Photolyase Current Applications

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The photolyase family consists of flavoproteins with enzyme activity able to repair ultraviolet light radiation damage by photoreactivation. DNA damage by the formation of a cyclobutane pyrimidine dimer (CPD) and a pyrimidine-pyrimidone (6-4) photoproduct can lead to multiple affections such as cellular apoptosis and mutagenesis that can evolve into skin cancer. The development of integrated applications to prevent the negative effects of prolonged sunlight exposure, usually during outdoor activities, is imperative.

UV enzyme photolyase

1. Current Photolyase Production

As stated previously in the manuscript, there are many organisms capable of producing photolyase to repair DNA damage from UV exposure, and currently, the industry is focusing on the production of this enzyme to take advantage of its properties to improve crops and its potential use in therapeutic products [1].

The current application of the photolyase enzyme is focused on the enhancement of UV resistance not only in microorganisms, but also in other organisms and areas. An example of photolyase application is the use of it to improve agriculture practices, which has been reported to improve plants. For example, in Japan, researchers successfully modified African rice to overexpress the gene. Cyclobutane pyrimidine dimer (CPD) repaired enzyme photolyase, demonstrating an increased UVB resistance compared to the rice plants without these modifications [2]. Similarly, there is open research about improving the UV irradiation resistance of fungal insecticides to improve their pest control [3].

2. Sunscreen with Photolyase as an Ingredient

The use of products to protect the skin from the sun is something humankind has undertaken for centuries, from the Egyptians' use of different plant extracts to the sunscreens people know today, composed of a wide variety of filters offering protection beyond UV radiation [4][5]. In the last few decades, the use of sunscreens has been promoted and advertised to prevent damage to the skin by UV radiation; thus, the sunscreen market is expected to reach USD 24.4 billion by 2029 [4][6].

Despite the proven advantages of regular sunscreen application (from reducing the effects of photoaging to protecting against skin cancer) [7][8], there are some concerns about the systematic and regular use of sunscreens and the effect on vitamin D synthesis, especially in older people; nonetheless, there is plenty of evidence that deny those claims and assure that the usage of sunscreens does not affect levels of vitamin D [9][10][11]. Another concern with sunscreens is the skin absorption of the most used active ingredients, such as avobenzone and oxybenzone, among others, resulting in high plasmatic levels [12][13]. In addition to these health concerns, the damage these organic ingredients cause to the environment has been studied [14][15]. However, these findings prove the importance and the need to further assess the products used in sunscreens, and to find active ingredients that can offer the same benefits for all ages and skin types without a detrimental effect on human and environmental health [16].

The use of the photolyase has been around for the last few decades, with the first patent in 1988 [17], and since then it has been tested and proven that this enzyme can prevent and reverse sunlight-induced skin damage when used as an active ingredient in traditional sunscreen formulations [18][19][20][21].

There are sunscreens containing DNA repair enzymes obtained from microalgae and labeled as “plankton extract” available on the market. Some companies that offer this product are Isdin (Barcelona, Spain) with the product Eryfotona® AK-NMSC, Kwizda Pharma GmbH (Vienna, Austria) with Ateia®, and Pharma Cosmetics (Oradell, NJ, USA), with a variety of products such as Neova Active®, Neova Everyday®, and Neova Silc Sheer® 2.0. Many other companies are also releasing new products containing photolyase [21]. For a more in-depth listing of all the products currently available on the market, researchers recommend consulting the Supplementary Material of the review by Yarosh et al. [22].

3. Photoaging

Normal signs of aging are the appearance of fine lines, pigmentation, and wrinkles in the skin, all of which appear over time and are generally attributed to getting older; however, there is evidence that multiple factors contribute to accelerating the aging process, including lifestyle factors such as smoking, sleep, diet, the chronic use of drugs, environmental factors such as contact with polluted air, exposure to visible and infrared light [23], and UV radiation, with the last one accounting for up to 90% of visible changes on the skin [24][25].

Photoaging is a term that has been used since 1986 [26] to reference the effect on the skin produced by chronic exposure to UV radiation that causes damage to DNA [21][23][27][28] and leads to premature aging. All of these signs overlap with natural signs of aging, such as wrinkles, thin and dry skin due to a loss of underlying fat, more fragile skin, and pigmentation; however, the effects of photoaging go beyond these appearances with, depending on the skin type, the formation of fine to coarse wrinkles, a leather-like appearance to the skin, and hyperpigmentation or dyschromia. All of these signs are presented even when normal signs of aging have not appeared [24][29][30][31].

Given that photoaging only occurs in areas of the skin that have been exposed to the sun for a prolonged time, it is recommended to avoid sun exposure and apply sunscreens that provide protection against UVA and UVB radiation

and can even in some cases reverse damage [7][24][32]. Listed below are some studies related to the use of photolyase in clinical trials intended to assess the efficacy of this enzyme to mitigate the effects of photoaging.

Corinne Granger et al. conducted a study in which they tested, over 28 days, a tinted sunscreen containing encapsulated photolyase on 30 women of ages ranging from 45 to 65 with slight-to-moderate photoaging signs [33]. The patients were evaluated on day zero and on the last day of use and signs of photoaging were analyzed and evaluated. The results showed an improvement between 6 and 12% for each factor analyzed in the treated women compared to the control.

Another study was conducted to prove the efficacy of using photolyase from the microalgae *Anacystis nidulans* to prevent damage to DNA produced by UV radiation on the skin. This was performed by comparing the use of a regular sunscreen with a sun protection factor (SPF) 50, and the same sunscreen supplemented with photolyase [34].

The results from this research revealed that, for the 10 participants (5 males and 5 females, with ages ranging from 26 to 36 years old and Fitzpatrick skin type II), the formation of CPDs and apoptosis of the skin cells was reduced by 93%, and 82%, respectively, with the use of the sunscreen containing photolyase compared with the control that received only radiation.

Similarly, Emanuele et al. [35] compared a novel topical product containing a traditional sunscreen with SPF 50, a mixture of DNA repair enzymes encapsulated in liposomes, one of them being photolyase, and an antioxidant complex versus other topical products with similar characteristics. The study demonstrated the novel topical products as the most effective in reducing the three parameters analyzed: the formation of CPD, 8-oxo-7,8-dihydro-2′-deoxyguanosine (8OHdG), and protein carbonylation (PC). This was attributed to the synergistic effect of all the components within the product.

4. Actinic Keratosis

Actinic keratosis (AK) is a skin disease that is characterized by squamous lesions that histologically show keratinocyte neoplasms occurring on skin that has had long-term exposure to UV radiation [36]. AK is typically presented in people with light skin belonging to the Fitzpatrick skin types of I to III in areas of the skin on which they experience solar exposure regularly, such as the head (especially in areas with hair loss), ears, neck, forearm, and the dorsum of the hand [19][37]. The lesions of AK can progress to keratinocyte carcinoma, the most common type of skin cancer in the United States [38]. Therefore, AK must be prevented or treated early to avoid further disease progression. The method to prevent skin damage is to avoid sun exposure, but when the exposure is inevitable it is recommended to use protective clothes and at least 2 mg per cm^2 of sunscreen in the exposed areas [39]. However, these measures are not enough once the skin damage is present and the use of active molecules capable of stopping and even reversing this damage is essential [40].

Some studies have been published with diverse findings. For example, the efficacy of photolyase in sunscreen and a combination of topical antioxidants in the treatment of patients with AK were assessed in Brazil [41]. A total of 80 patient forearms were tested using either regular sunscreen or sunscreen containing photolyase during the day and the night. They either applied topical antioxidant or placebo cream to one forearm for 8 weeks. The researchers found that all groups tested showed a significant improvement at the end of the study; however, there were little to no significant differences between the groups using regular sunscreen and those with additional photolyase. The authors attributed this to the short time period of the treatment.

Puig-Butillé et al. [42] evaluated the use of a film-forming medical device containing photolyase in liposomes on a small group of patients from a wide range of ages, composed mainly of males that presented multiple AK and two patients with xeroderma pigmentosum. The study was conducted for 4 weeks, and at the end of the study, all groups showed an improvement in their condition. Notably, some showed total clearance on the assessed area from lesions caused by UV radiations. With the same medical device with photolyase, Eibenschutz et al. [43] analyzed the effect of the product with the enzyme compared to a regular sunscreen on 30 patients that underwent photodynamic therapy (PDT) with a total of 225 AK lesions for 9 months. At the end of the treatment, it was shown that the group treated with the film-forming medical device did better than the group treated with regular sunscreen. PDT was not needed, nor was any other medical procedure, and no new AK lesions were observed.

A research study in 2015 compared the effects of sunscreen containing photolyase and traditional sunscreens in 28 patients during 6 months of treatment [44]. The findings showed that both treatments reduced hyperkeratosis; however, for the field cancerization and the levels of CPDs, the results showed a better performance in the group that used the sunscreen containing photolyase than the group that used the traditional sunscreens.

5. Skin Cancer

Skin cancer remains a major global public health threat [45]. As the human body naturally grows, cells are divided when needed and die when they lose their normal function, or due to natural cell-aging. Cancer starts as a result of an interference in the cycle of cell growth division and death. This condition is characterized by an overproduction of cell division and the permanency of abnormal cells, instead of their death [46].

According to the American Cancer Society, there are five types of skin cancer: basal and squamous cell skin cancer, melanoma skin cancer, Merkel cell skin cancer, lymphoma of the skin, and Kaposi sarcoma. The basal and squamous cell skin cancers are mostly found on the body areas commonly exposed to the sun without protection, such as the head, neck, and arms. These two types are the most common, and they start in the epidermis [46]. In early-stage cases, a skin excision is the treatment for squamous cell carcinoma (SCC) [47].

The precursor cell of SCC is AK, and for BCC it is hypothesized that its occurrence is related to interfollicular epidermal basal keratinocytes with retained basal morphology from the follicular outer root sheath or sebaceous gland-derived keratinocytes [48]. Malignant melanoma is a serious form of skin cancer that begins in cells known as melanocytes. While it is less common than SCC and BCC, melanoma is the most severe type of skin cancer due to

its capacity to spread if it is not treated at an early stage [49][50]. Merker cell, lymphoma, and Kaposi cancers are less common types of skin cancer [46].

Field cancerization refers to the replacement of the normal cell population by a cancer-primed cell population that may show no morphological change [51]. Some studies have focused on this topic and the role of photolyase as a potential treatment. A study with a topic product categorized as a medical device containing photolyase showed positive results for treating cancerization areas with long-term use versus the use of commercially available sunscreen, not only in terms of Baseline Severity Index (BSI) and total Clinical Score (TCS), but also by reducing the occurrence of new AK lesions [52].

In 2016, Naverrete-Dechent et al. [53] showed that subjects with skin field cancerization showed a partial positive response to the treatment with a photolyase-added sunscreen and at least a 50% reduction in their lesion number. These findings are consistent with the work of Laino et al. [51], where 30 individuals with AK were treated with a photolyase-added medical device, which improved their lesions.

References

1. He, Y.; Qu, C.; Zhang, L.; Miao, J. DNA photolyase from Antarctic marine bacterium Rhodococcus sp. NJ-530 can repair DNA damage caused by ultraviolet. 3 Biotech 2021, 11, 102.
2. Mmbando, G.S.; Teranishi, M.; Hidema, J. Transgenic rice Oryza glaberrima with higher CPD photolyase activity alleviates UVB-caused growth inhibition. GM Crop. Food 2021, 12, 435–448.
3. Tong, S.; Feng, M. Molecular basis and regulatory mechanisms underlying fungal insecticides' resistance to solar ultraviolet irradiation. Pest Manag. Sci. 2022, 78, 30–42.
4. Ma, Y.; Yoo, J. History of sunscreen: An updated view. J. Cosmet. Dermatol. 2021, 20, 1044–1049.
5. Lyons, A.B.; Trullas, C.; Kohli, I.; Hamzavi, I.H.; Lim, H.W. Photoprotection beyond ultraviolet radiation: A review of tinted sunscreens. J. Am. Acad. Dermatol. 2021, 84, 1393–1397.
6. Guan, L.L.; Lim, H.W.; Mohammad, T.F. Sunscreens and Photoaging: A Review of Current Literature. Am. J. Clin. Dermatol. 2021, 22, 819–828.
7. Singer, S.; Karrer, S.; Berneburg, M. Modern sun protection. Curr. Opin. Pharmacol. 2019, 46, 24–28.
8. Seité, S.; Fourtanier, A.M.A. The benefit of daily photoprotection. J. Am. Acad. Dermatol. 2008, 58, S160–S166.
9. Passeron, T.; Bouillon, R.; Callender, V.; Cestari, T.; Diepgen, T.L.; Green, A.C.; van der Pols, J.C.; Bernard, B.A.; Ly, F.; Bernerd, F.; et al. Sunscreen photoprotection and vitamin D status. Br.

J. Dermatol. 2019, 181, 916–931.

10. Neale, R.E.; Khan, S.R.; Lucas, R.M.; Waterhouse, M.; Whiteman, D.C.; Olsen, C.M. The effect of sunscreen on vitamin D: A review. Br. J. Dermatol. 2019, 181, 907–915.
11. Marks, R.; Foley, P.A.; Jolley, D.; Knight, K.R.; Harrison, J.; Thompson, S.C. The Effect of Regular Sunscreen Use on Vitamin D Levels in an Australian Population: Results of a Randomized Controlled Trial. Arch. Dermatol. 1995, 131, 415–421.
12. Matta, M.K.; Zusterzeel, R.; Pilli, N.R.; Patel, V.; Volpe, D.A.; Florian, J.; Oh, L.; Bashaw, E.; Zineh, I.; Sanabria, C.; et al. Effect of Sunscreen Application Under Maximal Use Conditions on Plasma Concentration of Sunscreen Active Ingredients. JAMA 2019, 321, 2082.
13. Matta, M.K.; Florian, J.; Zusterzeel, R.; Pilli, N.R.; Patel, V.; Volpe, D.A.; Yang, Y.; Oh, L.; Bashaw, E.; Zineh, I.; et al. Effect of Sunscreen Application on Plasma Concentration of Sunscreen Active Ingredients. JAMA 2020, 323, 256.
14. Siller, A.; Blaszak, S.C.; Lazar, M.; Olasz Harken, E. Update About the Effects of the Sunscreen Ingredients Oxybenzone and Octinoxate on Humans and the Environment. Plast. Surg. Nurs. 2018, 38, 158–161.
15. Schneider, S.L.; Lim, H.W. Review of environmental effects of oxybenzone and other sunscreen active ingredients. J. Am. Acad. Dermatol. 2019, 80, 266–271.
16. Rigel, D.S.; Lim, H.W.; Draelos, Z.D.; Weber, T.M.; Taylor, S.C. Photoprotection for all: Current gaps and opportunities. J. Am. Acad. Dermatol. 2022, 86, S18–S26.
17. Mezei, M.; Gulasekharam, V.; Straubinger, R.; Hong, K.; Friend, D. Purification and administration of dna repair enzymes. Int. J. Pharm. 1988, 173, 3415–3422.
18. Kavakli, I.H.; Ozturk, N.; Gul, S. DNA repair by photolyases. Adv. Protein Chem. Struct. Biol. 2019, 115, 1–19.
19. Puig, S.; Granger, C.; Garre, A.; Trullàs, C.; Sanmartin, O.; Argenziano, G. Review of Clinical Evidence over 10 Years on Prevention and Treatment of a Film-Forming Medical Device Containing Photolyase in the Management of Field Cancerization in Actinic Keratosis. Dermatol. Ther. 2019, 9, 259–270.
20. Garinis, G.A.; Jans, J.; van der Horst, G.T.J. Photolyases: Capturing the light to battle skin cancer. Futur. Oncol. 2006, 2, 191–199.
21. Luze, H.; Nischwitz, S.P.; Zalaudek, I.; Müllegger, R.; Kamolz, L.P. DNA repair enzymes in sunscreens and their impact on photoageing—A systematic review. Photodermatol. Photoimmunol. Photomed. 2020, 36, 424–432.
22. Yarosh, D.B.; Rosenthal, A.; Moy, R. Six critical questions for DNA repair enzymes in skincare products: A review in dialog. Clin. Cosmet. Investig. Dermatol. 2019, 12, 617–624.

23. Addor, F.A.S. Beyond photoaging: Additional factors involved in the process of skin aging. Clin. Cosmet. Investig. Dermatol. 2018, 11, 437–443.
24. Huang, A.H.; Chien, A.L. Photoaging: A Review of Current Literature. Curr. Dermatol. Rep. 2020, 9, 22–29.
25. The Skin Cancer Foundation. Photoaging: What You Need to Know about the Other Kind of Aging. Available online: https://www.skincancer.org/blog/photoaging-what-you-need-to-know/ (accessed on 25 January 2022).
26. Kligman, L.H. Photoaging. Manifestations, prevention, and treatment. Dermatol. Clin. 1986, 4, 517–528.
27. Gilchrest, B.A. Photoaging. J. Invest. Dermatol. 2013, 133, E2–E6.
28. Megna, M.; Lembo, S.; Balato, N.; Monfrecola, G. “Active” photoprotection: Sunscreens with DNA repair enzymes. Ital. J. Dermatol. Venereol. 2017, 152, 302–307.
29. Berneburg, M.; Plettenberg, H.; Krutmann, J. Photoaging of human skin. Photodermatol. Photoimmunol. Photomed. 2000, 16, 239–244.
30. Han, A.; Chien, A.L.; Kang, S. Photoaging. Dermatol. Clin. 2014, 32, 291–299.
31. Krutmann, J.; Schalka, S.; Watson, R.E.B.; Wei, L.; Morita, A. Daily photoprotection to prevent photoaging. Photodermatol. Photoimmunol. Photomed. 2021, 37, 482–489.
32. Fisher, G.J.; Kang, S.; Varani, J.; Bata-Csorgo, Z.; Wan, Y.; Datta, S.; Voorhees, J.J. Mechanisms of photoaging and chronological skin aging. Arch. Dermatol. 2002, 138, 1462–1470.
33. Granger, C.; Trullàs, C.; Bauza, G.; Garre, A. 17895 Anti-photoaging effect of a novel tinted facial sunscreen with high sun protection, peptide complex, and encapsulated photolyase after 1 month of use. J. Am. Acad. Dermatol. 2020, 83, AB202.
34. Emanuele, E. Reduced ultraviolet-induced DNA damage and apoptosis in human skin with topical application of a photolyase-containing DNA repair enzyme cream: Clues to skin cancer prevention. Mol. Med. Rep. 2011, 5, 570–574.
35. Emanuele, E.; Spencer, J.M.; Braun, M. An experimental double-blind irradiation study of a novel topical product (TPF 50) compared to other topical products with DNA repair enzymes, antioxidants, and growth factors with sunscreens: Implications for preventing skin aging and cancer. J. Drugs Dermatol. 2014, 13, 309–314.
36. Eisen, D.B.; Asgari, M.M.; Bennett, D.D.; Connolly, S.M.; Dellavalle, R.P.; Freeman, E.E.; Goldenberg, G.; Leffell, D.J.; Peschin, S.; Sligh, J.E.; et al. Guidelines of care for the management of actinic keratosis. J. Am. Acad. Dermatol. 2021, 85, e209–e233.

37. Salasche, S.J. Epidemiology of actinic keratoses and squamous cell carcinoma. J. Am. Acad. Dermatol. 2000, 42, S4–S7.
38. Albert, M.R.; Weinstock, M.A. Keratinocyte Carcinoma. CA. Cancer J. Clin. 2003, 53, 292–302.
39. Krutmann, J.; Berking, C.; Berneburg, M.; Diepgen, T.L.; Dirschka, T.; Szeimies, M. New Strategies in the Prevention of Actinic Keratosis: A Critical Review. Skin Pharmacol. Physiol. 2015, 28, 281–289.
40. Rosenthal, A.; Stoddard, M.; Chipps, L.; Herrmann, J. Skin cancer prevention: A review of current topical options complementary to sunscreens. J. Eur. Acad. Dermatol. Venereol. 2019, 33, 1261–1267.
41. Alvares, B.A.; Miola, A.C.; Schimitt, J.V.; Miot, H.A.; Abbade, L.P.F. Efficacy of sunscreen with photolyase or regular sunscreen associated with topical antioxidants in treating advanced photodamage and cutaneous field cancerization: A randomized clinical trial. An. Bras. Dermatol. 2022, 97, 157–165.
42. Puig-Butillé, J.A.; Malvehy, J.; Potrony, M.; Trullas, C.; Garcia-García, F.; Dopazo, J.; Puig, S. Role of CPI-17 in restoring skin homoeostasis in cutaneous field of cancerization: Effects of topical application of a film-forming medical device containing photolyase and UV filters. Exp. Dermatol. 2013, 22, 494–496.
43. Eibenschutz, L.; Silipo, V.; De Simone, P.; Buccini, P.L.; Ferrari, A.; Carbone, A.; Catricalà, C. A 9-month, randomized, assessor-blinded, parallel-group study to evaluate clinical effects of film-forming medical devices containing photolyase and sun filters in the treatment of field cancerization compared with sunscreen in patients after successful p. Br. J. Dermatol. 2016, 175, 1391–1393.
44. Carducci, M.; Pavone, P.S.; De Marco, G.; Lovati, S.; Altabas, V.; Altabas, K.; Emanuele, E.; De Marco, G.; Lovati, S.; Altabas, V.; et al. Comparative Effects of Sunscreens Alone vs. Sunscreens Plus DNA Repair Enzymes in Patients With Actinic Keratosis: Clinical and Molecular Findings from a 6-Month, Randomized, Clinical Study. J. Drugs Dermatol. 2015, 14, 986–990.
45. Parker, E.R. The influence of climate change on skin cancer incidence—A review of the evidence. Int. J. Women's Dermatol. 2021, 7, 17–27.
46. American Cancer Society; The American Cancer Society. Skin Cancer|Skin Cancer Facts|Common Skin Cancer Types. Available online: https://www.cancer.org/cancer/skin-cancer.html (accessed on 27 January 2022).
47. Chabaane, M.; Ayadi, K.; Rkhami, M.; Drissi, C.; Houimli, S.; Bahri, K.; Zammel, I.; Badri, M. Management of a recurrence of a squamous cell carcinoma of the scalp with extension to the brain: A case report and literature review. Surg. Neurol. Int. 2020, 11, 347.

48. Cobanoglu, H.B.; Constantinides, M.; Ural, A. Nonmelanoma Skin Cancer of the Head and Neck: Molecular Mechanisms. Facial Plast. Surg. Clin. N. Am. 2012, 20, 437–443.
49. The American Cancer Society. What Is Melanoma Skin Cancer? Available online: https://www.cancer.org/cancer/melanoma-skin-cancer/about/what-is-melanoma.html (accessed on 27 January 2022).
50. Agamohammadi, D.; Reihan, M.D.; Mirzaei, F.; Payandeh, Z.; Farzin, H.; Marahem, M. New Therapies for Melanoma Cancer Strategies. Crescent J. Med. Biol. Sci. 2021, 8, 3–9.
51. Laino, L.; Elia, F.; Desiderio, F.; Scarabello, A.; Sperduti, I.; Cota, C.; DiCarlo, A. The efficacy of a photolyase-based device on the cancerization field: A clinical and thermographic study. J. Exp. Clin. Cancer Res. 2015, 34, 84.
52. Moscarella, E.; Argenziano, G.; Longo, C.; Aladren, S. Management of cancerization field with a medical device containing photolyase: A randomized, double-blind, parallel-group pilot study. J. Eur. Acad. Dermatol. Venereol. 2017, 31, e401–e403.
53. Navarrete-Dechent, C.; Molgó, M. The use of a sunscreen containing DNA-photolyase in the treatment of patients with field cancerization and multiple actinic keratoses: A case-series. Dermatol. Online J. 2016, 23, 4–7.