 min of irradiation, F1 had a 44% decrease in SPF while F2 and F3 decreased 34 and 42% (Figure 2A), respectively. Regarding the critical wavelength, F2 was the most impacted formulation after irradiation; however, all samples showed a decrease in this parameter after 120 min (Figure 2B). Since F2 composition was half of avobenzone concentration, our results suggested that avobenzone was the main photostability restriction [42]. Despite this drawback, it is one of the few UVA filters approved. Some studies using the combination of antioxidants and avobenzone showed good outcomes to prevent photodegradation [17]. We hypothesized that RA could also contribute to stabilize avobenzone, since it is an antioxidant compound; however, all formulations showed no photostability during the 120-min test.

Considering this scenario, we further investigated the effect of RA in an in vivo SPF trial. Our in vivo SPF trial resulted in a significant raise of over 44% in the presence of RA (F3) compared to the control (F1) (Figure 3). According to the specialized literature, when antioxidants were used in combination with UV filters, there were observed SPF improvements and reductions of UVB-induced erythema and UVA-induced skin roughness and sagginess [43]. The mechanisms more accepted for the efficacy enhancement are related to the absorption spectra in the UV range of antioxidants and oxidative stress reduction. For RA, previous studies with oral administration showed a delayed in malonyldialdehyde formation, which is a peroxidation marker, and up-regulation of tyrosinase activity, stimulating melanin production [44]. Those outcomes suggested that RA may induce endogenous defense mechanisms and also act as a radical scavenger for ROS after UVA-induced stress.

According to Nicolai and coworkers, the association of 10.0% (*w*/*v*) *Plectranthus ecklonii* Benth extract, rich in RA, with an UV filter known as benzophenone-4 at 6.0% (*w*/*v*), induced an increment of 19.49% of the in vitro SPF value. Moreover, the skin permeation, antibacterial activity, and acetylcholinesterase inhibition, as well as the no cytotoxicity for human keratinocytes, revealed the multifunctional activity of RA derived from natural resources in the production of antiaging dermocosmetics [45]. Our findings,

interestingly, showed that F2 had statistically the same SPF value in vivo when compared to F1. Considering that F2 has half of the avobenzone concentration, RA showed a positive effect with this UVA filter, maintaining the photoprotection profile. Since the critical wavelength of formulations was not ameliorated for the samples (Table 2), it is feasible to suggest that the in vivo SPF increase was not associated exclusively with the UV-absorbing properties of RA.

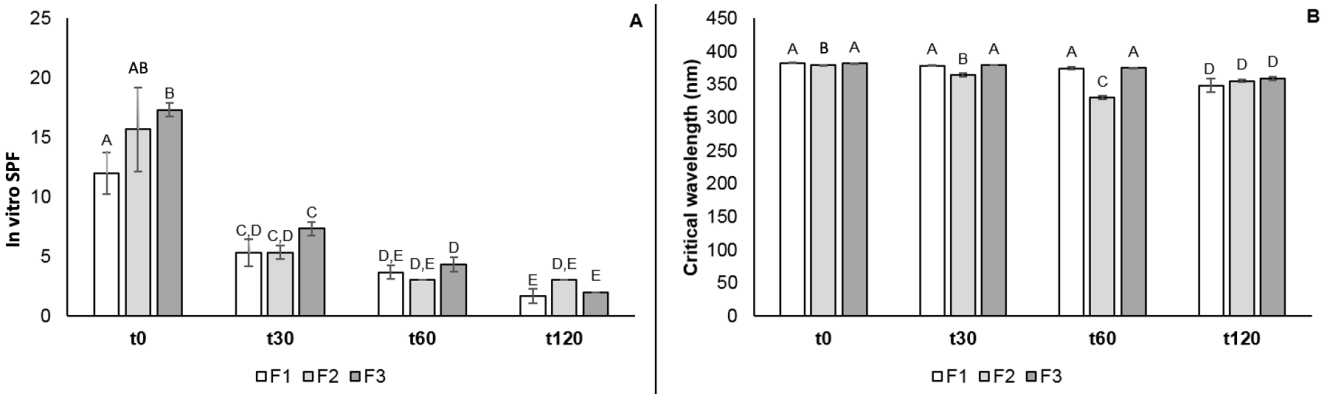

Figure 2. Photostability test. (**A**) In vitro sun protection factor (SPF) before and after irradiation; (**B**) critical wavelength (nm) before and after irradiation. Samples that share a letter are statistically equal (Tukey test: $p \leq 0.05$). No irradiation (t0), 30 min irradiation (t30), 60 min irradiation (t60), and 120 min irradiation (t120). F1—ethylhexyl methoxycinnamate 10.0% *w*/*w* + avobenzone 5.0% *w*/*w*; F2—ethylhexyl methoxycinnamate 10.0% *w*/*w* + avobenzone 2.5% *w*/*w* + rosmarinic acid 0.1% *w*/*w*; F3—ethylhexyl methoxycinnamate 10.0% *w*/*w* + avobenzone 5.0% *w*/*w* + rosmarinic acid 0.1% *w*/*w*.

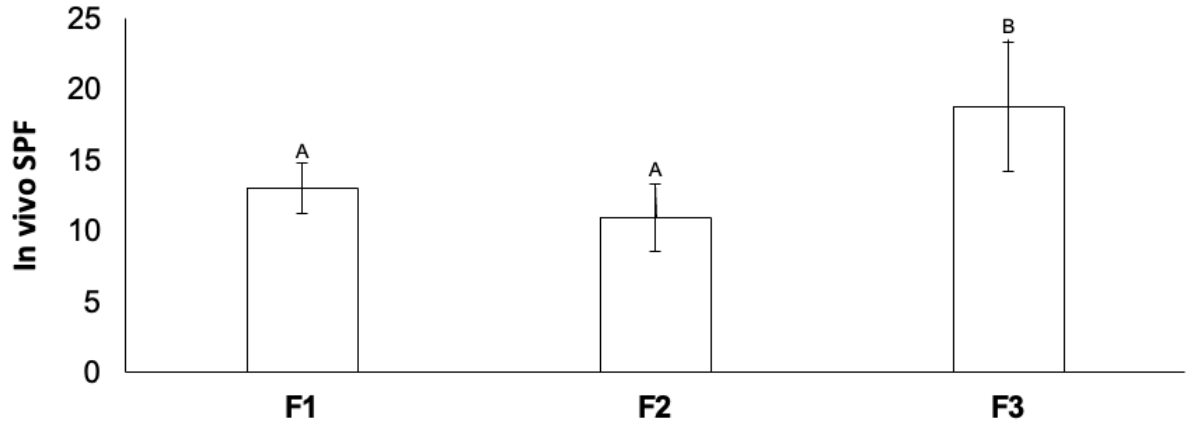

Figure 3. In vivo sun protection factor (SPF). Samples that share a letter are statistically equal (Tukey test: $p \leq 0.05$). F1—ethylhexyl methoxycinnamate 10.0% *w*/*w* + avobenzone 5.0% *w*/*w*; F2—ethylhexyl methoxycinnamate 10.0% *w*/*w* + avobenzone 2.5% *w*/*w* + rosmarinic acid 0.1% *w*/*w*; F3—ethylhexyl methoxycinnamate 10.0% *w*/*w* + avobenzone 5.0% *w*/*w* + rosmarinic acid 0.1% *w*/*w*.

4. Conclusions

Rosmarinic acid, in vitro, was able to improve the SPF of the samples F2 (ethylhexyl methoxycinnamate 10.0% *w*/*w* + avobenzone 2.5% *w*/*w* + RA 0.1% *w*/*w*) and F3 (ethylhexyl methoxycinnamate 10.0% *w*/*w* + avobenzone 5.0% *w*/*w* + RA 0.1% *w*/*w*), which also presented broad-spectrum profiles; however, no expressive effects were observed for the critical wavelength (nm). By the in vivo trial, RA showed an increment in the F3 SPF value. Moreover, RA maintained the sample effectiveness even when avobenzone was at 2.5% (F2). Nonetheless, no increase in photostability was observed.

Our findings suggest that incorporating natural molecules with antioxidant activities into sunscreens could decrease the proportion of conventional UV filters in the final product,

with the advantage of providing other functional properties. Further investigation of higher RA concentrations, even from other sources, and other UV filter combinations could reveal important data for the development of multifunctional sunscreens.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Faculty of Pharmaceutical Sciences (protocol code 1.181.993, 06/02/2015).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Not applicable.

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Conflicts of Interest: The authors declare no conflict of interest.

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