



Research Article

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Assessment of Hydroxycinnamic Acids Potential for Use as Multifunctional Active Ingredients in Sunscreens, Via a Comparative UV Spectroscopy Analysis

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ABSTRACT

There is a need to identify non-toxic UV filters of natural origin for use in sunscreen products due to concerns about potential health and environmental toxicity of synthetic UV filters. Hydroxycinnamic acids (HCAs) are plant metabolites that exhibit excellent antioxidant properties, and absorb efficiently solar UV radiation. A comparative UV spectroscopy analysis of HCAs was performed to determine the feasibility of their use as multifunctional UV filters with simultaneous antioxidant capacities. Sun protection factor (SPF) values were calculated using the Mansur equation. The UVA/UVB ratio and critical λ , which are indicators of sunscreen ability to offer broadband UVB/UVA protection, were calculated from UV spectra. Our analysis indicates that each of HCAs, specifically caffeic acid, ferulic acid, and sinapic acid absorb efficiently and simultaneously in multiple regions of UV solar radiation, specifically UVB (290 nm-320 nm), UVA II (320 nm-340 nm), and to some extent in the UVA I (340 nm-400 nm) region. We concluded that HCAs incorporating at least one catechol moiety, such as sinapic acid, caffeic acid, and ferulic acid, could provide broadband UVB/UVA screening comparable or superior to commercial UV filters, in addition to antioxidative capabilities. Thus, HCAs, if properly modified to ensure emulsification into sunscreens, have the potential to provide an alternative to multiple current UV filters suspected of health and environmental toxicity.

Keywords: Hydroxycinnamic acids; Caffeic acid; Ferulic acid; Sinapic acid; SPF; UVA/UVB; Critical λ ; Sunscreens; Mansur equation

INTRODUCTION

The use of sunscreens is deemed indispensable by dermatologists to protect skin from prolonged exposure to UV solar radiation [1,2]. Sunscreens are formulated with UV filters, which are lipophilic aromatic compounds that absorb in specific regions of UV solar radiations. UVB filters in sunscreens absorb the 290 nm-320 nm band of UV

solar radiation, which is the cause of erythema (sunburn), basal carcinoma, and melanoma. UVA filters absorb the 320 nm-400 nm band, which is the cause of ROS generation, lipid peroxidation, and DNA photosensitized products [3,4]. Concerns have been raised about the toxicity of sunscreens active ingredients [5-7]. Studies confirm that UV filters diffuse into blood stream within two hours upon sunscreen's application, and are present in concentrations higher than 0.5 ng/ml threshold established by FDA for waiving toxicity studies [8]. UV filters can pose a risk of skin carcinogenicity, developmental, and embryofetal toxicity because of their endocrine disruption action [9,10]. The environmental impact of UV filters is another area of great concern [11]. Studies have confirmed widespread presence of oxybenzone, octocrylene, octinoxate, and octisalate in marine waters around the world [12]. UV filters are not easily removed by wastewater treatment, often forming toxic byproducts with chlorine [13]. Oxybenzone, 4-methylbenzylidene camphor, octocrylene, and octinoxate are identified in species of fish worldwide, thus could be present in the food chain [14]. Oxybenzone is implicated as the potential cause of coral reef bleaching [15]. The environmental concerns are real. The state legislature of Hawaii passed a bill on May 1st 2018 that bans the sale and distribution of sunscreens containing oxybenzone and octinoxate, which will go into effect in 2021. Nevertheless, it must be noted that sunscreen usage is an absolute necessity, and sunscreens are a safe precaution to prevent the advent of skin cancers as result of exposure to UV radiation, according to the American Academy of Dermatology Association [3].

On average 15-20% of sunscreens weight consists of UV filters. On average, at least three or four UV filters are combined to provide an efficient protection against UVB/UVA radiation. In addition sunscreens are formulated with additional aromatic compounds to provide antioxidant capabilities to sunscreens [16]. To address issues of environmental impact, and potential toxicity to humans, a two directional strategy can be considered. First, the concentration of UV filters in sunscreens could be minimized, without loss of UV protection. This can be achieved by replacing combination of UV filters and antioxidants with one multifunctional UV filter. Second, multifunctional UV filters could be chosen to be biodegradable, derived from natural products, thus most likely to be non-toxic. Multi functionality is defined as the ability of one UV filter to simultaneously 1) absorb efficiently UVB (290 nm-320 nm), UVAIL (320 nm-340 nm), UVAIL (340 nm-400 nm) radiation, and 2) reduce at a fast rate reactive oxygen species *in vivo*. The FDA ruling of 2011 is another way multi functionality can be defined. It states that a broadband sunscreen must have a sun protection factor *in vivo* SPF ≥ 15 , and a critical $\lambda_c \geq 370$ nm, such that: $\int_{290}^{\lambda_c} A(\lambda) d\lambda = 0.9 * \int_{290}^{400} A(\lambda) d\lambda$.

Nature once again can provide a solution to this problem. Plants, fruits, and vegetables contain medicinal compounds, phenolic antioxidants that absorb efficiently UV radiation [17]. Hydroxycinnamic acids (HCAs), such as caffeic acid, ferulic acid, and sinapic acid can be used as primary sources of biodegradable and multifunctional UV filters [18-20]. HCAs absorb in the combined UVB/UVA spectral range, are considered photostable, and efficient antioxidants [21-23].

The question we want to answer through a comparative UV spectroscopy study is the following: Can HCAs, if used in high concentrations that are typical for UV filters in sunscreens, provide broadband UV protection similar to commercial UV filters? There is literature precedent to support the above assumptions. Caffeic acid, and ferulic acid were tested as antioxidant additives, in low concentrations up to 1%, in sunscreen. In these studies, besides efficient

antioxidant capacities, an increased SPF was observed as result of the presence of HCAs [20,24]. In addition, there is ample literature data on antioxidant capacities of HCAs, and their inhibitory effects on reactive oxygen species (ROS) [18,25]. We found very interesting the fact that esters of HCAs are reported to be more reactive toward ROS than their corresponding free HCAs [26,27]. Esterification is used routinely to improve lipophilic behavior of aromatic UV filters, to ensure emulsification. Moreover, polyphenolic HCAs are found to react fast with ROS, in rates comparable to vitamin E, and Trolox. All literature data indicates that HCAs could be useful aromatic core structures for use as multifunctional UV filters with intrinsic antioxidant properties.

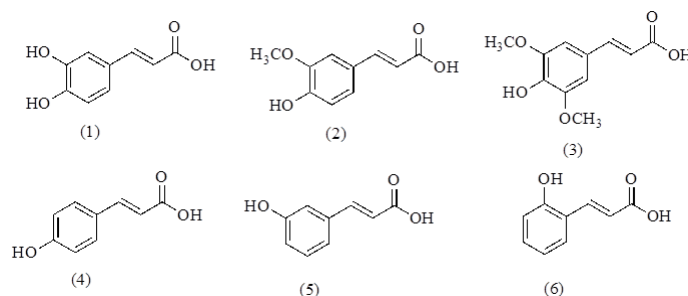


Figure 1. Structures of naturally occurring hydroxycinnamic acids (HCAs). (1) Caffeic Acid. (2) Ferulic Acid. (3) Sinapic Acid. (4) p-Coumaric Acid. (5) m-Coumaric Acid. (6) o-Coumaric Acid.

MATERIALS AND METHODS

UV spectra were recorded on UVV 5 Mettler Toledo spectrophotometer, using quartz 1 cm length cuvettes. Chemicals were purchased from commercial suppliers, Sigma Aldrich and Fisher Scientific, and used without further manipulation. UV spectroscopy grade absolute ethanol was used for measurements. Each value is an average of three individual measurements. Sun protection parameters were calculated for six HCAs (Figure 1), six commercial UV filters (Figure 2), and three commercial sunscreen emulsions.

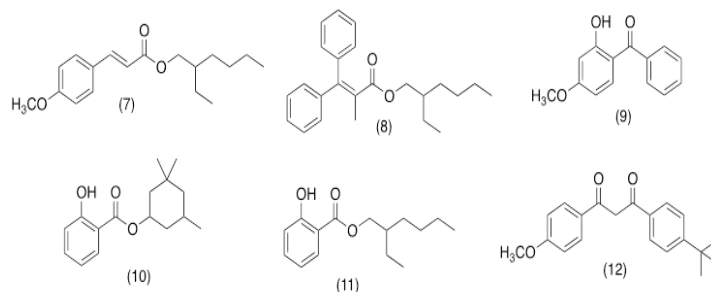


Figure 2. Commercial UV filters. (7) Octinoxate. (8) Octocrylene. (9) Oxybenzone. (10) Homosalate. (11) Octisalate. (12) Avobenzone.

Absorbance values are obtained from UV spectra of pure compounds at the appropriate dilutions, which satisfy the Mansur equation [28]. For pure compounds the stock solution was prepared by dissolving in 100 ml of ethanol the amount in mg equal to the desired (or allowed) % concentration in sunscreen multiplied by a factor of 10. For sunscreen emulsions the stock solution was prepared by dissolving 1 g of sunscreen in 100 ml of ethanol, and filtering through number 1 filter paper. The stock solution was diluted 50 times. The final dilution was used to obtain the UV spectra, and absorbance values, for all reported calculations including sun protection factors (SPF),

UVA/UVB area under the curve ratios, and critical λ . Critical λ is the wavelength that satisfies the equation

$$\int_{290}^{\lambda_c} A(\lambda)d\lambda = 0.9 * \int_{290}^{400} A(\lambda)d\lambda.$$

SPF values were estimated from UV spectra of pure HCAs, pure commercial UV filters, or sunscreens using the Mansur equation. In this equation $EE(\lambda)$ =erythema effect spectrum, $I(\lambda)$ =solar intensity spectrum, $Abs(\lambda)$ =absorbance of sunscreen product, and CF is a correction factor (=10). Normalized values of $EE \times I$ used for calculations were determined by Sayre *et al.* [29].

$$SPF = CF * \sum_{290}^{320} EE(\lambda) * I(\lambda) * Abs(\lambda)$$

RESULTS AND DISCUSSION

Estimated values of sun protection parameters for HCAs, commercial UV filters, and three broadband commercial sunscreen emulsions are summarized in Table 1. SPF *in vivo* indicates the ability to block the UVB radiation. SPF *in vivo* is defined, as the ratio of radiation exposure requires to achieving a persistent minimal skin erythema, with or without the application of sunscreen [30]. The Mansur equation is used to approximate the SPF values from UV absorbance spectra of sunscreens solutions in ethanol. The SPF by Mansur estimates the ability to absorb the radiation relative to the % weight of the UV filter in sunscreen, but does not correlate well with the ability of the sunscreen film to physically block, scatter and reflect UV radiation. As such it underestimates values relative to the SPF *in vivo*. However, our aim is to compare HCAs with commercial UV filters and sunscreen, therefore all other factors being equal, SPF by Mansur is a suitable choice to compare aromatic structures for their ability to offer protection against UVB solar radiation. We have estimated the SPF values for HCAs assuming 8% concentration in sunscreens. This is close to 7.5% concentration allowed for the commercial UV filter octinoxate, which incorporates a p-hydroxycinnamic acid aromatic structure. A better estimate of protection is offered by a comparison of UV spectral shape and molar absorption coefficients (ϵ) in the UVB/UVA range. The absorption efficiency in the UVA range is estimated through comparison of critical λ_c , and UVA/UVB area under the UV curve. Higher λ_c coupled with higher UVA/UVB ratios imply better protection in the UVA region. Commercial UV filters were used to provide benchmark values for comparison purposes.

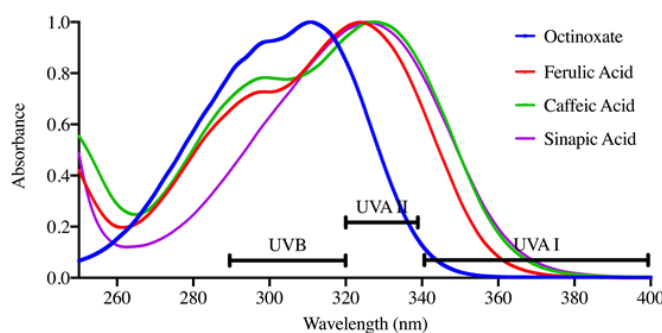


Figure 3. Normalized UV spectra for a series of HCAs.

Table 1. Estimated SPF, critical λ , UVA/UVB, for select active ingredients and sunscreens.

Active ingredients	SPF	λ_{\max}	ϵ ($M^{-1}cm^{-1}$)	UVA/UVB	λ_c (nm)
Caffeic Acid (8%)	12.5	327	17,800	1.24	348
Ferulic acid (8%)	12.5	324	19,600	1.05	344
Sinapic Acid (8%)	10	326	19,500	1.39	349
p-coumaric acid (8%)	19.3	312	21,900	0.42	331
o-coumaric acid (8%)	6.3	326	9,900	1.28	346
m-coumaric acid (8%)	5.9	313	4,900	0.43	335
Values estimated for FDA approved UV filters					
Octocrylene (10%)	7.1	303	13,200	0.58	341
Avobenzone (3%)	1.7	362	34,400	6.42	378
Oxybenzone (6%)	5.6	325	16,800	0.97	349
Octinoxate (7.5%)	10.3	311	21,100	0.36	329
Octisalate (5%)	1.6	307	2,800	0.21	324
Homosalate (15%)	4.4	307	2,800	0.21	324
Commercial sunscreens					
^a Sunscreen 1 (50+)	8.4	-	-	1.63	371
^b Sunscreen 2 (100+)	10.9	-	-	1.49	368
^c Sunscreen 3 (100+)	19.7	-	-	1.11	364

Active ingredients: a) Avobenzone 3%, Homosalate 10%, Oxybenzone 6%; b) Avobenzone 2%, Octocrylene 8%, Oxybenzone 3%; c) Avobenzone 3%, Homosalate 15%, Octisalate 5%, Octocrylene 10%, Oxybenzone 6%.

Figure 3 summarizes normalized UV spectra for a collection of polyphenolic hydroxycinnamic acids (HCAs) and octinoxate. HCAs can be thought of as derivatives of p-coumaric acids, formed by introduction of additional hydroxyl groups. Octinoxate is a very efficient, and one of the most used UVB-only commercial UV filter. Note that octinoxate is an highly alkylated derivative of p-coumaric acid; thus two compounds have the same aromatic core, and identical UV absorption profiles with $\lambda_{\max}=311$ nm. Introduction of one 3-ortho hydroxyl group (caffeic acid), or 3-ortho methoxy group (ferulic acid) leads to a shift of the UV profile in UVA II range, with $\lambda_{\max}\sim 327$ nm. The UV spectra of caffeic acid and ferulic acid exhibit two overlapping bands, covering the UVB and the UVA II region respectively. In spite of the 20% drop in molar absorption coefficients (ϵ) compared to octinoxate in the UVB region, HCAs still exhibit excellent absorption in the UVB region with $SPF\approx 12$ for both caffeic and ferulic acids. Caffeic acid, ferulic acid, and sinapic acid offer much better protection in the UVB range compared to other UVB-only filters, homosalate and octisalate, as demonstrated by their molar absorption coefficients at λ_{\max} , and SPF values (Table 1). Perhaps most significant is the excellent multiband absorption in the UVB/UVA II range between 290 nm-350 nm offered by HCAs. The critical $\lambda_c\approx 348$ nm, and UVA/UVB ≈ 1.2 -1.4 for both caffeic and ferulic acids imply excellent protection in the UVA II range, besides very efficient protection in the UVB range. By comparison octinoxate and p-coumaric acid measure UVA/UVB ≈ 0.5 and critical $\lambda_c\approx 330$ nm, which are typical of sunscreens

that offer protection only in the UVB range. Sinapic acid is a very interesting compound. Because of the presence of two methoxy groups ortho to para-hydroxyl group, the UV spectra is symmetric with $\lambda_{\max}=326$ nm. It nevertheless exhibits efficient absorption in the UVB range with high $\text{SPF}\approx 10$ comparable to caffeic and ferulic acid. Due to the symmetric spectral profile, the bulk of the UV absorption curve is more shifted towards UVA range. This is illustrated by the $\text{UVA/UVB}=1.39$ and critical $\lambda_c=349$ nm, which means sinapic acid offers even better protection in the UVA II range compared to caffeic and ferulic acid.

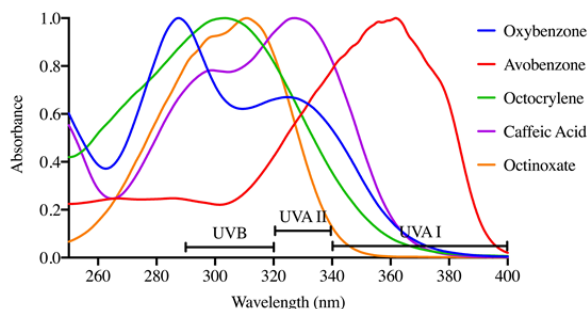


Figure 4. Normalized UV spectra of commercial filters and caffeic acid.

The sun protection parameters of *o*-coumaric acid and *m*-coumaric acid do not compare well with the values of their isomer *p*-coumaric acid, or any of the HCAs, ferulic acid, caffeic acid, and sinapic acid. However, SPF and ϵ values of *o*-coumaric acid, and *m*-coumaric acid compare well with those of homosalate and octisalate. In addition *o*-coumaric acid could provide UVA II coverage, as shown by its $\text{UVA/UVB}=1.28$ and critical $\lambda_c=349$ nm.

Commercial sunscreens use a combination of oxybenzone and octocrylene to provide UVB/UVAII protection. Usually octinoxate and avobenzone are added to provide UVB-only and UVA-only protection respectively. In Figure 4, we have superimposed the normalized UV spectra of these four, very common, commercial UV filters with the spectrum of caffeic acid. Caffeic acid, ferulic and sinapic acid, absorb UV solar radiation more efficiently than oxybenzone and octocrylene, in the UVA region as demonstrated by their higher critical λ , UVA/UVB ratios and molar absorption coefficient (ϵ) at λ_{\max} , as well as in the UVB region as demonstrated by higher SPF and ϵ values. Finally we calculated the SPF values, UVA/UVB ratios, and critical λ_c of three broadband commercial sunscreens, which use a combination of at least 3 synthetic UV filters to achieve broadband protection in the UVB/UVA range. The SPF by Mansur is consistent with the % concentrations of the UV filters contained in the sunscreen. It is obvious that avobenzone is absolutely necessary to provide broadband protection deep in the UVA region, according to the FDA established threshold of $\lambda_c \geq 370$ nm. All three commercial sunscreens use combinations of avobenzone with octocrylene or oxybenzone to provide broadband protection in the UVB/UVAII range, where the avobenzone coverage is limited. The bulk of UVB protection is provided by a combination of octinoxate, octisalate, and homosalate. The UVA/UVB ratio of 1.11-1.6 for three tested sunscreens is similar to that of sinapic acid, ferulic acid, and caffeic acid. Note the SPF value any of the sunscreens could be easily achieved by using one, or a combination of HCAs.

CONCLUSION

Due to health and environmental concerns, there is a need to minimize the use of synthetic active ingredients such as UV filters and antioxidants in sunscreen formulations. Biodegradable active ingredients of natural origin could be

used as health-conscious alternative to synthetic active ingredients. HCAs, such as caffeic acid, ferulic acid, and sinapic acid, are naturally occurring antioxidants, with known beneficial medicinal properties. Our UV spectroscopy analysis of sun protection values indicate that either one of caffeic acid, ferulic acid, or sinapic acid could be capable of providing an excellent protection against UVB/UVA solar radiation, comparable or better than a combination of commercial UV filters, octinoxate, oxybenzone, octocrylene, octisalate, and homosalate. Therefore, HCAs would be ideal lead compounds to start a search for truly multifunctional UV filters in the broadband UVB/UVA region, with simultaneous antioxidant capabilities. HCAs are not particularly soluble in either aqueous or oil phase. Work needs to be done to produce non-toxic alkylated derivatives of HCAs that are easily emulsified, and can be incorporated in high % concentrations, which are typical of sunscreen formulations.

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