



A comparative review of natural and synthetic UV filters: Gadusol and benzophenone-3 as representative examples

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ABSTRACT

The need for extra protection to mitigate the harmful effects of ultraviolet (UV), such as direct or indirect DNA damage, has become of great importance in the last decades. Synthetic photoprotectors, commonly used in sunscreen formulations, are associated with a large number of genotoxic, photoallergic, and environmental problems. Thus, the interest of both scientific research and industry has notably increased, aiming to advance in new developments that will improve effectiveness, minimizing detrimental effects. Nevertheless, due to the high benefit-risk ratio of synthetic photoprotectors, there is still a dilemma between either continuing their use or replacing them with more sustainable alternatives. In this regard, natural photoprotectors emerged as promising substitutes to synthetic ones, although they cannot usually be obtained on a large scale, and do not always represent an adequate option. Most of the scientific literature is biased towards natural or synthetic photoprotectors, and therefore a rigorous comparison between them is necessary to access a more accurate and critical view. In this work, a comprehensive one-to-one comparison was made between benzophenone-3 (oxybenzone) and gadusol, chosen as representative models of synthetic and natural photoprotectors, respectively. The review of their physicochemical properties allows an in-depth understanding of their behavior under UV solar radiation exposure and their environmental fate. Even though synthetic sunscreens cannot be completely replaced by natural ones immediately, the information provided in this work seeks to set a starting point for studies that aim the development of more efficient sunscreens.

1. Introduction

It is undeniable that solar radiation is essential to sustain life on Earth and human life, as we know it, would not be possible without the heat and light from the Sun. However, the Sun emits ultraviolet (UV) radiation that can cause damage to health, ecosystems, and materials (Dantas Mota et al., 2019). While hazardous UVC photons (< 280 nm) are mostly absorbed by the atmosphere, dangerous levels of UVB (280–320 nm) and UVA (320–400 nm) radiation reach the surface of the planet. Living organisms have developed their own photoprotection mechanisms to minimize UV-induced detrimental effects. In humans, the interaction

with the outermost tissue, the skin, is the first line of defense against incoming radiation (Biniek et al., 2012). It is well-documented that long-term exposure to UV photons causes sunburns, photoaging, and skin cancer (D'Orazio et al., 2013). UVA photons are predominant in the UV distribution of solar radiation and can reach deeper skin layers, where they generate reactive oxygen and nitrogen species (ROS and RNS, respectively) which damage nucleic acids (DNA) and proteins via indirect photosensitizing reactions that contribute to photoaging. UVB photons are less abundant but can be directly absorbed by DNA, causing mutations that may be either naturally repaired or may induce cancer (Meinhardt et al., 2008, Hiraku et al., 2007).

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Effective photoprotection against UV radiation has become of great importance to humans. Changes in human lifestyle and longer lifetimes increase the cumulative exposure to solar radiation, and both skin aging and skin cancer became major health problems today. In this context, the need for extra protection is evident as a way to avoid the adverse effects of increasing levels of UV radiation. Minimizing the incidence of sunlight by covering the skin with clothes is one of the possibilities (Modenese et al., 2018). However, it should be considered that moderate UV exposure is essential for different biological processes. The use of topical formulations that incorporate synthetic (artificial) sunscreens such as UV filters in a cosmetic preparation seems to be the widest applied solution (Fig. 1).

Despite scientific and technological advances, photoprotection is a complex and dynamic field, where the safety and efficacy of sunscreens are currently subject to debate. Besides, the need for education of the general public to promote proper photoprotective behaviors is a priority (Wang and Lim, 2016, Losantos et al., 2017, Sondenheimer and Krutmann, 2018, Shaath, 2010). Current active research also aims to enhance the protection from visible and IR radiation, as well as evaluating the application of antioxidants, DNA repair enzymes, and nanotechnology (Sondenheimer and Krutmann, 2018). Even more, today the analysis must be necessarily extended to the environmental dimension.

Upon the massive use of topical sunscreens, it becomes crucial considering the multiple ways of impact that commercial photoprotective agents will have on the planet. Apart from protecting us from the damages that UV radiation causes, a good sunscreen should be non-toxic to the ecosystems, i.e., bacteria, algae, fungi, plants, and animals, which may come into contact with it. In this context, beyond their toxic potential, it definitely counts the manner sunscreens will be produced, utilized, and disposed after use (Labille et al., 2020).

On this basis, some artificial UV filters are nowadays pointed out as emerging pollutants (Tovar-Sánchez et al., 2013, Downs et al., 2022). Among the most common ones, benzophenone-3, avobenzone, octocrylene, and octinoxate are receiving growing attention regarding their impacts on the health of living organisms and the environment (Nohynek and Schaefer, 2001, Zhong et al., 2020). Genotoxic effects have been found in some fish, mammals, and corals. Considering the pseudo-persistent character of these contaminants, even when the concentrations found in fish are usually low, it is necessary to take into account the effects of bioaccumulation and biomagnification, together with the continuous release to the environment (Kim and Choi, 2014, Downs et al., 2016, Schneider and Lim, 2019, Santamaria et al., 2020). Notably, the level of benzophenones in biota is comparable to the presence of other persistent pollutants such as polychlorinated

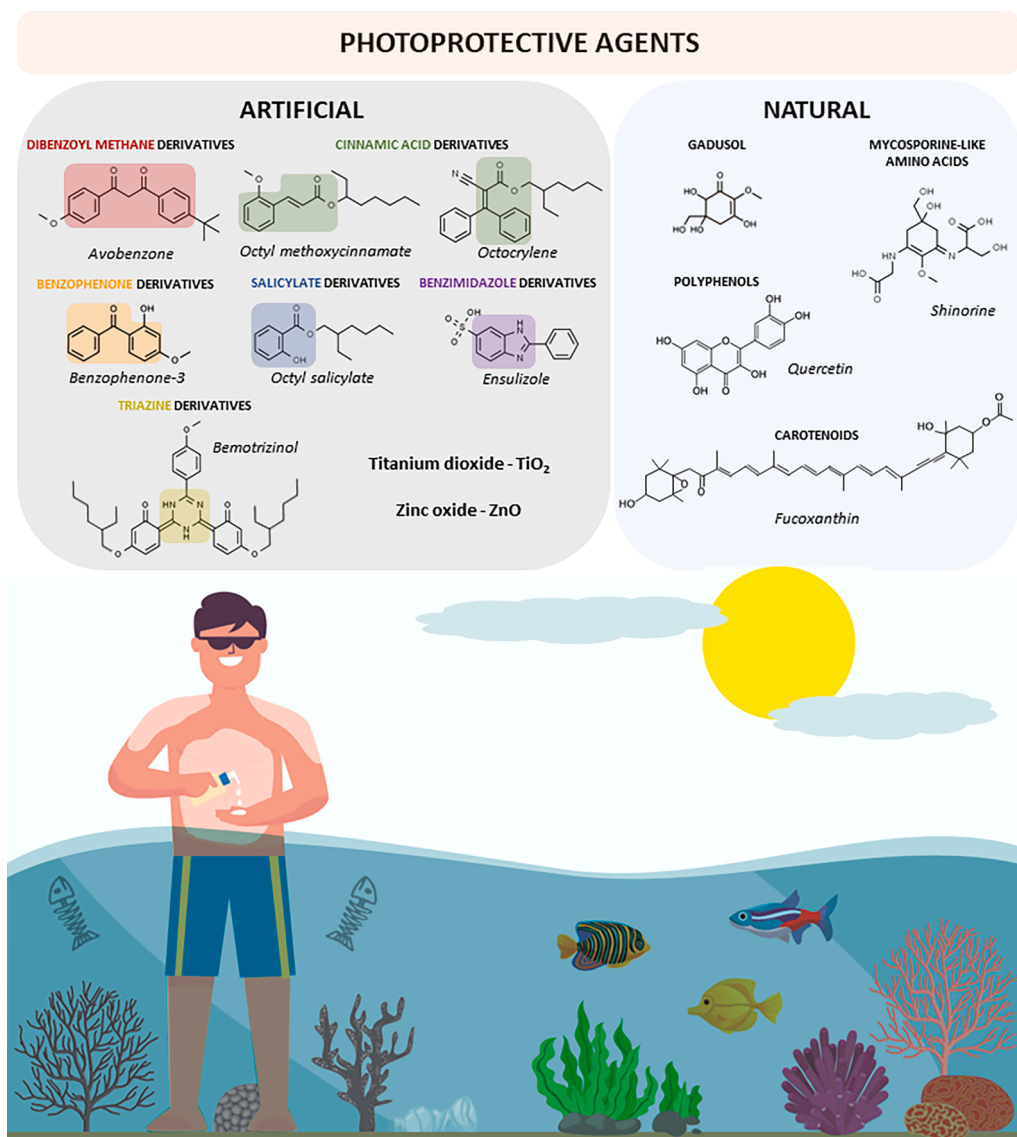


Fig. 1. Relevant types of artificial and natural photoprotective compounds and the chemical structures of representative examples.

biphenyls (PCBs) banned decades ago (Silvia Díaz-Cruz et al., 2008). As a consequence, benzophenone-3 and octinoxate, two of the most commonly used photoprotective ingredients in sunscreen formulations, are now banned in several island jurisdictions (Miller et al., 2021).

On the other hand, the most widely used inorganic photoprotective agents, ZnO and TiO₂, have not shown significant impact on human health, although potential risk of carcinogenesis by inhalation has been demonstrated in animal models (Schneider and Lim, 2019). Since they are usually incorporated in sunscreens formulations in particle sizes under 100 nm, the main concern regarding ZnO and TiO₂ is their ability to penetrate the dermis and finally reach the bloodstream, carrying oxidative stress and cellular toxicity (Osmond and McCall, 2010, Grande and Tucci, 2015, Sharma et al., 2019). These hypotheses are currently held in a somewhat controversial focus since the USA-FDA establishes both compounds as safe photoprotectors to be used, but the International Agency for Research on Carcinogens has classified TiO₂ as a possible carcinogen when inhaled at high doses (Schneider and Lim, 2019). Botta et al. (2011) estimated an average content of nano-TiO₂ of approximately 4.6% on sunscreens formulations, and a release of

36-56 tons of nano-TiO₂ residues from sunscreens in reef areas. As a matter of fact, this is a very low quantity in comparison with the 4,000–6,000 tons per year of organic UV filters released in reef areas (Danovaro et al., 2008). Still, it remains significant and it should be considered for the life cycle assessment of these nanomaterials.

In this scenario, natural UV filters appear as a promising alternative based on a large number of natural compounds which show good performance as active ingredients of sunscreens or are currently being studied regarding potential photoprotective applications (Fig. 1) (Ngoc et al., 2019, Morabito et al., 2011, Saewan and Jimtaisong, 2015, Amador Castro et al., 2020). Natural photoprotective substances include various secondary metabolites present in plants, animals and microorganisms. A key point regarding natural UV filters is that most of these compounds already work as efficient photoprotectors in the living organisms where they are found, and contribute with additional antioxidant properties in many cases (Amador Castro et al., 2020, Cefali et al., 2019, Li et al., 2022). Among them, polyphenols such as flavonoids from plants absorb intensively with broad bands, generally within 280 and 400 nm, due to the presence of aromatic or conjugated bond structures

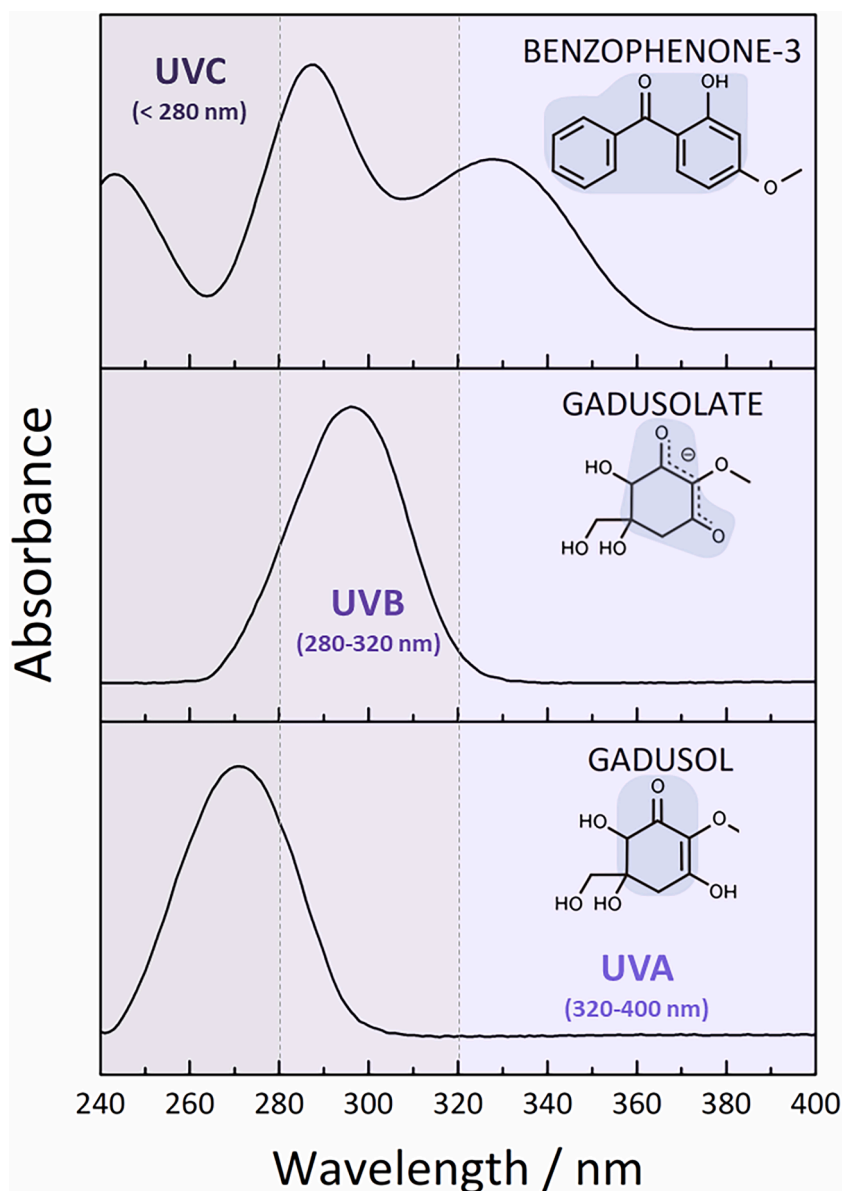


Fig. 2. Absorption spectra of selected UV filters. Benzophenone-3 in methanol (upper panel), anionic gadusol in water- pH 7 (middle panel), gadusol in water - pH 2.5 (lower panel). Chromophores are indicated with a blue shade over the chemical structures.

(Cefali et al., 2019, Li et al., 2022). Marine metabolites such as mycosporine-like amino acids (MAAs), consisting of cyclohexenone or cyclohexenimine cores attached to amino acid groups (see the example of shinorine in Fig. 1), typically offer an intense absorption in the UVA portion of the solar spectrum with maxima between 310 and 360 nm (Amador Castro et al., 2020). Besides, structurally and biosynthetically related gadusols present a strong band in the UVB or UVC, depending on pH (see Fig. 2) (Grant et al., 1980, Plack et al., 1981). Another prominent class of photoprotective molecules in nature involves carotenoids occurring in plants, bacteria, fungi, and algae. Their polyisoprenoid structure results in a long conjugated chain of double bonds absorbing in the visible, but they can exert photoprotective activity through efficiently scavenging singlet molecular oxygen and peroxy radicals generated by photosensitization (Britton, 1995, Sies and Stahl, 2004).

It is worth noting that negative effects of these natural molecules on human health are usually not found and their use is in line with the new tendencies of the cosmetic industry in response to the demands of consumers who are increasingly aware of the preservation of the environment and sustainable development (Morabito et al., 2011, Thompson et al., 2021, Fortunati et al., 2020, Fernandes et al., 2015).

Still, current biotechnological obstacles limiting the commercial exploitation of natural UV filters are found around obtaining them in large quantities (Pandika, 2018). An emerging practice, that ensures in addition sustainability and socioeconomic benefits, is the recovery of molecules of interest from agro-industrial residual biomass, to achieve their conversion into bioactive and functional ingredients for their further use in cosmetics, as well as in other industries (Fröhlich and Steinbiß, 2021). For example, waste from fishing industry can provide gadusol, a metabolite detected in marine teleost fishes that effectively protect embryos from sun damage (Shimizu and Satsuma, 2011) and generally occurs in fish roes and eyes (Grant et al., 1980, Plack et al., 1981, Arbeloa et al., 2010, Guedes et al., 2022, Bandaranayake, 1998). More recently, the photoprotective and antioxidant properties of gadusol have prompted efforts directed to the large-scale production of this molecule by genetic engineering, for possible uses in pharmaceuticals and cosmetics (Osborn et al., 2015, Sondenheimer and Krutmann, 2018).

An alternative and easy approach to overcome the yield limitations at the industrial level involves combinations of natural and synthetic photoprotective components. This in turn contributes to reducing the adverse impact of synthetic UV filters on human health and ecosystems by decreasing their minimum effective concentration in the formulations (Thompson et al., 2021, Chiari et al., 2014, Mota et al., 2019). Furthermore, in addition to the UV-absorbing properties, most natural compounds include antioxidant, anti-inflammatory, and immunomodulatory properties (Saewan and Jimtaisong, 2015, Chiari et al., 2014, Mota et al., 2019, Arianto et al., 2019), leading to an extended package of advantageous uses. Also, the combination of inorganic (*i.e.* ZnO, TiO₂) and natural photoprotectors may result in a synergistic effect in the sun protection factor (SPF) values (Choquet et al., 2008). In any case, the potential interactions between the UV filters components combined in a given formulation should be verified for the sake of safety and efficiency related to instabilities or the production of reactive harmful species (Lhiaubet-Vallet et al., 2010).

In summary, the concern raised around the environmental and health impacts of synthetic UV absorbers has stimulated the search and discussion about readily available sustainable choices (Egambaram et al., 2020, Pawlowski and Petersen-Thiery, 2020). UV filters from natural resources show good potential but their incorporation is not straightforward and still represents a challenge with respect to technological viability and competitiveness (Saewan and Jimtaisong, 2015, Amador Castro et al., 2020).

Generally, when contrasting natural and synthetic photoprotectors, the conclusion about which is the best option is far from obvious, and integral deep analyses, involving the physicochemical and mechanistic approaches, appear as unavoidable. Multiple factors need to be taken

into account to evaluate the UV-protective capacity together with potential effects on health and environmental safety. In this sense, Thompson et al. have recently investigated different classes of compounds with the potential to provide UV protection by following a comparative multidimensional approach that considers human and environmental safety as the main performance criteria (Thompson et al., 2021).

A comparative analysis based on the available physicochemical data of the compounds, including crucial thermodynamic and kinetic parameters that determine their behavior under sun irradiation and their environmental fate, is appropriate. We believe that this approach is not only helpful to face the inherent complexity of the task but can also illustrate the advantages of dominating the molecular basis of the photoprotective action.

Assuming the numerous choices among synthetic and natural UV filters, here we propose to evaluate the pros and cons of one representative case of each class: benzophenone-3 and gadusol. As said above, benzophenone-3 (also named oxybenzone) is a synthetic UV filter massively used in sunscreens formulations all over the world. Its negative effects on health and the environment have gained increasing visibility in recent times (Kim and Choi, 2014, Schneider and Lim, 2019, Carstensen et al., 2022). The alternative of using a naturally occurring photoprotector, such as gadusol, might become an option for its total or partial substitution, as it is being invoked lately in the context of innovation initiatives for the design and production of eco-friendly sunscreens (Nohynek and Schaefer, 2001, Zhong et al., 2020, Cole, 2014).

The focus is directed to compare the performance of the two selected organic filters, as respective archetypes of widespread and alternative active ingredients for sunscreen formulations. For this purpose, the review privileges the physicochemical properties and data on photoactivity, toxicological and environmental impact of both UV filters, as main criteria to assess efficacy and sustainability.

2. What makes a sunscreen effective?

The chemistry of sunscreens is very complex and, for this reason, a deep understanding of the interaction between solar radiation and the active compounds is necessary to obtain valuable information to improve their efficacy (Shaath, 2010). Sun screening agents work mainly through a combination of absorption, reflection, and scattering of radiation, thus preventing hazardous UV photons from reaching the skin, and dissipating the excess energy harmlessly (Cantrell et al., 2001).

Considering a typical organic sun screening agent, the general photophysical and photochemical mechanism starts with the absorption of solar radiation which promotes the molecule to an excited state (usually a singlet state) with the consequent electronic redistribution (Fig. 3). The physical deactivation of the excited state includes radiative (fluorescence) and non-radiative processes (vibrational relaxation, internal conversion, and intersystem crossing to triplet states). Triplet states are generally much longer-lived than upper singlet states, and therefore, more susceptible to intermolecular quenching (Cantrell et al., 2001). Particularly, the formation and lifetime of triplet states are of central importance concerning the efficiency of the photoprotection. This is because excited triplet states can be quenched by molecular oxygen and produce reactive oxygen species (ROS) that are harmful to living organisms. The fate of either singlet or triplet excited states includes chemical changes such as photoisomerization, photofragmentation, and photorearrangement (Tarras-Wahlberg et al., 1999).

Thus, in the first place, a good topical sunscreen product should absorb a broad range of the UV spectrum, implying both UVB and UVA protection to prevent acute and long-term potential damages. UVB protection, rated by the SPF value of the sunscreen, is critical since the action spectra for erythema and photocarcinogenesis are essentially linked to this portion of the UV. Besides, UVA radiation induces oxidative free radical damage that can lead to early skin aging and indirect damage to DNA, also associated with skin cancer risks. Protection in this

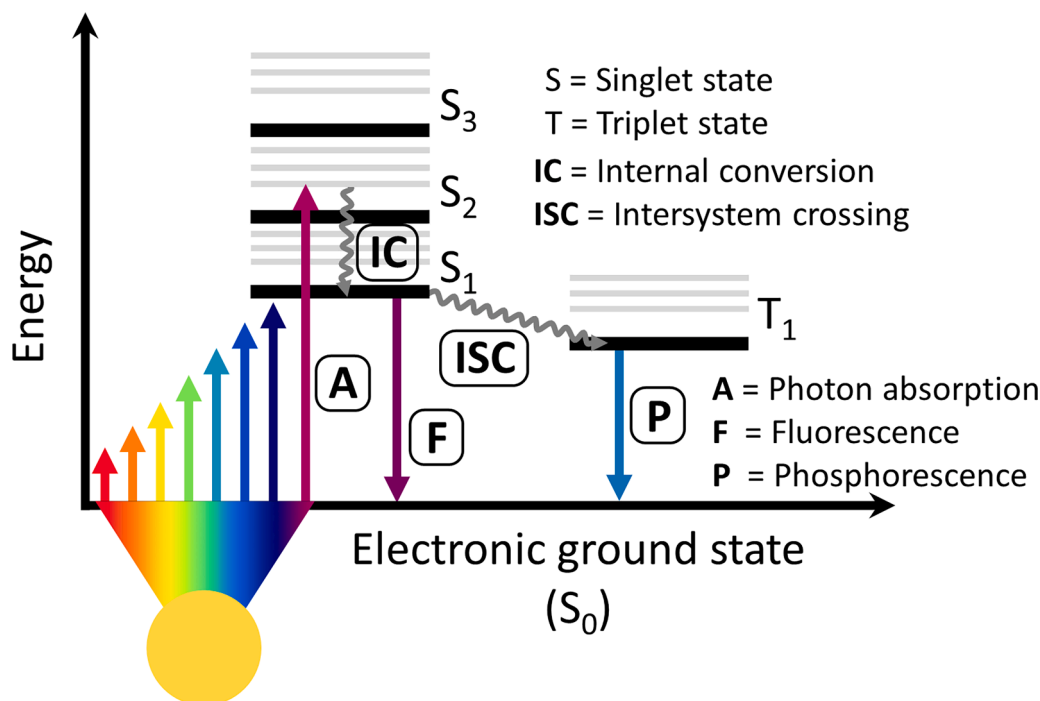


Fig. 3. Jablonski diagram illustrating electronic and vibrational energy levels and the transitions between them after photoexcitation of an organic molecule. Nonradiative transitions (internal conversion and intersystem crossing) are indicated by wavy arrows and radiative transitions (fluorescence and phosphorescence) by straight arrows.

range is assessed by *in vivo* test protocols that result in a UVA-PF or PFA protection factor value or by *in vitro* spectrophotometric measurements, such as that of the critical wavelength test (Cole, 2014).

Secondly, the optimal sunscreen must be highly photostable, meaning that there should not be modifications of the absorption spectrum or production of reactive species upon irradiation. Finally, the ideal UV photoprotector agent should undergo relaxation by efficient thermal delivery of the absorbed energy (Sohn, 2016).

3. Benzophenone-3 vs. Gadusol: comparing archetypes of UV filters

3.1. Analysis of physicochemical properties

The selected UV filters, benzophenone-3 and gadusol, represent respectively an artificial and a natural UV filter. Basic information on both organic molecules, as well as those physical and chemical parameters that are relevant for predicting the behavior of each one in the environment, and under irradiation, have been compiled and summarized in Table 1 and Fig. 4.

As indicated in Table 1, Fig. 2 (middle and lower panel) and Fig. 4 (left panel), gadusol in aqueous solution exhibits one absorption band assigned to a $\pi-\pi^*$ transition in the UVC region at acidic pH, consistently with the presence of the conjugated cyclohexenone ring chromophore (Arbeloa et al., 2011). This band shifts to the UVB and increases in intensity at higher pH. The behavior is due to the acid-base equilibrium characterized by a pKa value of 4.2 (Grant et al., 1980). The deprotonated anionic form, gadusolate, not only is the major species under physiological pH conditions but also is the most appropriate to boost the SPF value. However, the combination of gadusolate with other UVB and UVA filters might be necessary to formulate a broad-spectrum product (Cole, 2016).

Benzophenone-3 instead presents three bands within the UVC and UVA regions, as illustrated in the upper panel of Fig. 2. The two peaks at lower wavelengths are assigned to $\pi-\pi^*$ transitions, while the third one to an $n-\pi^*$ transition in the UVA. These absorptions are in consonance

with the substituted aromatic phenyl chromophores conjugated with the ketone moiety. Although the molar absorption coefficients for the bands in the UVB and UVA are lower in comparison with those of gadusol (see Table 1), they may provide better to the breadth of protection.

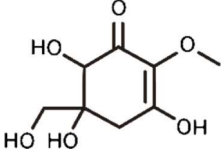
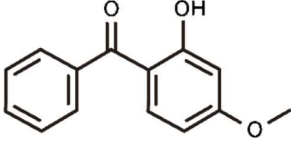
While gadusol is highly soluble in water, benzophenone-3 is not, resulting in much more lipophilic than gadusol, as verified by the value of Kow. This trend correlates with the tendency of benzophenone-3 to be retained in soil and biota, denoted by the magnitudes of Koc and BCF parameters, which are consistent with the high persistence that prompted its classification as an emerging pollutant (Nohynek and Schaefer, 2001, Zhong et al., 2020).

In terms of the suitability of oil- or water-soluble UV filters for the formulation of the sunscreen, it should be considered that different formats of delivery systems are available (emulsions, sprays, gels) which in turn should fit the intended use of the product. In this way, water-soluble UV filters such as gadusol could be acceptable for a daily moisturizer that does not require water resistance, as it does in the case of a recreational product (Cole, 2016).

Both UV filters meet the requirement of high photostability. For gadusol, this is especially achieved for the anionic form, dominating under the pHs compatible with cosmetic formulations.

The state diagrams included in Fig. 4 illustrate the main steps determining the fate of excited gadusol and benzophenone-3. It is worth noting that neither of the forms of gadusol exhibits radiative decay, as both lack fluorescence. The formation of triplet states also appears to be a rather inefficient pathway for the molecules after absorption of UV photons (indicated with full arrows/A in Fig. 4) that lead the systems to singlet excited states (S₁, S₂, and S₃, in Fig. 4). No transient signal, assignable to intermediate species, has been observed by direct laser excitation of gadusolate in solution, as verified by laser flash photolysis. However, triplet sensitization experiments revealed the ability of gadusol to deactivate triplet sensitizers ($^3\text{Sens}^*$, in Fig. 4) via reductive quenching (Arbeloa et al., 2011). This is one of the potential mechanisms underlying the antioxidant capacity of gadusol in biological environments (see below). Moreover, a thermodynamic analysis of this reactive scheme was carried out by Arbeloa et al. and indicated that

Table 1
Structural and physicochemical data on representative UV filters.

	Gadusol	Benzophenone-3	Refs.
Chemical name	3,5,6-trihydroxy-5-hydroxymethyl-2-methoxycyclohex-2-en-1-one	2-hydroxy-4-methoxybenzophenone	
Molecular formula & structure			
Molecular weight	C ₈ H ₁₂ O ₆ 204.18 g mol ⁻¹	C ₁₄ H ₁₂ O ₃ 228.25 g mol ⁻¹	
pKa	4.2	9.94 (12.1 % ETOH:H ₂ O) 9.65 (H ₂ O)	Grant et al. (1980), Li et al. (2016), Castro et al. (2003)
UV Absorption bands λ _{max}	268 nm (pH 2.5; ε = 12400 M ⁻¹ s ⁻¹) 296 nm (pH 7; ε = 21800 M ⁻¹ s ⁻¹) π-π* transitions (H ₂ O)	285 nm (ε = 8700 M ⁻¹ s ⁻¹) π-π* transition 321 nm (ε = 5900 M ⁻¹ s ⁻¹) n-π* transition (H ₂ O)	Plack et al. (1981), Losantos et al. (2015), Arbeloa et al. (2011), Serpone et al. (2002)
Solubility in water	1 × 10 ⁶ mg L ⁻¹ †	68.56 mg L ⁻¹	Hessen, 2008, Anastas and Eghbali (2010)
Log Kow	-2.98 [†]	3.79 [†]	Hessen, 2008
Log Koc	-1.441 [†]	3.103 [†]	Hessen, 2008
BCF	3.162 L per kg wet weight [†]	38.24 L per kg wet weight [†]	Hessen, 2008
Φ _f	n.d.	n.d.	Arbeloa et al. (2011), Ignasiak et al. (2015)
Φ _T	n.d.	n.d.	Arbeloa et al. (2011), Kumasaka et al. (2014)
Φ _r	3.65 × 10 ⁻² (254 nm; H ₂ O pH 2.5) 1.42 × 10 ⁻⁴ (303 nm; H ₂ O pH 7)	3.07 × 10 ⁻⁵ (365 nm; H ₂ O pH 6.5)	Arbeloa et al. (2011), Vione et al. (2013)
Main deactivation pathway from singlet excited state	Internal conversion (IC)	Excited-state intramolecular proton transfer (ESIPT)	Arbeloa et al. (2011), Ignasiak et al. (2015)
Φ _Δ	n. d.	0.0027 ± 0.0003 (c-hexane) < 10 ⁻⁴ (acetonitrile) < 10 ⁻⁴ (methanol)	Orallo et al. (2020), de Sola et al. (2007)
k _q (O ₂ (¹ Δ _g))	1.3 × 10 ⁸ M ⁻¹ s ⁻¹ (D ₂ O pH 7) < 1.8 × 10 ⁵ M ⁻¹ s ⁻¹ (D ₂ O pH 2.4)	2.0 × 10 ⁵ M ⁻¹ s ⁻¹ (H ₂ O pH 6.5)	Vione et al. (2013), Orallo et al. (2020)

K_{ow}: octanol-water partition coefficient

K_{oc}: soil organic carbon-water partitioning coefficient

BCF: bioconcentration factor

Φ_f: fluorescence quantum yield

Φ_T: triplet quantum yield

Φ_r: reaction quantum yield

Φ_Δ: singlet oxygen O₂(¹Δ_g) production quantum yield

k_q (O₂(¹Δ_g)): rate constant for the total quenching of singlet oxygen O₂(¹Δ_g)

† Estimated with the Estimation Programs Interface (EPI) SuiteTM

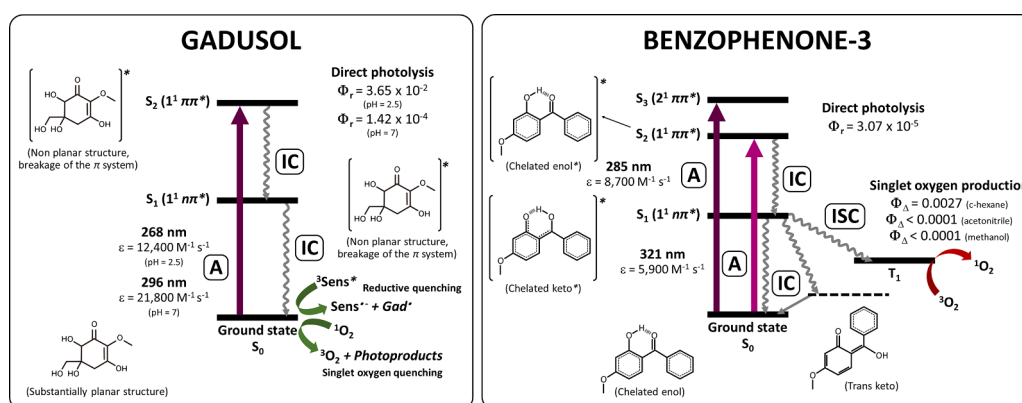


Fig. 4. Jablonski diagrams for gadusol and benzophenone-3 with structural and physicochemical data on the selected UV filters.

gadusol at physiological pH should be able to reduce natural photosensitizers such as riboflavin (Arbeloa et al., 2011).

Instead, excited singlet benzophenone-3 (S₁) has been reported to undergo intersystem crossing (depicted in Fig. 4, right panel, as wavy

arrows/ISC) to triplets (T₁) in some extent at room temperature (Kumasaka et al., 2014), being the yield of this process estimated at less than 15 % for the analogous 2-hydroxy-benzophenone (Bhasikuttan et al., 1999).

Photocalorimetric measurements, as well as theoretical calculations, consistently confirmed that the main deactivation route for photoexcited gadusolate is the fast internal conversion from the singlet states (wavy arrows/IC in the left panel of Fig. 4). According to quantum mechanical descriptions, the reaction occurs through a conical intersection of the potential energy surfaces for S_1 and S_0 , a typical feature denoting the large coupling between the states which allows a very efficient dissipation of the absorbed light energy as heat (Arbeloa et al., 2011, Losantos et al., 2015). On the other hand, photoexcited benzophenone-3 in organic solvents goes through ultrafast energy dissipation via enol-keto tautomerization, followed by efficient internal conversion and subsequent vibrational relaxation to the ground state (enol) tautomer (see the chemical structures in right panel Fig. 4) (Baker et al., 2015). This mechanism is currently described as an excited state intramolecular proton transfer (ESIPT). However, it should be taken into account that traces of phenoxyl radicals may be produced concomitantly as a result of photodegradation via H-O bond breakage in benzophenone-3, which may subsequently lead to harmful reactions towards biologically relevant compounds (Ignasiak et al., 2015).

Singlet oxygen ($O_2(^1\Delta_g)$) is another reactive species detected upon irradiation of benzophenone-3, but the production quantum yields Φ_Δ are low, especially in polar solvents, as it is shown in Table 1 and on the right panel of Fig. 4 (de Sola et al., 2007). On the contrary, gadusol does not produce $O_2(^1\Delta_g)$ above the sensing limits of time-resolved phosphorescence detection technique (Orallo et al., 2020). However, gadusolate is an efficient quencher of $O_2(^1\Delta_g)$. The total and reactive rate constants for the quenching were recently determined in aqueous solutions (Orallo et al., 2020). The results evidenced that the reaction occurs dominantly through a type II photooxidation process, pointing to the role of sacrificing antioxidant along with the UV-photoprotective function of gadusol in living organisms. This reactivity counts as an important attribute for sun photoprotection, given that exposure to UV radiation can photosensitize the generation of hydrogen peroxide and ROS, including $O_2(^1\Delta_g)$ and OH radicals, in addition to direct mutagenic effects on DNA. This is a consequence of the interaction of UV with different chromophores such as melanin, urocanic acid, porphyrins, nucleic acids, and the amino acids tryptophan and tyrosine, found in the dermic and epidermic layers where UV can penetrate (Farris and Valacchi, 2022).

The reactivity of gadusol towards peroxy radicals was also assessed together with the capacity to reduce the ABTS (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) cation radical. The tests demonstrated that the hydrophilic chain-breaking antioxidant capacity of this natural compound against peroxy and the ability to reduce the probe radical-cation are respectively stronger and comparable to ascorbic acid (Arbeloa et al., 2010).

Skin permeation depth profiles of gels loaded with gadusol and MAAs were assessed by *in-vivo* Raman spectroscopy. The study concludes that the gels can penetrate the skin to 6 μm depth and concentrate, in comparison to the outermost layer of the stratum corneum, mostly at 2 μm (Tosato et al., 2015). Then, it is clear that the antioxidant activity of these natural photoprotectors could benefit, additionally to their UV-absorbing capacity, by protecting against the ROS generation by photosensitization in deeper layers of the skin where UV radiation reaches. But the redox chemistry of gadusol should be kept in mind also regarding the extent of the balance and possible interplay of this molecule with other reactive species under physiological conditions and within the complex mixtures of sunscreen formulations.

3.2. Analysis of environmental and health impacts

To go further in comparing the performance of the selected photoprotectors, we must include sustainability criteria and toxicological effects. All life cycle phases of cosmetic products such as sunscreens should be contemplated. Regarding the production step, it is essential to select raw materials and make formulations with alternative ingredients

considered more sustainable (Fortunati et al., 2020). For the case of the synthetic example of UV filter, it should be considered that, even when benzophenones can be found in flowering plants, they are mainly produced by synthesis (from 100 to 1000 tons per year, only in Europe) (Carstensen et al., 2022). Aromatic ketones are traditionally produced on a large scale by the Friedel–Crafts acylation (Firouzabadi et al., 2004). In particular, benzophenone-3 is synthesized by the reaction of benzoyl chloride with 3-hydroxyanisole in the presence of $AlCl_3$ Lewis acid (de Sola et al., 2007, Cole, 2016). The major drawbacks of Friedel–Crafts acylation reactions are the production of large amounts of acidic gaseous emission and the need for both highly toxic alkyl halides and stoichiometric or super stoichiometric amounts of Lewis acids (Rueping and Nachtsheim, 2010). This results in vast amounts of undesirable products, making Friedel–Crafts acylation an extremely hazardous and wasteful process (Clark, 1999). Furthermore, $AlCl_3$ is highly hygroscopic and requires the use of both moisture-free solvents and reactants in a dry atmosphere, a rather costly procedure (Shimizu and Satsuma, 2011).

Another large-scale reaction route for the synthesis of benzophenone-3 consists of the condensation of benzoic acid with resorcinol monomethyl ether in the presence of zinc chloride and polyphosphoric acid (de Sola et al., 2007, Cole, 2016). Unlike $AlCl_3$, polyphosphoric acid is a much weaker acid. However, due to its high viscosity, elevated temperatures and strong mechanical agitation are required during the synthesis (Aldabbagh, 2005). Furthermore, in addition to the harsh reaction conditions, $ZnCl_2$ is very difficult to recycle and generates toxic and corrosive waste (Shimizu and Satsuma, 2011, Iqbal et al., 2020). Several patents and scientific reports describe alternative routes for the preparation of benzophenone-3 by using benzene, benzoyl chloride, toluene, chlorobenzene, and bromobenzene as precursors and solvents (Li et al., 2007, Galdorfini Chiari et al., 2014, Hao et al., 2016). Their most problematic aspect is the use of organic solvents that are hard to handle and also lead to the generation of hazardous waste. In particular, the removal of residual solvents from products, usually achieved by evaporation or distillation, results in air pollution due to the release of volatile organic compounds (Sheldon, 2005). Furthermore, many organic solvents, such as benzene, are highly toxic, carcinogenic, mutagenic, have a low flash point, and present serious environmental risks, among other drawbacks (Joshi and Adhikari, 2019). All the above-mentioned synthetic routes for benzophenone-3 fall far away from the principles of Green Chemistry (Anastas and Eghbali, 2010, Gałuszka et al., 2012).

Therefore, looking forward to better alternatives is necessary since stricter environmental regulations and a growing awareness of consumers are gradually making hazardous and contaminant processes obsolete. It must be mentioned that some approaches leading to the environmental-friendly production of benzophenone-3 have been explored. For instance, it is possible to use catalytic alternatives as a substitution for the inorganic reagents in the Friedel–Crafts acylation (Sheldon, 2005), and employ more easily handling reactants (Shimizu and Satsuma, 2011). Anyhow, a solution to green chemical synthesis of benzophenone-3 represents major challenges that have not yet been achieved.

The substitution of benzophenone-3 by natural photoprotective agents, such as gadusol, would be a sustainable alternative. This is in line with the concept of "circular beauty" (Fröhlich and Steinbiß, 2021), which expresses the advancement of "circular economy" in the cosmetic industry, considering that gadusol can be obtained from various marine origins, and its presence has been demonstrated in different fishery by-products (Grant et al., 1980, Plack et al., 1981, Guedes et al., 2022). Thus, gadusol becomes a promising alternative for the valorization of fishery residues. In this context, it is essential to conduct bioprospecting studies to explore biodiversity and to identify active compounds for commercial purposes (Puchkova et al., 2021).

The subsequent task would be to face the extraction of gadusol from the biomass. On a laboratory scale, the separation and purification of

this secondary metabolite from marine resources, such as fish roes, involves the maceration of the homogenized tissues in aqueous ethanol, and successive purification steps by flask washings of the filtrates with ethanol, chloroform and water, before column chromatography with ionic exchange resins (Plack et al., 1981, Arbeloa et al., 2010). Apart from demanding the use of halogenated restricted solvents (Byrne et al., 2016), the whole procedure is considerably time consuming, and the yields are rather limited (from ca. 200 mg wet kg⁻¹ to 4 g dry kg⁻¹) (Plack et al., 1981, Arbeloa et al., 2010).

It is worth mentioning that synthetic approaches to obtain UV photoprotective compounds belonging to this family were attempted by White et al. (White et al., 1989, White et al., 1995) around 30 years ago. They performed the total synthesis of natural mycosporines structures with quinic acid as starting material. The procedure involved 15 steps and only reached low yields of ca. 1% with respect to the initial quinic acid, suggesting that a similar production of synthetic gadusol would be rather discouraging.

Promising options to produce gadusol and some UVA-absorbing hybrid structures of gadusol and MAAs (gadusporines) by engineered biosynthetic pathways imply genes from zebrafish and yeast or Gram-(+) bacteria (Osborn et al., 2015, Osborn and Mahmud, 2019). This strategy led to a patent application by Bakalinsky et al. (Sondenheimer and Krutmann, 2018) offering different sunscreen formulations to be used as topical for human and animal skins that combine natural and synthetic UV filters including ZnO and/or TiO₂. The proposal conceives that gadusol can work both as a new sunscreen or an SPF booster. The authors also established that the cellular toxicity of this natural UV filter towards fibroblasts is lower than that of benzophenone-3, and found no evidence of mutagenic capacity and toxicity towards *E. coli* (Sondenheimer and Krutmann, 2018). Furthermore, Shimizu and Satsuma, 2011 demonstrated that gadusol takes part in the UV radiation protection of zebrafish embryos, playing a more important role than melanin. Gadusol was shown to prevent DNA damage and apoptosis in early development stages but, according to the responses of the embryos to increasing oxidative stress, it seems not to mainly work as an antioxidant *in vivo* (Shimizu and Satsuma, 2011).

Regarding the toxicological effects of benzophenone-3, the implication of this UV filter in coral reefs bleaching and death was one of the earliest concerns (Schneider and Lim, 2019, Miller et al., 2021, Moeller et al., 2021). Coral reefs are extremely sensitive to environmental changes, and the produced damage has a negative domino impact on other forms of life, since corals directly or indirectly support a great variety of biological species (Miller et al., 2021). Furthermore, benzophenones affect genetic material via oxidative damage of DNA, formation of pyrimidine cyclobutane dimers, single-stranded DNA breaks, cross-linking of DNA to proteins, and increased formation of DNA abasic sites (Cuquerella et al., 2012). A recent publication by Santamaria et al. (2020) reports that dermal exposure to benzophenone-3 in pregnant mice induces negative effects on the outcome of the progeny.

4. Concluding remarks

Current public health issues and environmental concerns about synthetic photoprotectors result in significant controversies regarding their broad and transversal use in several areas of the sunscreen industry (Skotarczak et al., 2015).

Highly efficient natural UV filters, although an attractive alternative to synthetic ones, present large-scale application disadvantages due to their low extraction and purification yields from biomass (Losantos et al., 2017).

The comparative analysis of benzophenone-3 and gadusol reveals that both types of UV filters, evaluated through the two representative examples, show different but significant drawbacks. It is evident that new natural photoprotectors will not be an immediate replacement for the existing synthetic filters. Moreover, natural compounds must go through a series of trials and tests.

Auspiciously, the significant amount of information at a molecular level that has been accumulated for natural UV filters such as gadusol, is available to stimulate new developments towards the design of more efficient photoprotective systems.

Still, profitable manufacturing methods should be developed to obtain the natural compounds (Candelo and Llewellyn, 2023). In this sense, bioprospection studies, circular economy concepts, and biotechnological approaches are expected to move forward to increase their participation in the economic capacities of the cosmetic industrial sector (Duraismy et al., 2011).

Some potential ways-through are found in decreasing the concentration of synthetic UV filters in the formulations together with the incorporation of natural compounds.

Besides, the performance of the synthetic UV filters can be also enhanced by optimizing their photostability and their ability to trap the reactive species formed upon irradiation that may lead to phototoxic and photo-allergenic intermediates and detrimental effects in the environment (Serpone et al., 2002). Different materials for encapsulation of the photoactive molecules can be very helpful. Micro and nanoparticles as matrices for carrying UV filters have been broadly reported in the scientific literature and patents, some of them applied to benzophenone-3. Relevant studied matrices include cyclodextrins, ethylcellulose-type biopolymers, glycosides, lipids, synthetic polymers, such as polymethylmethacrylate, mesoporous silicas, zeolites, metal-organic frameworks, and micelles, which are assumed to be benign to the environment (Anselmi et al., 2002, Damiani and Puglia, 2019, Hayden et al., 2018, Wu et al., 2014, Chrétien et al., 2006, Horcajada et al., 2010, Franco et al., 2020). In-depth knowledge at the physicochemical level of properties and mechanisms of action as well as the possible interactions of UV filters is essential to select the most appropriate carrier matrices. These matrices should promote greater stability and mitigation of undesirable effects through modifications in the transport properties and fate of the synthetic compounds in the environment, thus guaranteeing efficiency and sustainability requirements.

CRediT authorship contribution statement

P. Gigena Carvalho: Investigation, Writing – original draft. **R. Isla Naveira:** Investigation, Writing – original draft. **L.I. Granone:** Investigation, Visualization, Writing – original draft. **C.B. Mendive:** Conceptualization, Funding acquisition, Writing – review & editing. **A.E. Massa:** Conceptualization, Funding acquisition, Writing – review & editing. **M.S. Churio:** Conceptualization, Funding acquisition, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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