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Introduction to actinic damage and actinomycetes as a promising source for eco-friendly photoprotective compounds

Introducción al daño actínico y los actinomicetos como fuente prometedora de compuestos fotoprotectores ecoamigables

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Abstract

The use of sunscreens is a fundamental strategy of an effective photoprotection scheme. Currently, several ultraviolet (UV) filters have been questioned for their side effects, mainly those that harm the environment. Therefore, there is a demand to find compounds with photoprotective properties. In this regard, natural products have traditionally been a promising source of compounds with diverse biological activities, including those related to photoprotection. Recently, natural microbial products have shown very promising opportunities supported by biotechnological advances, including those possibilities opened by computer-aided tools. Under this scenario, several studies have recognized the great potential of the phylum Actinomycetota as a source of compounds with photoprotective properties. This review examines how solar radiation induces skin photodamage, explores existing photoprotection strategies, and highlights the immense potential that lies in the specialized metabolism of actinomycetes. These microorganisms offer a rich and untapped source for the development of innovative products that could transform the sun protection industry.

Keywords**:** photodamage; sunscreen; natural products; actinomycetota; actinobacteria.

Resumen

El uso de filtros solares es una estrategia fundamental de un esquema eficaz de fotoprotección. En la actualidad, varios filtros ultravioletas (UV) han sido cuestionados por sus efectos secundarios, principalmente aquellos que dañan el medio ambiente. Por ello, existe una demanda para encontrar compuestos con propiedades fotoprotectoras. En este sentido, los productos naturales han sido tradicionalmente una fuente prometedora de compuestos con diversas actividades biológicas, incluidas las relacionadas con la fotoprotección. Recientemente, los productos naturales microbianos han mostrado oportunidades muy prometedoras apoyadas por los avances biotecnológicos, incluyendo las posibilidades abiertas por las herramientas asistidas por ordenador. En este escenario, varios estudios han reconocido el gran potencial del filo Actinomycetota como fuente de compuestos con propiedades fotoprotectoras. Esta revisión examina cómo la radiación solar induce el fotodaño cutáneo, explora las estrategias de fotoprotección existentes y destaca el inmenso potencial que reside en el metabolismo especializado de los actinomicetos. Estos microorganismos ofrecen una fuente rica y sin explotar para el desarrollo de productos innovadores que podrían transformar la industria de la protección solar.

Palabras clave**:** fotodaño; bloqueador solar; productos naturales; actinomycetota; actinobacteria.

1. Introduction

Practicing sun protection, such as the regular use of sunscreen, is essential to maintaining skin health. Exposure to ultraviolet (UV) radiation from the sun can cause irreversible damage, including premature aging and an increased risk of skin cancer [1]. Photoprotection not only preserves the skin's youthful appearance but also serves as a vital defense against serious dermatological diseases [2], [3]. Incorporating this habit into a daily routine is an investment in long-term health. It protects the integrity of the skin and promotes healthy aging.

Although sunscreens play an important role in preventing UV-induced skin damage, there have been growing concerns about the adverse effects on human health and the environment of various UV filters currently used in sunscreen formulations [4], [5]. The scientific community and the cosmetics industry are

currently seeking innovative and environmentally friendly alternatives that do not compromise product effectiveness [6], [7]. In this context, searching for new compounds with photoprotective properties has become an exciting and crucial endeavor.

Natural resources have historically been the primary source of pharmaceuticals [8]. Specifically, in the case of antibiotics, bacteria of the genus *Streptomyces* (phylum Actinomycetota) have been the primary source [9]. Furthermore, actinomycetes have been found to produce compounds with a diverse range of biological activities [10]. The success in producing bioactive compounds is largely attributed to the evolutionary success of these compounds in adapting to diverse environments. They exist both independently (i.e., free-living forms) and in association with a wide range of hosts. As a result of these and several other reasons, actinomycetes are currently a widely used chassis for the large-scale production of various compounds of industrial interest [11], [12]. Due to the diversity exhibited by the phylum Actinomycetota and its ability to produce bioactive compounds, bioprospecting research involving actinomycetes remains an interesting prospect for both the industry and scientific community.

This paper aims to present in a summarized way the relevance of photoprotection research, focusing specifically on the potential of microorganism derived natural products, especially on bacteria belonging to the phylum Actinomycetota. The article starts by presenting the basic aspects of the damage caused by overexposure to solar radiation, photoprotection and natural products. It also highlights the imperative need to explore the specialized metabolism of bacteria, which have been shown to contain compounds with significant photoprotective properties [13], [14]. This work highlights the importance of a thorough understanding of the possibilities that these microorganisms offer to transform the sunscreen industry. Through rigorous and precise analysis, we seek to recognize the potential of natural compounds derived from actinomycetes in the development of safer and eco-friendly sunscreens.

2. Solar Radiation Dynamics

Sun exposure is a vital activity in most living organisms. In humans, sunlight is crucial for several biological processes such as vitamin D synthesis (and, therefore, all vitamin D-dependent mechanisms) and hormone release regulation (e.g., αmelanocyte-stimulating hormone, calcitonin gene-related peptide, neuropeptide substance P) [15]. However, overexposure to sunlight can result in harmful effects [16]. For instance, ultraviolet (UV) radiation emitted from the sun is the main etiological factor of skin-related diseases such as photoaging, melasma, and even cancer [17]. These deleterious effects are known as actinic damage or photodamage. It is emphasized that the pathophysiology of photodamage depends on the type of UV light; therefore, it is important to differentiate between them.

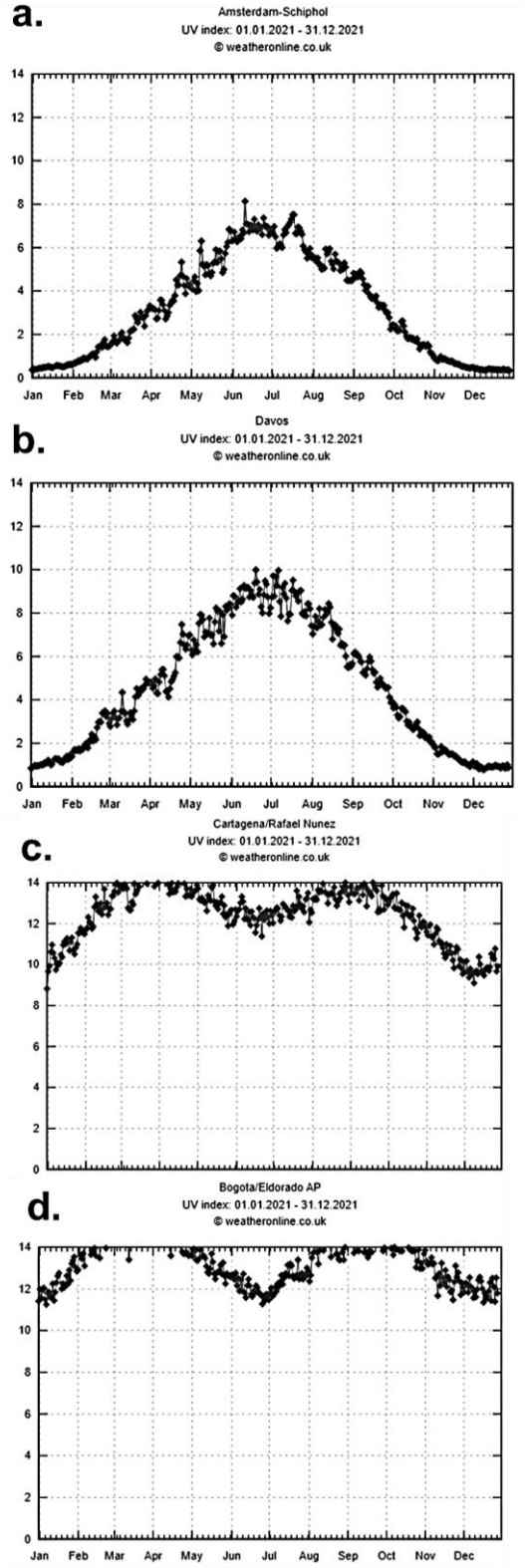

Figure 1. Comparison of UV indices during 2021. UV index levels between January and December 2021 are shown for Amsterdam, Netherlands (a), Davos, Switzerland (b), Cartagena, Colombia (c), and Bogota, Colombia (d). Data retrieved from www.weatheronline.co.uk.

Sunlight comprises a segment of the electromagnetic radiation emitted by the Sun, encompassing UV, visible, and infrared regions according to the wavelength (i.e., 100-400 nm, 400-800 nm, 800 nm – 1 mm, respectively). Additionally, UV radiation is also subdivided into UV-A (400-320 nm), UV-B (320-290 nm), and UV-C (290-100 nm) [18]. The latter one, fortunately, is filtered by the ozone layer. Instead, UV-B is filtered around 90-95% by the ozone layer, while UV-A barely reaches 5-10% of retention [19], [20]. Although UV-B arrives in such a low proportion, it is the one with the highest energy, and its deleterious effect is significant. For example, erythema caused by sunburn (acute effect) is due to UV-B [21]. In the case of UV-A, its effect is chronic and is responsible for skin weakening typical of aging [18].

Another essential factor to consider is the differential occurrence of solar radiation intensity based on geographical location [22]. The areas around the equator (tropical zone) have the highest UV radiation levels, which are almost constant throughout the year. While the other zones (i.e., subtropical, temperate, and polar) have lower UV radiation levels that vary over the year. To illustrate these marked differences, Figure 1 compares UV radiation levels (UV indices between 6 and 7 are considered **high**, between 8 and 10 are **very high**, and >11 are **extreme** [23]) during 2021 in cities located in different geographic regions. In temperate zones, even in cities at high elevations (>1000 m), UV radiation levels vary widely throughout the year (Figure 1a, Amsterdam, The Netherlands, at -2 m; Figure 1b, Davos, Switzerland, at 1,560 m). On the other hand, in the tropics, cities such as Cartagena, Colombia (2 m; Figure 1c) and Bogotá, Colombia (2,640 m; Figure 1d) register UV index levels higher than 9 (very high) and 11 (extreme), respectively, throughout the year. This situation makes attention in the field of photoprotection even more mandatory for tropical countries such as Colombia, and those having elevations such as the Andean region.

3. Photodamage and Photoprotection

UV radiation induces alterations in biomolecules such as proteins, lipids, and nucleic acids (i.e., photosensitizer molecules) [24]. These perturbations cause disruptions in the cellular functions to which these molecules are associated, resulting in a dysfunction of the compromised tissue [25]. This complex of deleterious effects induced by UV radiation is called actinic damage [26] or photodamage [27]. In contrast, photoprotection is the set of measures to prevent UV-induced damage [27].

UV radiation penetrates the skin differentially, while UV-B is concentrated in the epidermis, UV-A reaches deeper levels, and its damage is mainly manifested in the dermis [28]. In addition, the harmful effects of UV-B and UV-A are developed by different molecular mechanisms.

UV-B and the nearest band of UV-A (320 – 340 nm, called UV-A2) mainly affect DNA, the main chemical mechanisms are reviewed in detail by Schreier *et al*. [29]. For instance, pyrimidine-pyrimidone adducts (i.e., (6-4) lesion) and cyclobutane pyrimidine dimer photoproducts are the most frequent UV-B induced lesions [29]. These photolesions may involve coding sequences of crucial genes to control cellular homeostasis, thus initiating cell malignancy [24], [30]. In the case of UV-A, its deleterious effect is mediated through photosensitizers, which mainly involve oxidative stress [31]. Although the biological impact of UV-A as a tumor inducer is low, its role in promoting tumor progression has been well-documented [30].

Since it is impossible to avoid UV radiation completely, exposure to sunlight with protective measures is essential. The use of sunscreens is a measure that has shown promising results as a photoprotection strategy [3], [32]. For instance, a study involving 120 patients showed that using sunscreens reduced the development of pathological skin conditions such as actinic keratoses and squamous and basal cell carcinomas [33]. Additionally, in a randomized controlled trial of 1621 patients conducted to evaluate the prevention of solar keratoses through the use of sunscreens, it was shown that daily sunscreen use is more effective in preventing the appearance of UV-induced lesions than in promoting regression of prevalent lesions [34]. Evidence has supported the prophylactic capacity of sunscreen in sun keratoses, and has led countries heavily affected (e.g., Australia and New Zealand) to recommend its daily use [35].

Sunscreens work primarily by preventing or minimizing the amount of UV radiation reaching the skin. For this purpose, sunscreens use compounds (organic or inorganic) that filter UV radiation (i.e., UV filters), mainly by absorption [36]. While there are only two inorganic compound options for sunscreen formulation, there are more than 50 organic compound alternatives [37]. However, the number of viable ingredients is limited depending on the legislation in force of each country [38].

Like many pharmaceuticals, the first UV filters were obtained from natural resources (Ma and Yoo recently published a review on the history and evolution of sunscreens, including some regulatory aspects [39]). Acidified quinine sulfate (obtained from the bark of the *Cinchona* species [40]) was the first compound used as a UV filter [39]. Oxybenzone (also known as benzophenone-3 –BP-3–), one of the most widely used UV filters, has a natural origin and has been used as a UV filter since 1965 [41]. In addition to benzophenones, options such as octyl salicylate and 4-aminobenzoic acid are natural UV filters [42], [43]. However, several UV filters have been linked to health and environmental concerns [44]–[46], which has stated the need to search for novel photoprotective agents. This fact can be evidenced by the steady increase in research related to photoprotection (Figure 2).

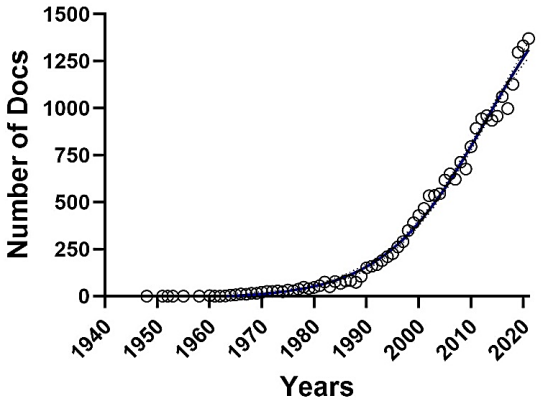

Figure 2. Evolution of the research related to photoprotection produced between 1948 and 2021. A Scopus search was performed using "(sunscreen* OR photoprotect*)" as a query (without time restriction).

4. Marine Natural Products

Sessile marine invertebrates are prolific sources of bioactive compounds. Sponges and corals (mainly octocorals) have provided several metabolites that have resulted in drug development (e.g., cytarabine, vidarabine, and eribulin mesylate) [47]. However, this progress has been limited by several common factors in the field of natural product research. Among the most important challenges usually faced by a promising, naturally-occurring compound are the low yield percentage during isolation, complex structures that hinder its synthesis, and limited availability of source organisms [48]–[50]. For instance, producing the quantities required for a clinical trial, taking into account the levels at which these specialized metabolites are normally biosynthesized, requires a large amount of biological material that is difficult to supply (this constraint is therefore known as the supply problem) [51], [52]. In the case of marine invertebrates such as corals and sponges, it can be even more complex since the growth rate of these organisms is slow, and they hardly adapt to captive conditions (e.g., aquarium) [53], [54]. In addition, these changes may compromise the ecological interactions that promote target compound synthesis.

The influence of the associated microbiota on the specialized metabolism of macroorganisms is well established. In fact, in some cases, metabolites previously isolated from macroorganisms are found to be synthesized by microorganisms [55]. This event partially explains the increased interest in researching natural products produced by microorganisms [56]. Interestingly, sponges and soft corals are among the main sources from which microorganisms have been isolated for this type of studies [56]. Unlike macroorganisms, microbes offer engaging possibilities (e.g., medium engineering, heterologous expression) for exploiting their specialized metabolism-related arsenal and offer a valuable opportunity to the biotechnology field [57], [58].

5. Microbiota Associated with Sponges and Corals

In 2019, Zhiyong Li edited the book "*Symbiotic Microbiomes of Coral Reefs Sponges and Corals*." It summarizes key aspects about the importance of coral reefs as ecosystems and their prominent members, i.e., sponges and corals [59]. This book also discusses topics such as the structure and diversity of sponge/coral microbiomes and the biosynthesis of naturally occurring compounds by associated microbes. Actinomycetes are a significant group of microbiota associated with sponges and corals, particularly when targeting microorganisms that produce bioactive compounds [60]. Therefore, it is common for these marine invertebrates to have a high content of microorganisms, exceeding the 10^6 microbial cells per cubic centimeter of tissue [61], [62].

Due to their sessile nature, sponges and corals rely heavily on their specialized metabolisms to overcome the selection pressures they are subjected to [63], [64]. For this reason, it is not surprising that corals and sponges are among the marine organisms from which the most bioactive compounds have been isolated. There is increasing evidence supporting the role of the associated microbiota in the biosynthesis of specialized bioactive metabolites [65]–[67]. Despite the diversity of microbial taxa, the phylum Actinomycetota has traditionally been the group of bacteria with the greatest potential in microbial natural products [68].

6. Specialized Metabolism of Actinomycetes

Specialized metabolism (also known as secondary metabolism) refers to metabolic pathways used to synthesize compounds that are not required for the organism's survival (which, in contrast, is defined as primary metabolism) but play essential roles in its ecological niches and adaptive capacity [69], [70]. These naturally-occurring compounds are synthesized in a sequential series of steps involving enzymes encoded by genes that are often arranged together in genome regions called biosynthetic gene clusters (BGCs) [71]. These BGCs usually consist of one or several core genes (which could be identified using an algorithm based on hidden Markov models [72]), additional biosynthetic genes, transport-related genes, regulatory genes, and resistance genes (especially those involving metabolites with antimicrobial activity or defensive effects), as well as other genes (i.e., genes that could not be annotated by homology according to the information available in the databases). For instance, Figure 3 shows the structure of the BGC responsible for salinomycin synthesis. In this regard, understanding BCGs provide relevant information on the synthesis and its plausible control of various bioactive molecules, including antibiotics, pigments, and other natural products, and may have applications in fields such as medicine, agriculture, and industry.

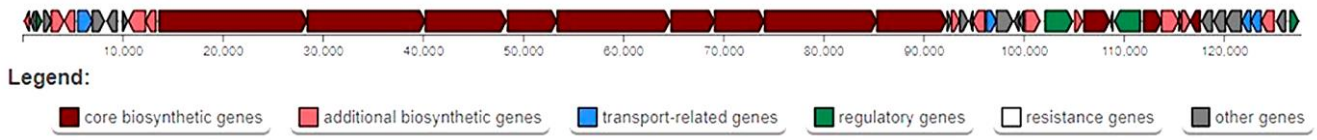

Figure 3. Salinomycin BGC from *Streptomyces albus*. Diagram of a biosynthetic gene cluster taken from "Minimum Information about a Biosynthetic Gene cluster" (MIBiG) [71].

The specialized metabolism of bacteria is vastly diverse [73]. However, this diversity is not homogeneously distributed across bacterial taxa, and richer clades (e.g., *Actinomyces*, *Bacillus*, *Streptomyces*) can be found more than others [74]. Recently, a study mapped the occurrence of BGCs in 10,000 bacterial genomes involving 68 phyla [75]. By far, most BGCs of different types were found in the phylum Actinomycetota. Even though the genus *Streptomyces* was the richest and most abundant in terms of BGC content, other less explored actinobacterial genera such as *Actinosynnema*, *Kibdelosporangium*, *Kitasatospora*, *Kutzneria*, *Nocardia*, and *Saccharothrix* showed interesting potential [75]. This is partially explained by the role played by the vertical evolution of this genetic background and thus justified the significance of actinomycetes (including non-streptomycetes, also referred to as rare actinomycetes) in microbiological bioprospecting [74].

The presence of BGCs in a microorganism indicates its potential to produce specialized metabolites. *Streptomyces* is a genus with a highest occurrence of BGCs [76] and is also known for producing a large number of bioactive compounds [77], [78], many of which are commercially exploited [79]. Although the connection between BGCs and the synthesized metabolites is not yet fully understood [80], this correlation is not accidental. The clearer the regulation of specialized metabolite synthesis in microorganisms, the better the chances of using microbial biotechnology to address human challenges.

Microorganisms offer an interesting opportunity for the sustainable use of natural resources [81], [82]. With the advancement in molecular (e.g., heterologous expression, ribosome engineering, CRISPR/Cas9) and computer-aided (e.g., bio- and chemoinformatics) tools, there are increasing possibilities for developing bio-based products [83], [84]. As the available biodiversity information is expanded and its function and biosynthetic possibilities are revealed, there will be sufficient insights to identify important opportunities for biotechnological innovation.

7. Photoprotective potential of actinomycete-derived metabolites

Actinomycetota phylum is a group of bacteria with great potential to exploit their specialized metabolism, in which *Streptomyces* are the most prominent. However, its application has been concentrated in antimicrobial (several FDA-approved drugs) and cytotoxic agents, even though they have been described as having several bioactivities. For example, novobiocin is a *Streptomyces*-derived compound [85] that has a potent antioxidant capacity, even higher than compounds such as vitamin C; butylated hydroxytoluene, and vitamin E (α- tocopherol) [13]. This fact demonstrates the unexplored potential of actinomycetes. Therefore, we conducted a systematic review to comprehensively analyze the production of photoprotective compounds by *Streptomyces*.

We find that *Streptomyces* have a high potential for application in photoprotection [13]. Interestingly, although several strains were found to produce compounds with antioxidant and anti-inflammatory capacity, their ability to absorb UV radiation has been scarcely examined, and we only found this evaluation for prodiginines (i.e., prodigiosin and undecylprodigiosin). This statement is supported by the fact that only studies on prodiginines [86], [87] intentionally investigated anti-UV applications. Thus, the potential of *Streptomyces* as a producer of photoprotective compounds has been overlooked.

The study revealed a diverse range of chemical compounds, including polyketides, phenylpropanoids, terpenoids, flavonoids, amides, alkaloids, and compounds from mixed/hybrid pathways. Notably, nitrogen-containing compounds were particularly prominent. This result is not unexpected, given that compounds such as NRPS are among the most abundant in specialized microbial metabolism [75]. Most of these compounds did not contain substructures associated with irritant risk effects, unlike the UV filters used in sunscreen formulations [13]. This fact makes the arsenal exhibited by *Streptomyces* even more valuable, increasing the chance of discovering compounds with a lower risk of undesirable effects.

Streptomyces is definitely a priceless genus, characterized by a high number of BGCs [75] and a seemingly inexhaustible chemodiversity. Since the discovery of streptothricin and streptomycin in the 1940s [88], *Streptomyces* have shown tremendous biodiversity and chemodiversity. For instance, of the 720 *Streptomyces* species described to date, 63 were discovered between 2021 and 2023 (20 new species have been reported so far in 2023) [89]. This data indicates that the full range of *Streptomyces* genus diversity has not yet been fully explored.

Regarding chemodiversity, new compounds are described every year (for some examples of new compounds published

between 2018 and 2022 see [90]–[95]), and it has been estimated that the chemical space associated with *Streptomyces* could be 100,000 compounds [96]. However, the success exhibited by *Streptomyces* has resulted in the overlooking of other actinomycete genera. These genera (i.e., rare actinomycetes) have also been shown to be a valuable source of bioactive compounds [97].

To obtain more data on the extent of underestimation of rare actinomycetes, we performed a systematic review of the genus *Gordonia*. As expected, we found a limited amount of information available compared to *Streptomyces* [98]. In fact, no reports were found on activities related to photoprotection. Nevertheless, we took advantage of the available genome data to investigate their bioprospecting value and to provide new information on an underexplored resource. We found that several of the compounds isolated from *Gordonia* are related to *Streptomyces* [98]. Like other bacteria, NRPS-type BGCs are prominent in these strains, which have relatively high content (between 8 and 23) and diverse BGCs [98]. *Gordonia* bacteria are distributed in different environments, occupying niches both as host-associated and as free-living organisms [99]. This ubiquity, like *Streptomyces*, reflects their evolutionary success and adaptability, which is strongly associated with their specialized metabolism. These data suggests that *Gordonia*, along with other rare actinomycetes, are valuable bioresources for bioactive compounds, including those that can be used for photoprotection.

As studies evaluating the photoprotective potential of actinomycetes are limited, we used an *in silico* approach to explore the potential of *Streptomyces*-derived compounds, a representative group of the phylum Actinomycetota, as inhibitors of signaling pathways involved in photodamage (influencing these signal transduction pathways would lead to photoprotective effects [100]). Using this computer-aided analysis, we found 34 compounds exhibiting high *in silico* affinities against more than one of the targets screened (i.e., serotonin-receptor subtype 5-HT_{2A}, platelet-activating factor receptor, IL-1 receptor type 1, epidermal growth factor receptor, and cyclooxygenase-2) [101]. Although different compound types were identified, those of the alkaloid and phenylpropanoid types were the most prominent. Interestingly, the compounds with the broadest affinity spectrum (against 4 targets) were asymmetric dimers (i.e., aspergilazine A and phaeochromycin F). Dimeric compounds are a rational way to increase structural complexity that has been shown to enhance interaction with amino acid residues of protein targets [102]–[104]. These findings support the use of actinomycetes strains as biofactories for high value-added metabolites in the skin care industry.

Data indicate that actinomycetes are a valuable natural resource for developing photoprotective products. This is particularly noteworthy given the potential for discovering additional strains, particularly those associated with marine organisms [10]. In a study evaluating the photoprotective potential of actinomycetes derived from the sponge *C. varians*, several strains (i.e., *Gordonia*, *Micrococcus*, *Promicromonospora*, and *Streptomyces*) were identified as producing metabolites with antioxidant and UV-absorbing capacities [105]. All these strains were isolated for the first time from this bio-eroding sponge. Among these strains, streptomycetes exhibited the highest activities. Nevertheless, the strains of the other genera are important findings that reveal the remarkable possibilities of the associated actinomycetes of *C. varians*. If we consider the diversity of sessile marine invertebrates, such as sponges and corals, it becomes evident that a significant task lies ahead. In the future, investing effort in bioprospecting studies will provide more opportunities to discover eco-friendly solutions to the current issue of UV filters.

8. Final Remarks

Given the severity of the problems associated with UV-induced damage, sunscreen use is highly recommended [35], [106]. However, most of the ingredients available for sunscreens formulation are associated with adverse issues to human health and the environment to a greater or lesser extent. Compounds such as oxybenzone and octyl methacrylate (most used in sunscreens and other skincare products) have been associated with allergic reactions, endocrine-disrupting effects, reproductive toxicity, and carcinogenicity [107]–[110]. These compounds have also been found to persist in aquatic ecosystems and behave as toxicants [111], even contaminating the food chain [112]. Therefore, there is a need to find safer and eco-friendly compounds with photoprotective properties.

Concerns about the safety of UV filters have been increasing considerably in recent times, especially regarding their ecotoxicity [108], [113]. A paper by Fivenson *et al*. published in 2021 [114] has rigorously compiled the available information on these issues, highlighting the negative effects of UV filters on coral reef ecosystems. Coral reefs are critical ecosystems for biodiversity conservation; they are the habitat of many organisms and provide various direct and indirect benefits to society [115]. For this reason, alarm about the harmful effects on marine environments has led to extreme measures such as Hawaii's ban on using some UV filters [114]. Furthermore, several authors state that it is imperative to pursue a portfolio of safer and eco-friendly photoprotection options [114], [116], [117].

In conclusion, our research has shed light on the vast potential of actinomycete-derived products (e.g., nitrogen-containing compounds, such as prodiginines, are strong candidates), broadening the focus beyond the commonly studied *Streptomyces* [13], [101], [105]. These findings highlight a valuable opportunity for the scientific community by demonstrating that numerous ecological environments remain to be explored for photoprotective compounds. This

work represents only the beginning of an exciting journey towards the discovery of renewable and sustainable sources for the development of safe and eco-friendly sunscreens. By betting on strategies focused on microorganisms such as actinomycetes, we are laying the groundwork for a future in which sun protection is not only effective for our skin, but also friendly to our precious natural environment. This path, marked by innovation and sustainability, promises to transform the sunscreen industry and, more importantly, preserve the beauty and integrity of our planet for generations to come.

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