

# UV Filters

Subjects: Pharmacology & Pharmacy

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The use of sunscreens is a recommended practice to protect skin from solar-induced damage. Around 30 UV filters can be used in sunscreen products in the European Union. However, low photostability and putative toxicity for humans and environment have been reported for some UV filters. Therefore, it is important to develop new UV filters with improved safety profile and photostability. Over the last two decades, nearly 200 new compounds have revealed promising photoprotection properties. The explored compounds were obtained through different approaches, including exploration of natural sources, synthetic pathways, and nanotechnology. Almost 50 natural products and around 140 synthetic derivatives have been studied aiming the discovery of novel, effective, and safer future photoprotective agents.

Keywords: UV filters ; challenges ; toxicity ; photostability ; prospects ; natural products ; synthetic derivatives

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## 1. Introduction

Sunlight has several beneficial effects in human, such as the production of vitamin D, and induction of  $\beta$ -endorphin expression, which improve well-being <sup>[1]</sup>. However, excessive sunlight exposure is responsible for photo-induced skin damage, namely solar sunburn, hyperpigmentation, photoaging, skin photosensitisation, and skin cancer <sup>[2]</sup>, when protective measures, namely the use of sunscreen and the use of adequate clothes and accessories, are not adopted <sup>[3]</sup>. Photoprotective measures are more ancient than the first sunscreen's appearance in the 1900s, and ancient civilisations used plant extracts to protect their skin from sunburns for a long time <sup>[4]</sup>. Many of the chemical compounds present in natural extracts with photoprotective properties are now part of sunscreens. In fact, most of UV filters are inspired in natural products, specifically of botanical, animal, or mineral origin <sup>[5]</sup>. In 1928, benzyl salicylate was discovered for its photoprotective action against UVB radiation, but it was only commercialised in 1935 in the first sunscreen "Ambre Solaire" <sup>[6][7]</sup>. Later, almost 50 years, avobenzone and its derivatives appeared as the first UV filters that ensure protection against UVA radiation <sup>[8]</sup>. Currently, in Europe, there are a total of 29 approved UV filters <sup>[9]</sup>, complying with the regulations that ensure their effectiveness and safety for humans. UV filters can be classified concerning their ability to absorb the UV radiation (UVR), as UVA, UVB or broad-spectrum UV filters (UVA and UVB) <sup>[10]</sup>. Additionally, these products can also be branched into organic or inorganic, where organic filters are only capable to absorb the UVR, while inorganic filters can reflect and scatter the UVR <sup>[10]</sup>. In recent decades, the safety of UV filters for humans and environment has been called into question. In fact, many studies have confirmed the detection of UV filters in human biological samples <sup>[11][12]</sup> and in marine organisms <sup>[13][14][15][16]</sup>, thus confirming the hypothesis of UV filter-derived toxic effects. The presence of particular chemical moieties in UV filter structures confers intrinsic toxicity <sup>[17][18]</sup>. Photoinstability occurs for UV filters that photoisomerise or photodegrade, and consequently can generate toxic photodegradation products and loss of photoprotective action <sup>[19]</sup>. Therefore, over the last two decades, new natural products from botanical and marine sources <sup>[20][21][22]</sup> and synthetic derivatives <sup>[23][24][25][24]</sup> have been investigated, along with the use of nanotechnology approaches <sup>[26]</sup> as strategies to find new, more effective, safer and more stable UV filters.

## 2. Challenges

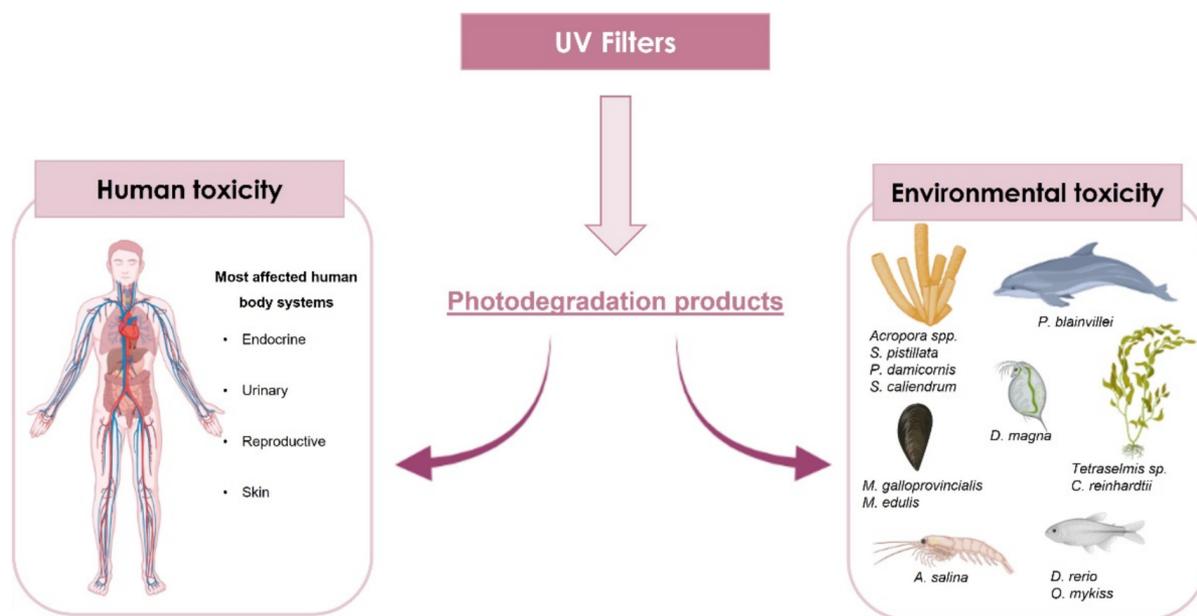
The main challenges associated with the UV filters present in sunscreens are their photoinstability, environmental impact, and human toxicity. As mentioned before, these are some points to consider in the development of new effective and safer photoprotective agents.

The stability of sunscreens is an essential requisite to ensure photoprotection and safety. UV filters absorb UVR and enter in excited energetic levels <sup>[27]</sup>. Then, the energy is released, and the chemical molecule returns to its initial energetic level. During this process, some UV filters undergo photoisomerisation and even irreversible cleavage of bonds <sup>[28]</sup>. The mechanisms associated with this phenomenon include the formation of photodegradation products, which can negatively influence the sunscreen's effectiveness. These degraded derivatives could also be toxic due to interaction with the

constituents present in cells and/or damage the DNA. Moreover, they can also affect the stability of the other ingredients present in the formulation [28].

Several approaches could be used in order to ameliorate the photostability of photoprotective agents, such as the introduction of antioxidants [29], encapsulation [30], multiple association of UV filters [31][32][33], and the addition of quenching molecules [34] in the sunscreen's formulation [35][36].

The concern about the negative impact of UV filters on environment and organisms is growing day-by-day. The research community is trying to find alternatives and solutions to minimise the risks posed by these actual emergent pollutants [37]. The impact that sunscreen agents could have in organisms is relevant, namely in marine organisms. Recently, several studies revealed the dangerous and noxious effects of UV filters towards diverse aquatic species, such as mussels [38][39], algae [40], crustaceans [40], corals [41][42][43], sea urchins [40], fish [44], and even in dolphins [45]. There are two ways of studying the toxicological effects in marine organisms: by determining the concentration of UV filters in a specific organism, by collecting the marine organism in the environment, or through the organism's exposure to a specific range of UV filters' concentrations and subsequently verifying the effects [46]. In the next sections, the possible effects that UV filters may have in human beings and in the environment, namely in marine organisms, will be described. **Figure 1** depicts the main human systems and marine organisms that suffer the negative impact of the UV filter's toxicity.



**Figure 1.** Resume of the main systems affected by UV filter's toxicity.

The occurrence of UV filters in different locations worldwide with concentration values between ng/L and µg/L has been studied in lakes, seawaters, sediments, rivers, estuaries, and in aquatic organisms [46]. In fact, the harmful effects of UV radiation led to an extensive production and use of photoprotective products during vacations, which resulted in an increase in UV filters present in an environment, namely in aquatic ecosystems [46]. The contamination of terrestrial environment could also occur by wastewaters discharges, disposal of product packages in inappropriate locations, and even in indoor dust that drives to an environment issue, contaminating both land and terrestrial organisms [47]. Bioaccumulation and toxicological effects are the main issues associated with marine contamination by UV filters that could induce the persistence of these emergent contaminants through the food chain [47]. Considering the relevance of this topic, herein some studies reporting the bioaccumulation and negative impact of UV filters in marine organisms are discussed.

### 3. Prospects

Several improvements in sunscreens were made in recent decades, particularly aiming to obtain new UV filters with increased photoprotective effectiveness, photostability, environmental and human safety, and improved sensory properties [48]. With this purpose, many sources have been explored by the scientific community, namely extracts and natural products isolated from both terrestrial and marine sources and new synthetic derivatives.

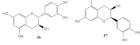
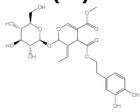
### 3.1. Nature as a Source of Potential Photoprotective Agents and UV Filters

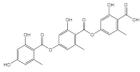
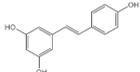
Nature has been widely used for many decades, as the main source for the discovery of new bioactive compounds. Considering skin care applications, several botanical and marine organisms' extracts with photoprotective and antioxidant effects have been reported. Additionally, some natural products isolated from these sources have proved to be promising bioactive compounds.

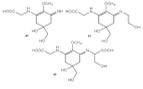
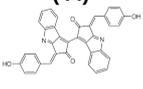
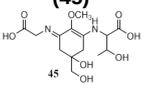
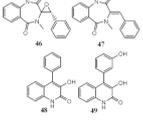
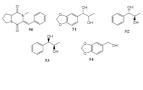
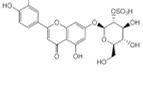
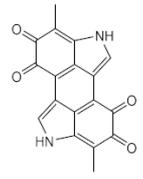
Every day, plants are exposed to UVR, which increases their resistance to the noxious UV rays. As a result of this natural resistance, secondary metabolites with diversified scaffolds possessing UV photoprotective and antioxidant properties are produced, specially terpenoids, anthocyanins, flavonoids, carotenoids, and phenolic acids [20]. Algae, cyanobacteria, bacteria, and marine fungi are some of examples of marine organisms that produce secondary metabolites with photoprotective effects through UV filter and antioxidant activity. In **Table 1**, natural extracts and metabolites (36–56) of botanical and marine sources with photoprotective and antioxidant activities are presented.

to be the most promising compounds obtained from botanical extracts, considering their good photostability, photoprotective, antioxidant potential, and non-cytotoxic profile at the concentrations mentioned. Interestingly, the presence of hydroxyl groups is a common structure feature for the most promising secondary metabolites with antioxidant activity. Considering marine-derived metabolites, MAAs, palythine (41), asterina-330 (42), shinorine (43), porphyra-334 (45), and scytonemin (44) have an excellent protective ability against UVR, being 44 an UVA/UVB absorber. Comparing both botanical and marine natural sources, marine-derived extracts and metabolites possess improved ability to protect against photo-induced damage. The antioxidant potential and easily introduction in cosmetic formulations are the main strengths of botanical extracts and metabolites. Despite all the advances on analytic techniques, it is not always possible to identify the active metabolite. Moreover, the isolation and purification of the botanical and marine natural products with photoprotective activity is a time-consuming process, being obtained in a low amount, which is a major drawback for obtaining compounds to be further explored for skin care applications. Therefore, some of these natural products were used as lead compounds to obtain synthetic derivatives with promising photoprotective effects.

**Table 1.** Natural extracts and metabolites of botanical and marine sources with photoprotective and antioxidant activity.

Organism and Species	Main Identified Secondary Metabolites	Activity	Values	References
<b>Botanical Extracts and Metabolites</b>				
Methanolic extract of grape seeds (from Village Farm and Winery; Nakhon Ratchasima, Thailand)	(+)-catechin (36) and (-)-epicatechin (37) (determined by HPLC) 	Photoprotective (% cell viability)  Photodegradation	At 25 µg/mL 10 J/cm <sup>2</sup> (110%) 20 J/cm <sup>2</sup> (68%)  36 = 35.1%; 37 = 31.3% Combination with UV filter: 36 (4.6%); 37 (7.0%)	[33]
Hydroethanolic extract of <i>Vitis vinifera</i> L.	Flavonoids, phenolic compounds, procyanidins, among others (determined by HPLC)	Antioxidant (DPPH) at 1mg/mL  Photoprotection	707.00 ± 0.03 µmol/g (pH = 5) 1098.00 ± 0.01 µmol/g (pH = 7)  SPF = 20–76 λ <sub>c</sub> = 360–381 nm (pH = 5)	[34]
Ethanolic commercial extract of olive leaves	20% of oleuropein (38) 	Antioxidant (DPPH)  Photoprotective	38: IC <sub>50</sub> = 11.75 ± 1.01 µg/mL Extract: IC <sub>50</sub> = 13.8 ± 0.8 µg/mL  λ <sub>max</sub> = 376 nm SPF = 22	[35]
Ethanolic Extract of varied <i>Lippia</i> species ( <i>L. brasiliensis</i> , <i>L. rotundifolia</i> , <i>L. rubella</i> and <i>L. sericea</i> )	Phenols and flavonoids	Antioxidant (DPPH)  Photoprotective	IC <sub>50</sub> = 0.604 mg/mL  SPF = 1.7–7.6 (formulation with 10% of the extract) λ <sub>c</sub> = 375 nm	[36]

Organism and Species	Main Identified Secondary Metabolites	Activity	Values	References
<b>Botanical Extracts and Metabolites</b>				
Ethanollic extract of Amazonian <i>Cecropia obtusa</i> leaves	Polyphenols	Antioxidant  Photoprotective  Cytotoxicity (HaCaT keratinocyte cell line)	IC <sub>50</sub> = 1.63 µg/mL (DPPH) IC <sub>50</sub> = 0.34 µg/mL(O <sub>2</sub> <sup>-</sup> ) IC <sub>50</sub> = 0.55 µg/mL( <sup>1</sup> O <sub>2</sub> )  SPF = 16  At 20 µg/mL: cell viability = 100%	[37]
Ethanollic extract of <i>Acacia catechu</i> heartwood	-	Photoprotective	SPF = 24–30	[38]
Hydroalcoholic extract of five wild Brazilian bamboo species ( <i>Chusquea</i> spp., <i>Aulonemia aristulata</i> , and <i>Merostachys pluriflora</i> )	Phenolic compounds	Antioxidant (DPPH)  Photoprotective	IC <sub>50</sub> = 137.55–260 µg/mL  SPF (before irradiation) = 34–86 SPF (after irradiation) = 14–44	[39]
Dichloromethane/acetone (1:1) extract from <i>Lasallia pustulata</i>	Lichenic metabolites, being gyrophoric acid (39) identified by HPLC 	Antioxidant (DPPH)  Photoprotective  Cytotoxicity (HaCaT keratinocytes cell line)	25 % at 500 µg/mL  λ <sub>max</sub> = 300 nm SPF = 5.03  IC <sub>50</sub> = 168 ± 33 µg/mL (before radiation) IC <sub>50</sub> > 200 µg/mL (after radiation)	[40]
Wood powder	-	Photoprotective	SPF = 11 (formulation) SPF = 37 (formulation + 5% of wood powder)	[41]
Ethanollic extracts of <i>Alpinia galanga</i> , <i>Curcuma longa</i> and <i>Aloe vera</i>	Flavonoids, phenols and terpenoids	Photoprotective	SPF = 18.2 (extract of <i>C. longa</i> ) λ <sub>max</sub> = 290 nm ( <i>C. longa</i> ) SPF = 15.1 ( <i>A. galanga</i> ) λ <sub>max</sub> = 290 nm ( <i>A. galanga</i> )	[42]
Coconut oil	High quantity of saturated fatty acids	Photoprotective	λ <sub>max</sub> = 205 nm (coconut oil) λ <sub>max</sub> = 320 nm (coconut oil + BP-3)	[43]
Resveratrol (40) and ethanollic extract of green tea	Resveratrol (40) 	Antioxidant (DPPH)  Photoprotective	IC <sub>50</sub> = 38.67–85.44 % (resveratrol) IC <sub>50</sub> = 37.41–77.50 % (green tea extract)  λ <sub>max</sub> = 310 nm (40) λ <sub>max</sub> = 270 nm (green tea) SPF = 9.35 (40) SPF = 14.59 (green tea extract) SPF = 16.91 (40 and green tea extract)	[44]
<b>Marine Organisms Extracts and Metabolites</b>				

Organism and Species	Main Identified Secondary Metabolites	Activity	Values	References
<b>Botanical Extracts and Metabolites</b>				
Methanolic extract of red macroalgae <i>Curdiea racovitzae</i> and <i>Iridaea cordata</i>	MAAs, with major quantity of palythine (41), asterina-330 (42), and shinorine (43) 	Antioxidant (DPPH)  Photoprotective  Cytotoxicity (HaCaT keratinocytes cell line)	IC <sub>50</sub> = 970.00 µg/mL ( <i>C. racovitzae</i> ) IC <sub>50</sub> = 2960.00 µg/mL ( <i>I. cordata</i> )  λ <sub>max</sub> = 320 nm (both) λ <sub>c</sub> = 356 nm ( <i>C. racovitzae</i> ) λ <sub>c</sub> = 347 nm ( <i>I. cordata</i> )  At 1 mg/mL % cell viability = 89 ( <i>C. racovitzae</i> ) % cell viability = 73 ( <i>I. cordata</i> )	[45]
Ethanol extract of brown macroalgae <i>Sargassum cristafolium</i>	Palythine (41)	Photoprotective	λ <sub>c</sub> = 370 nm	[49]
Methanolic extract red alga <i>Corallina pilulifera</i>	-	Antioxidant (DPPH)	At 200 mg/mL: 80% scavenging activity	[50]
Metabolite from extracts of cyanobacteria <i>Stigonema</i> sp., <i>Scytonema</i> sp. and <i>Lyngbya</i> sp.	Scytonemin (44) 	Photoprotective	λ <sub>max</sub> = 252, 278, 300, 386 nm	[51]
Metabolites from aqueous methanolic extract of cyanobacteria <i>Microcystis aeruginosa</i>	MAAs shinorine (43) and porphyra-334 (45) 	Photoprotective	λ <sub>max</sub> = 334 nm	[52]
Metabolites from ethyl acetate extract of marine fungi <i>Penicillium echinulatum</i>	Quinolinic Alkaloids 	Photoprotective  Phototoxicity (HaCaT keratinocytes cells)	λ <sub>max</sub> = 287 (48) λ <sub>c</sub> = 335 nm (48) λ <sub>max</sub> = 330 (49) λ <sub>c</sub> = 334 nm (49)  Reduction of ROS (43%) at 200 µg/mL (49)	[53]
Metabolites from dichloromethane/methanol (2:1) extract of algae <i>Bostrychia radicans</i> - associated fungi <i>Annulohyphoxylon stygium</i>		Phototoxicity (3T3 murine fibroblasts)	PIF = 1.00 (50 and 51) PIF = 5.2 (54)	[54]
Metabolite from ethanol extract of plant <i>Thalassia testudinum</i>	Thalassiolin B (55) 	Antioxidant (DPPH)  Repair of Acute UVB-Damaged Skin	IC <sub>50</sub> = 100 µg/mL  Skin damage suppression (with 55 at 240 µg/cm <sup>2</sup> ) = 90%	[55]
Platyfish <i>Xiphophorus</i> metabolite	Melanin (56) 	Photo-repair of the skin	Stimulate the production of melanin, which reduced the formation of pyrimidine dimers.	[56]

Abbreviations: DPPH—2,2-diphenyl-1-picrylhydrazyl; SPF—solar factor protection; λ<sub>c</sub>—critical wavelength; λ<sub>max</sub>—maximum wavelength; IC<sub>50</sub>—concentration that reduces a response to 50% of its maximum; HPLC—high-performance liquid chromatography; PIF—photoirritation factor.

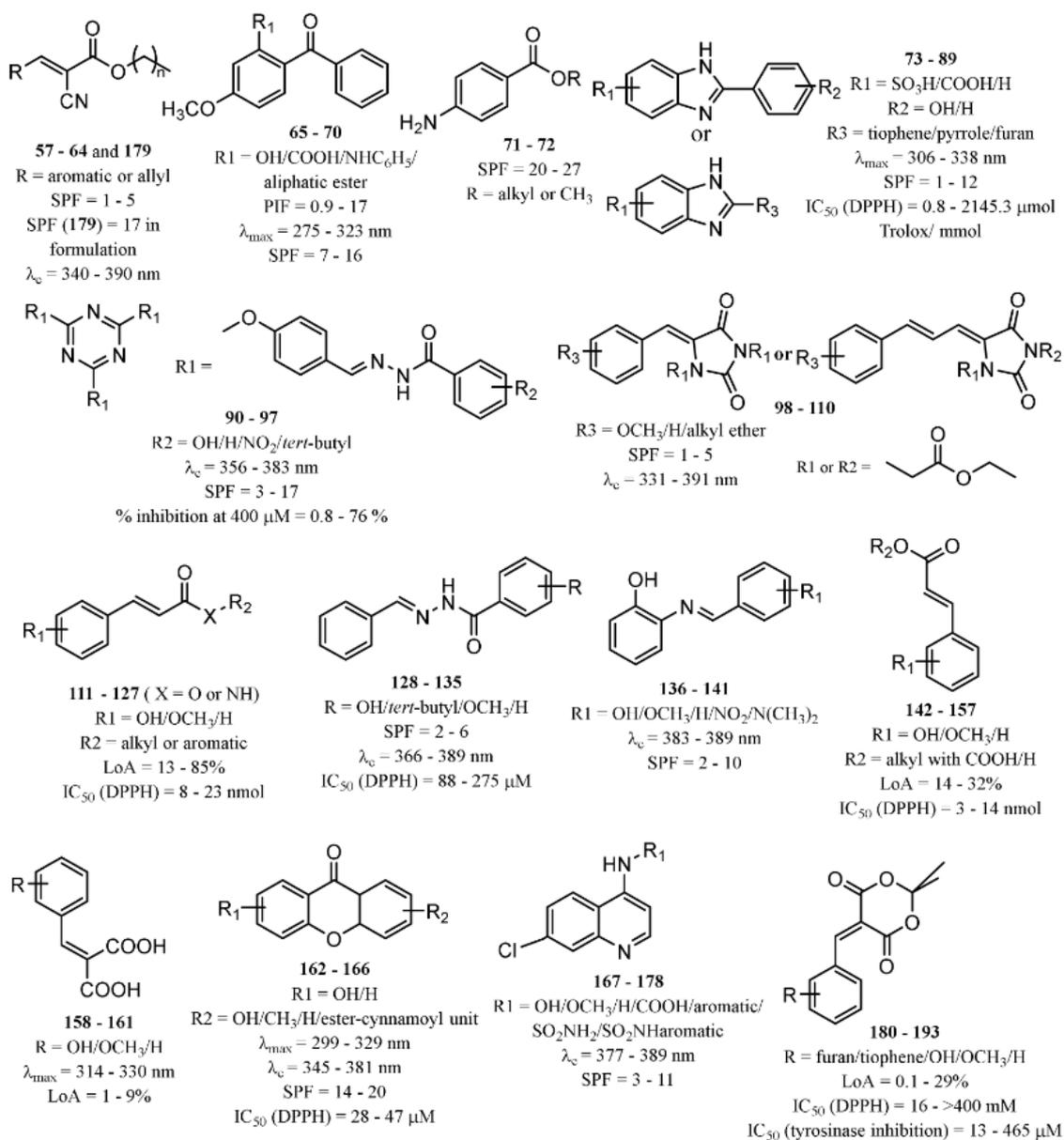
## 3.2. Synthetic Derivatives with Photoprotective and UV Filter Activity

### 3.2.1. Inorganic UV Filters

Cerium oxide ( $\text{CeO}_2$ ) was suggested as one possible UV filter. In fact, it is commercialised in some photoprotective formulations but with silica coating, due to its high photocatalytic activity, responsible for oxidation and degradation of other formulations' components [49]. The coating with amorphous silica also decreases its photoprotective UV-shielding potential [50]. However, this gap could be ameliorated if  $\text{CeO}_2$  was doped with  $\text{Ca}^{2+}$  and  $\text{Zn}^{2+}$  ions, which could reduce its photocatalytic activity and particle size, without interfering with its photoprotective potential [50]. Cerium phosphate ( $\text{CePO}_4$ ) was reported 10 years later by Seixas and Serra (2014) [50]. Similarly to  $\text{CeO}_2$ ,  $\text{CePO}_4$  was described for possessing high photocatalytic activity, low amount of white residue when applied on the skin, and increased stability. Some parameters regarding physical and chemical stability of  $\text{CePO}_4$  were evaluated, using  $\text{TiO}_2$  (34) and  $\text{ZnO}$  (35) as controls, as well as its behavioural and rheological properties, both alone and in formulation. The results revealed low interaction in formulation when combined with organic UV filters. Therefore,  $\text{CePO}_4$  is a potential future novel, stable, and efficient inorganic UV filter [50].

### 3.2.2. Organic UV Filters

Inspired by commercialised UV filters, as well as in natural products with photoprotective properties, several compounds have been synthesised and reported as potential UV filters, with antioxidant, anti-inflammatory, and anti-photoaging activities. Herein, a reference of the novel synthetic derivatives developed with the aim of obtaining UV filtering compounds with extra pharmacological properties are presented. **Figure 2** presents the chemical skeleton, and the range of values obtained for the biological activity assessed.



**Figure 2.** Chemical skeleton and values of biological activity assessed for the synthetic derivatives reported in the literature.

### 3.2.2.1. New Synthetic Derivatives Inspired by Commercialised UV Filters

One of the strategies followed by research groups to obtain new organic UV filters with improved photoprotective activity is through molecular modifications of actually marketed UV filters. Eight octocrylene (**30**)-related compounds (**57–64**) were prepared and evaluated for their photoprotective effect by Polonini et al. (2014) [51]. Among these, **60**, **61**, and **63** displayed the best UVB protection effect, while compounds **61–63** presented the best results concerning protection against UVA. The most promising derivative was **63**, which behaved as a broad band UVA/UVB filter [51].

Using benzophenone derivatives as lead compounds, benzophenones **65–68** were prepared and tested for their UV filtering properties [52]. Compounds **65** and **66** were considered as the most promising, showing photoprotective activity and non-phototoxic results, confirmed by PIF values as less than 1.3. In addition to these benzophenones, the structure-related benzophenone **69** and lactone **70** displayed UV filter properties, having lactone **70**, a more potent photoprotective effect (SPF = 16), but only ability to absorb UVB radiation, contrarily to benzophenone **69**, which demonstrated the ability to absorb UVA radiation [53].

Later, new PABA derivatives, PABA methyl ester (**71**) and PABA methyl stearate (**72**), were prepared and evaluated for their photoprotective potential, revealing SPF values of 20.60 and 26.17, respectively [54]. It is noteworthy to mention that the high molecular weight of **72** should avoid its penetration through the skin, making this compound a potential UV filter with a safer profile.

Inspired by benzimidazole and benzotriazole approved UV filters, several new heterocyclic compounds were prepared. Benzimidazole derivatives **73–86** were reported for their photoprotective activity, and compound **83** also demonstrated antioxidant activity and higher photostability (98.4%) when compared with the control phenylbenzimidazole sulfonic acid (PBSA) (**14**) (96.7%) [55]. Additionally, new 5-membered ring-benzimidazole derivatives (**87–89**) were also prepared, being compounds with pyrrole (**87**), furan (**88**), and thiophene (**89**) moieties which were the most promising regarding their antioxidant, photostability, and photoprotective activities [56]. Among these, the most photostable was the thiophene derivative **89**, followed by pyrrole derivative **87**, and the furan derivative **88** [56].

Using triazine UV filters as models, new 1,3,5-triazine derivatives (**90–97**) were synthesised and evaluated for their photoprotective properties [57]. Among 1,3,5-triazine derivatives **90–97**, **97** displayed the most promising antioxidant activity and revealed the highest SPF and UVA protection factor [57].

Inspired in 3-benzylidenecamphor (**7**), Popiół et al. (2019) planned a small library of potential UV filters (**98110**) by replacing the camphor moiety by 5-arylideneimidazolidine-2,4-dione (hydantoin) while maintaining the benzylidene portion. Although the synthesised compounds revealed moderate SPF values, they demonstrated the ability to absorb both UVA and UVB radiation ( $\lambda_c$  between 339 and 391 nm) [57]. Compounds **104** and **109** were considered the less toxic against HaCaT keratinocytes and human fibroblasts cell lines, and compound **99** revealed the best UVB photoprotective properties within the tested series, with a SPF = 4.7. Some structure–activity relationships (SAR) considerations could be drawn for these derivatives. For instance, methoxy substituents at the aromatic ring are associated with photoprotection against UVA radiation; in contrast, the absence of methoxy groups in the aromatic ring is associated with interesting UVB filter properties [57]. In addition, the presence of alkoxy groups at positions 4- (compounds **99**, **104**, and **109**) and 3,4- (compounds **102** and **107**) is associated with the highest values of critical wavelength, contrarily to what is observed with non-substituted benzene rings [57].

Sinapic acid analogues of EHMC (**21**) with ester (**111–124**), amide (**125–126**), and ketone (**127**) groups revealed promising UV filter activity. Interestingly, **111** and **114–127** showed multifunctional properties, combining antioxidant and photoprotective effects. Among all compounds, the derivatives **125** and **127** showed the best antioxidant activities with IC<sub>50</sub> values lower than 8.9 ± 0.3 nmol [58]. Additionally, sinapic acid analogue **111** and its methylated derivative **112**, aliphatic sinapate derivatives **116** and **118**, and amide derivative **125** presented higher photostability than EHMC (**21**) [58].

Molecular hybridisation avobenzone (**11**), EHMC (**21**), and *trans*-resveratrol (**40**) resulted in the identification of a novel series of hybrids (**128–135**) with UV filter effect [59]. All compounds revealed photoprotective activity with SPF values varied between 2 and 5, and an ability to absorb the UVA region of the electromagnetic spectrum, confirmed by their  $\lambda_{max}$  values in the range of 369 nm and 389 nm [59]. Additionally, three hybrids of the total synthesised compounds **128–135** possess antioxidant potential, with an IC<sub>50</sub> between 88  $\mu$ M and 275  $\mu$ M (compounds **128**, **134**, and **135**) [59]. Amongst all, compounds **128** and **131–135** possess characteristics of broad-spectrum molecules, having **128**, **134**, and **135** an interesting DPPH radical scavenging activity.

### 3.2.2.2. Nature-Inspired Synthetised Compounds

Naturally occurring stilbenes, *p*-hydroxycinnamic acids, and xanthenes have been used as inspiration to obtain new potential UV filters. Inspired in the photoprotective activity of *trans*-resveratrol (**40**), compounds **126–141** were prepared and tested for their UV filter effect. All compounds revealed promising UV filter properties, with SPF values between 2 and 20 [59].

Sinapoyl-*L*-malate (**142**) is a sinapoyl ester widely described for its UV protection in plants [60]. Taking this into account, the UV filter activity of sinapoyl-*L*-malate **142** and its analogues **143–157** were explored by Peyrot et al. (2020) [61]. All compounds presented good water solubility, as a result of the presence of a free carboxylic acid in their structure which could facilitate the incorporation into sunscreen's formulation. Among all the compounds, **142–157**, **142**, **144**, **147**, and **150–157** showed promising photoprotective activity with LoA < avobenzone (**11**), and antioxidant activity, being **151** and **155–157** the most promising. Moreover, **142**, **151**, and **154–157** revealed photostability with LoA values less than 20% [61].

Based in natural-inspired *p*-hydroxycinnamic acids, *p*-hydroxycinnamic diacids were prepared (**158–161**), being sinapic diacid (**160**) and caffeic diacid (**161**) the derivatives that displayed the best photoprotective characteristics [62].

Xanthone derivatives were studied in order to disclose their profiles as future UV filtering molecules. Resende et al. (2020) reported three hydroxylated xanthone derivatives (**162–164**) with promising antioxidant activity and UV filtering characteristics [63]. Compounds **162–164** proved to absorb in the UVB range (280–320 nm). Additionally, xanthone **162** showed a dual ability to protect the skin against UV damage, through DPPH scavenging action and UV-filter capacity, without phototoxicity in the HaCaT keratinocyte cell line [63]. Popiół et al. (2021) also reported novel potential and innovative UV filtering compounds, combining the xanthone scaffold with  $\epsilon$ -cinnamoyl moiety [61]. Active xanthone-cinnamoyl hybrid compounds **165** and **166** were synthesised and evaluated for their photoprotective, antioxidant, and mutagenic activities [22]. Compound **166** was revealed to be the most promising, displaying  $\lambda_c$  of 381 nm, confirming the ability to absorb both UVA and UVB radiations and with a SPF of 19.69 [61]. Comparing these two groups of xanthenes, the combination of the cinnamoyl and xanthonic moieties allows the correct electronic delocalisation, which improves the UV absorber properties and, because of that, compounds reported by Popiół et al. [61] possess action against UVA and UVB radiation, in contrast to compounds with a simple xanthone scaffold reported by Resende et al. [63].

### 3.2.2.3. Other New Synthetic Derivatives

Other potential synthetic UV filters with different scaffolds have been described, namely those with heterocyclic rings, such as the new UV absorbers **167–178** based on quinoline derivatives with SPF and  $\lambda_c$  values between 2 and 11 and 376 and 388 nm, respectively, being the quinoline derivative **176** considered as the most promising compound with the highest SPF value [63]. (*E,Z*)-2-ethylhexyl-2-cyano-3-(furan-2-yl)acrylate (**179**) has also been described for its good capacity to absorb UVA radiation ( $\lambda_{max}$  = 339 nm) and good solubility in oils for the formulation [64].

Recently, Peyrot et al. (2020) developed a small library of compounds from Meldrum's acid and *p*-hydroxycinnamic acids (**180–183**), furans (**184–190**), and pyrroles (**191–193**), displaying interesting UV filter properties and photostability. Moreover, *p*-hydroxycinnamic acid-based Meldrum's derivatives (**180** and **183**) possess antioxidant and anti-tyrosinase properties, photoprotective characteristics, namely against UVA radiation and blue light, and photostability (with LoA < avobenzone (**11**)) [61] reinforcing their potential as multifunctional agents for cosmetic application. Interestingly, endocrine disruption assays were performed for compounds **182**, **184**, **187**, and **191**, that revealed non-interaction with receptors, showing the absence of agonistic (% receptor activity < 30%) and antagonistic (% receptor activity > 70%) effects [61].

## 4. Conclusions

Ultraviolet filters are incorporated in sunscreens aiming to protect the skin from the noxious effects of UV rays. Despite the strict regulation framework, new scientific evidences have raised concern about their toxic effects in humans and marine ecosystems. Neurotoxicity, endocrine disruption, malformations, decreased photosynthetic pigments, coral bleaching, and mortality, among others, are some of the confirmed negative effects that some UV filters, namely benzophenone-3, avobenzone, EHMC, and octocrylene can have in marine organisms. The decomposition of the UV filters detected in aquatic ambient was already reported, leading to the formation of toxic by-products with putative negative effects for human beings and accumulation in marine organisms. Beyond these environmental problems, UV filters can also have direct negative effects on humans, especially when photodegradation/photoisomerisation occurs. Avobenzone is the UV filter most studied regarding to its photoinstability and negative effects, hence being one of the most toxic UV filters when exposed to UV radiation. The presence of certain chemical groups, such as aromatic ketones, unsaturated systems, and camphor structure, are some of the chemical moieties susceptible of inducing allergic and sensitisation skin reactions.

Considering the mentioned pitfalls, the scientific community has been focused on creating new UV filters. The presence of labile groups suitable for hydrolysis degradation could be an approach, known in pharmaceutical sciences as “soft drugs”, aiming towards the degradation of the parent compound into inactive metabolites avoiding the oxidative pathway, and contributing to a decrease in bioaccumulation and toxicity.

The existence of privileged structures in nature, produced by plants and marine organisms, is vastly known. Natural products could be directly used, after their extraction, or could inspire the creative mind of the scientists to obtain synthetic derivatives with improved efficacy and safer profile. Botanical extracts and metabolites, namely catechin, epicatechin, gypic acid, and resveratrol are some of the plant-derived metabolites that could be highlighted for their photoprotective ability, but especially for their antioxidant potential due to the presence of hydroxyl groups in their structure. In addition to botanical extracts, marine secondary metabolites also exhibit photoprotection properties, namely MAAs, which are able to absorb both UVA and UVB radiation. Some derivatives inspired by marketed UV filters were also developed to overcome some of their drawbacks. To conclude, the development of innovative, safe, effective, and non-toxic UV filters is an ongoing need and a hot research topic.

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