Article

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Evaluation of Photosensitizing Ability of Antioxidants Used in Skincare Products

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Abstract. Singlet oxygen generation is possible by photosensitizer molecules able to absorb energy from light and transfer it to molecular oxygen. Singlet oxygen is able to react with components of cellular membranes such as cholesterol leading to peroxidation products implicated in photoaging. In order to prevent oxidative damage caused by reactive oxygen species, skincare products enriched with antioxidants have been developed; in spite of some pro-oxidant effects associated with antioxidants has been reported. Based on this data, the photosensitizing ability of 14 antioxidants commonly used in skincare products was evaluated through the photo-oxidation of ergosterol, using ergosterol as oxidizable substrate to quench singlet oxygen. Singlet oxygen indirectly detection was performed through ^{1}H-NMR mixtures analysis by ergosterol peroxide detection. The results revealed that fisetin, retinol, cyanidin and hesperetin they acted as photosensitizer antioxidants in generation of singlet oxygen. Conversely, caffeic acid, luteolin, rutin, vanillic acid, ascorbic acid, apigenin, epigallocatechin gallate, rosmarinic acid, myricetin and kaempferol were not able to generate singlet oxygen through a photosensitized mechanism. Our results allow us to suggest that the incorporation of antioxidants in skincare products as anti-aging treatments should be supported by their evaluation against photosensitizing ability in order to increase their safety.
Keywords: Antioxidants; singlet oxygen; photosensitizing ability; photo-oxidation of ergosterol.

Resumen. La generación del oxígeno singulete es posible a través de moléculas fotosensibilizadoras capaces de absorber energía proveniente de la luz y transferirla al oxígeno molecular. El oxígeno singulete es capaz de reaccionar con componentes de membranas celulares como el colesterol formando productos de peroxidación implicados en el foto-envejecimiento. Para prevenir el daño oxidativo causado por especies reactivas del oxígeno, se han desarrollado productos para el cuidado de la piel enriquecidos con antioxidantes, a pesar de que han sido reportados algunos efectos prooxidantes asociados a los antioxidantes. Con base en lo anterior, se evaluó la capacidad fotosensibilizadora de 14 antioxidantes comúnmente utilizados en productos para el cuidado de la piel mediante la foto-oxidación de ergosterol, utilizando ergosterol como sustrato oxidable para atrapar oxígeno singulete. La detección indirecta del oxígeno singulete se realizó mediante análisis de mezclas de RMN-^{1}H a través de la detección de peróxido de ergosterol. Los resultados mostraron que fisetina, retinol, cianidina y hesperetina actuaron como antioxidantes fotosensibilizadores en la generación de oxígeno singulete. Por el contrario, ácido cafeico, luteolina, rutina, ácido vainillínico, ácido ascórbico, apigenina, galato de epigalocatequina, ácido rosmarínico, miricetina y kaempferol no fueron capaces de generar oxígeno singulete mediante mecanismos fotosensibilizados. Los resultados permiten sugerir que la incorporación de antioxidantes en productos para el cuidado de la piel como tratamiento anti-envejecimiento debe respaldarse con la evaluación de la capacidad fotosensibilizadora para incrementar su seguridad.
Palabras clave: Antioxidantes; oxígeno singulete; capacidad fotosensibilizadora; foto-oxidación de ergosterol.

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Introduction

Constant exposure to solar radiation entails negative skin effects induced by reactive oxygen species (ROS) formation as singlet oxygen ($^1O_2$). $^1O_2$ is the first excited state of molecular oxygen ($^3O_2$) and can be endogenously generated in biological systems through photochemical reactions type II, where UVA/UVB radiation as well as visible light can convert photosensitizer molecules into excited states that transfers absorbed energy to $^3O_2$ to generate $^1O_2$ [1,2]. Of the total solar energy able to reach the earth´s surface, 6.8 % corresponds to UV light, 38.9 % to visible light and 54.3 % to near infrared light [3]. Likewise, from UV light, more than 50 % of UVA can penetrate the dermis, whereas only 14 % of UVB light reaches the epidermis, thereby photochemical generation of $^1O_2$ in the skin is possible due to the presence of endogenous photosensitizer molecules such as porphyrins, bilirubin, B_6 vitamers and vitamin K [2,4]. $^1O_2$ is the predominant ROS from type II reactions that is able to react with nucleic acids, unsaturated lipids and aminoacids to yield endoperoxides from [2 + 4] cycloadditions, dioxetanes from [2 + 2] cycloadditions and hydroperoxides from "ene" reactions [5,6].

In recent years due to multiple benefits attributed to natural antioxidants, the cosmetic and dermatology industry has focused on the development of skincare products such as anti-aging creams or sunscreens enriched with antioxidants in order to prevent oxidative damage caused by ROS [7–9]. In this sense, the term antioxidant has been defined as any substance that delays, prevents or removes oxidative damage to a target molecule [10]. Antioxidants can react by depleting molecular oxygen or decreasing its local concentration, removing pro-oxidative metal ions, trapping aggressive reactive oxygen species such as superoxide anion radical or hydrogen peroxide, scavenging chain-initiating radicals like hydroxyl (HO•), alkoxyl (RO•) or peroxyl (ROO•), breaking the chain of a radical sequence or quenching $^1O_2$ [11]. However, increasingly researches have reported pro-oxidant activities of antioxidants such as resveratrol and quercetin [12–14]. Likewise, we previously reported the photosensitizing ability to generate $^1O_2$ of curcumin, resveratrol and quercetin identified through the photo-oxidation of ergosterol method [15]. Also, through this method, the photosensitizing ability of cosmetic colorants to generate $^1O_2$ and the membrane cell damage caused by two of the nine cosmetic colourants evaluated has been reported [16,17]. Furthermore, we recently reported on the pro-oxidant effect of five synthetic hydroxycoumarin-based antioxidants by acting as photosensitizers in $^1O_2$ generation [18]. Therefore, the present study was aimed to determine whether natural antioxidants commonly used in the development of skincare products are able to generate $^1O_2$ by acting as photosensitizing molecules in the photo-oxidation of ergosterol reactions.

Experimental

Reagents

Fisetin, retinol, cyanidin, hesperetin, luteolin, rutin, L-ascorbic acid, apigenin, epigallocatechin gallate, myricetin, kaempferol, ergosterol, eosin yellowish, sodium azide (NaN_3) were purchased from Sigma-Aldrich (Corp., St. Louis, Mo., U.S.A.). Caffeic acid, vanillic acid and rosmarinic acid were kindly provided by Prof. Zaira Domínguez from the Universidad Veracruzana. Distilled ethanol, analytical grade was employed as a solvent in photo-oxidation reactions.

Photo-oxidation of ergosterol

Ergosterol was used as $^1O_2$ chemical trap in the determination of the photosensitizing ability through reactions of the photo-oxidation of ergosterol. 14 antioxidants were tested: Fisetin (**1**), retinol (**2**), cyanidin (**3**), hesperetin (**4**), caffeic acid (**5**), luteolin (**6**), rutin (**7**), vanillic acid (**8**), ascorbic acid (**9**), apigenin (**10**), epigallocatechin gallate (**11**), rosmarinic acid (**12**), myricetin (**13**) and kaempferol (**14**) (Fig. 1). For each reaction, 1 mM ergosterol and 144 μM antioxidant (initial concentration) was prepared in ethanol [15]. The solution was placed inside a photo-oxidation camera and irradiated (four compact fluorescent lamps) during 2 h under continuous oxygen flux (medicinal grade oxygen, flux rate: 75 mL/s), bubbled using a stainless-steel filter (10 μm HPLC filter). The light intensity was 19623 ±129 lux (YK-10LX light meter). The temperature inside the photo-oxidation camera was 32 °C ± 2. In order to establish reference controls, the photo-oxidation reaction by adding

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eosin yellowish 144 μM was established as positive control (+) and the reaction without a photosensitizer dye as negative control (−). Sodium azide (1 mM) was used to confirm $^1O_2$ generation in photo-oxidation reactions.

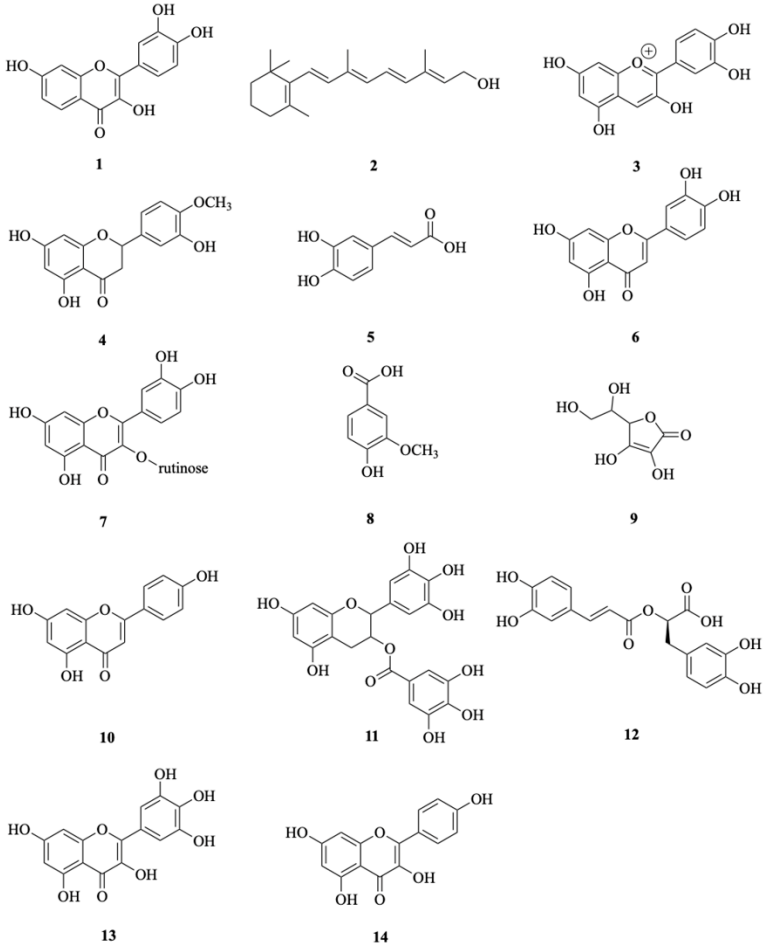

Fig. 1. Tested antioxidants through photo-oxidation of ergosterol.

Determination of singlet oxygen by nuclear magnetic resonance

Indirect detection of $^1O_2$ generation was made by proton Nuclear Magnetic Resonance (^{1}H-NMR) recorded on a Bruker Avance HD III spectrometer (500 MHz) and Agilent DD2 500 MHz spectrometer for NaN_3 reactions, using $CDCl_3$ as solvent and TMS as an internal reference. Ergosterol traps $^1O_2$ to form ergosterol peroxide. Both sterols were detected by ^{1}H-NMR mixtures analysis based on the comparison of integrals of vinyl signals of H-6 and H-7 protons of ring B of ergosterol ($\delta_{H\text{-}6}$= 5.57 ppm, dd, 1H; $\delta_{H\text{-}7}$= 5.38 ppm, dd) and ergosterol peroxide ($\delta_{H\text{-}6}$= 6.50 ppm, d, 1H; $\delta_{H\text{-}7}$= 6.25 ppm, d). Once these signals were identified, integration values were obtained from which the conversion ratio of ergosterol into ergosterol peroxide (E:EP) was calculated. This ratio was also calculated for the positive and negative controls.

Antioxidants classification was established taking into reference the E:EP conversion ratio from the negative control. Therefore, antioxidants used in photo-oxidation reactions where the ratio conversion E:EP was higher than the negative control were considered as photosensitizer antioxidants in the generation of $^1O_2$. Conversely, antioxidants used in photo-oxidation reactions where the ratio conversion E:EP was lower than the negative control were considered as antioxidant quenchers of $^1O_2$. MestReNova software (v6.0.2-5475) was used in ^{1}H-NMR analysis and data processing.

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Results and discussion

$^1O_2$ generation was quantified by ^{1}H-NMR mixtures analysis through the identification of ergosterol peroxide (**EP**), an oxidation product of ergosterol (**E**) formed through a Diels-Alder reaction between $^1O_2$ and a conjugate diene system of B ring of ergosterol. Indirect detection of $^1O_2$ through photo-oxidation of ergosterol reactions allowed us to establish the photosensitizing ability of four out of fourteen screened antioxidants: fisetin (**1**), retinol (**2**), cyanidin (**3**), hesperetin (**4**). Thereby, two double signals at 6.50 and 6.25 ppm attributed to H-6 and H-7 protons from **EP** were identified in the ^{1}H-NMR spectra, also two double-double signals attributed to H-6 and H-7 protons from **E** were observed at 5.57 and 5.38 ppm, respectively (Fig. 2). The E:EP conversion ratio was calculated from integration data of this signals and was also expressed as a percentage. Thus, the results obtained from photo-oxidation reactions carried out with **1** and **2** converted 20 % of **E** into **EP** and **3** and **4** allowed a 9 % of EP formation (Table 1). This suggests that fisetin, retinol, cyanidin and hesperetin were able to generate $^1O_2$ through a photosensitized mechanism because the **EP** quantity detected was higher than negative control (5 %).

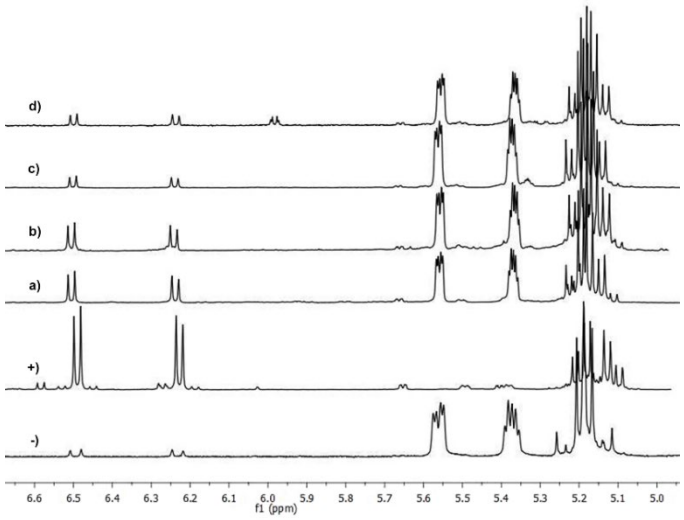

Fig. 2. ^{1}H-NMR spectra of mixtures reaction obtained from photo-oxidation reactions carried out with **(a)** fisetin, **(b)** retinol, **(c)** cyanidin and **(d)** hesperetin. Control (−): reaction without photosensitizer, Control (+): reaction with eosin yellowish as photosensitizer.

Table 1. Conversion ratio of Ergosterol into Ergosterol peroxide (E:PE) calculated from ^{1}H-NMR-signals assignment of H-6 and H-7.

Antioxidant	**Ergosterol**		**Ergosterol peroxide**		**Conversion E:EP**	
	∫ H-6	∫ H-7	∫ H-6	∫ H-7	Ratio	EP Percentage
Control (−)	18H	18H	1H	1H	18:1	5
Control (+)	NS	NS	1H	1H	0:1	100
Fisetin	4H	4H	1H	1H	4:1	**20**
Retinol	4H	4H	1H	1H	4:1	**20**

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Cyanidin	10H	10H	1H	1H	10:1	**9**
Hesperetin	10H	10H	1H	1H	10:1	**9**
Caffeic acid	177H	181H	1H	1H	179:1	1
Luteolin	146H	151H	1H	1H	148:1	1
Rutin	129H	138H	1H	1H	133:1	1
Vanillic acid	191H	203H	1H	1H	133:1	1
Ascorbic acid	76H	77H	1H	1H	76:1	1
Apigenin	62H	64H	1H	1H	63:1	2
Epigallocatequin gallato	51H	52H	1H	1H	52:1	2
Rosmarinic acid	42H	44H	1H	1H	43:1	2
Myricetin	26H	26H	1H	1H	26:1	4
Kaempferol	20H	20H	1H	1H	20:1	5

∫: integration values; NS: no signal detected.

Additionally, in order to confirm the presence of $^1O_2$, photo-oxidation of ergosterol reactions with fisetin, retinol, cyanidin and hesperetin were carried out adding sodium azide (1 mM) as specific quencher of $^1O_2$. After the reaction time, a substantial reduction in the quantity of **EP** generated during photo-oxidation reactions was observed (Fig. 3).

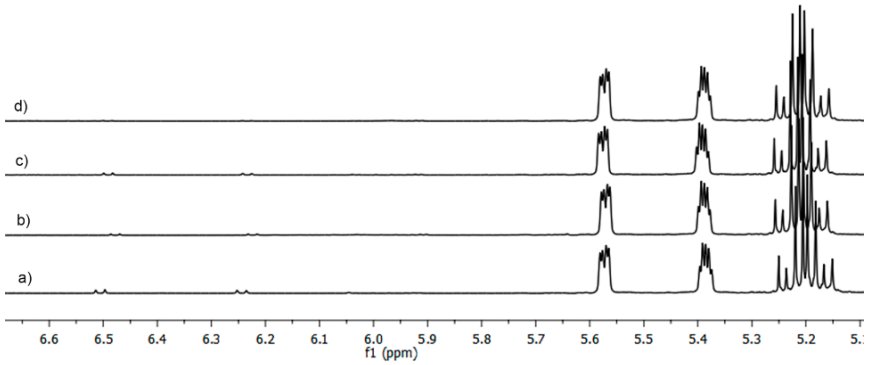

Fig. 3. ^{1}H-NMR spectra of mixtures reaction carried out with **(a)** fisetin, **(b)** retinol, **(c)** cyanidin, **(d)** hesperetin plus NaN_3 (1 mM).

On the other hand, signals attributed to **EP** were barely detected in the ^{1}H-NMR spectra of the remaining antioxidants tested, while signals corresponding to **E** were clearly visible (Fig. 4). Thus, the E:EP conversion ratios obtained were lower than negative control in photo-oxidation reactions carried out with caffeic acid (**5**), luteolin (**6**), rutin (**7**), vanillic acid (**8**) and ascorbic acid (**9**), in which only a 1 % of **EP** was formed. In a similar way, the E:EP conversion ratios in photo-oxidation reactions carried out with apigenin (**10**), epigallocatechin gallate (**11**) and rosmarinic acid (**12**) allowed the formation of 2 % of **EP**. Finally E:EP conversion ratios similar to the 5 % of **EP** detected in the negative control were obtained in photo-oxidation reactions carried out with myricetin (**13**) and

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kaempferol (**14**)(Table 1). Therefore, because of the **EP** quantity detected in photo-oxidation reactions was ≤ 5 % (negative control), we can assume that they were not able to generate $^1O_2$ through a photosensitized mechanism thereby they were considered as antioxidants able to quench $^1O_2$.

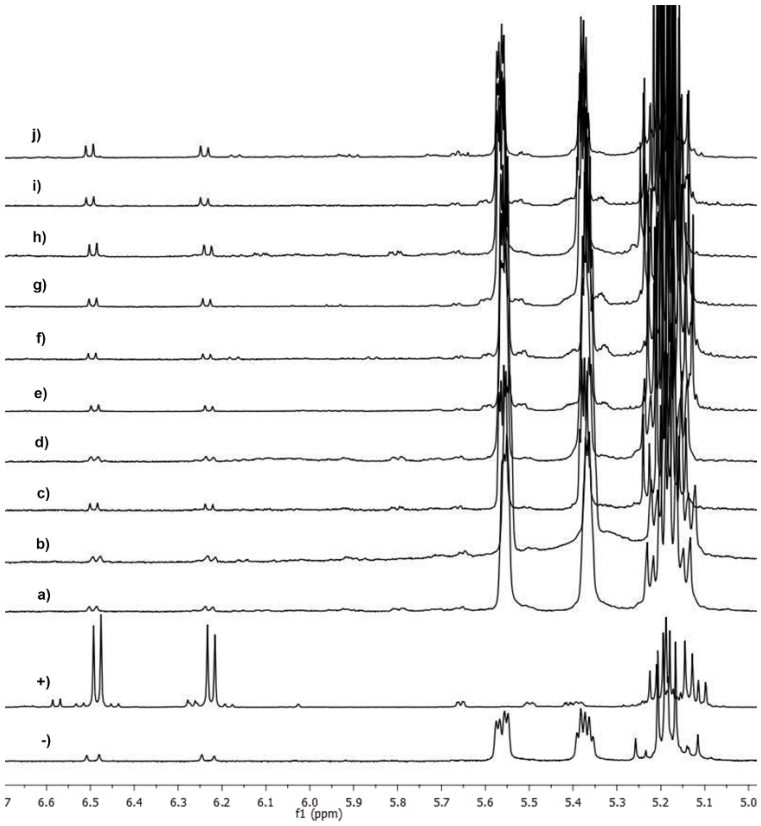

Fig. 4. ^{1}H-NMR spectra of mixtures reaction obtained from photo-oxidation reactions carried out with **(a)** caffeic acid, **(b)** luteolin, **(c)** rutin, **(d)** vanillic acid, **(e)** ascorbic acid, **(f)** apigenin, **(g)** epigallocatechin gallate, **(h)** rosmarinic acid, **(i)** myricetin, **(j)** kaempferol. Control (−): reaction without photosensitizer, Control (+): reaction with eosin yellowish as photosensitizer.

Identification of compounds with the ability to photosensitize the generation of $^1O_2$ should be considered an important issue owing to the fact that the presence of $^1O_2$ in cells is related to skin photoaging. Cholesterol peroxidation can be caused through ene-reaction between $^1O_2$ and the cholesterol double bond in carbons 5 and 6 to form cholesterol 5α-hydroperoxide, as the major product and cholesterol 6α/β-hydroperoxide as the minor products [19]. The significance of cholesterol peroxidation products in photoaging has been clearly established because a mixture of cholesterol 5-hydroperoxide and cholesterol 7-hydroperoxide induces the activation of matrix metalloproteinase-9 (MMP-9), a protein implicated in collagen degradation. Loss of collagen in the skin results in wrinkles appearing and sagging skin, a hallmark associated with skin photoaging [20]. Several researches have shown the efficient antioxidant, anti-inflammatory and anti-aging activity of fisetin [21,22], retinol [23], cyanidin [24] and hesperetin [25], however our results show that under specific conditions they are able to act as photosensitizer compounds in photochemical reactions and stimulate the generation of $^1O_2$. Hence, the evaluation of the photosensitizing ability of compounds used in skincare formulations should be considered an important issue by the dermatology and cosmetic industry.

Concerning antioxidants that show ability to quench $^1O_2$, several researches have reported, not only on their anti-inflammatory, anti-aging and free radical scavenging properties but also their ability to provide a

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protector effect against UVA/UVB-induced skin damage [26–30]. Likewise, no phototoxic effect has been reported on caffeic acid and rutin [31]. Therefore, the ability to quench $^1O_2$ added to all the beneficial properties reported for caffeic acid, luteolin, rutin, vanillic acid, ascorbic acid, apigenin, epigallocatechin gallate, rosmarinic acid, myricetin and kaempferol, allow us to suggest that they could be considered as promising compounds to diminish, prevent or avoid skin photoaging caused by $^1O_2$.

Through the photo-oxidation of ergosterol, the photosensitizing ability of antioxidant compounds was evidenced. Thus, fisetin, retinol, hesperetin and cyanidin aside from their antioxidant activity could show a pro-oxidant effect caused by $^1O_2$. Moreover, the identification of antioxidant compounds with the ability to quench $^1O_2$, was seen to be possible because they provided protection to ergosterol against oxidation caused by $^1O_2$. Consequently, the results obtained allow us to increase the antioxidant classification based on their activity against $^1O_2$ as we previously proposed [15]. Therefore, we suggest that caffeic acid, luteolin, rutin, vanillic acid, ascorbic acid, apigenin, epigallocatechin gallate, rosmarinic acid, myricetin and kaempferol can be classified as type 1 antioxidants: antioxidant quenchers of $^1O_2$; and fisetin, retinol, hesperetin and cyanidin as type 2 antioxidants: photosensitizer antioxidants in generation of $^1O_2$.

Conclusions

Antioxidants provide several health benefits. However, the endogenous generation of $^1O_2$ through photosensitized mechanisms joined to non-photosensitized mechanisms could increase the presence of $^1O_2$ in an organism, which can cause damage to cell membrane components and induce skin photoaging. Hence the incorporation of antioxidants in skincare products as anti-aging treatments or sunscreens should be supported by a previous evaluation of their photosensitizing ability in order to increase their safety.

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