

An Extensive Review of Sunscreen and Sun Tan Preparations

AK Mohiuddin*

*Department of Pharmacy, World University of Bangladesh, Bangladesh.

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ABSTRACT

The sunscreen industry is achieving remarkable worldwide prominence by responding to the growing need for skin protection with fast-paced innovation. Increased consumer awareness of the harmful effects of sunlight has fueled the demand for improved photo protection. The need for broad-spectrum protection from both UVA and UVB rays has inspired scientists worldwide to research new cosmetic formulations and delivery systems. More effective sunscreen actives, emollients and novel cosmetic and functional ingredients have been regularly added to the formulator's repertoire. Creativity in innovation has been hindered only by regulatory agencies and patent restrictions worldwide. Familiarity with the current restrictive regulations and patent law infringements has become integral to any research effort attempting to provide improved protection to individuals affected by the sun's damaging effects. The increasing incidence of skin cancers and photo damaging effects caused by ultraviolet radiation has increased the use of sun screening agents, which have shown beneficial effects in reducing the symptoms and reoccurrence of these problems. Unlike the situation in Europe where sunscreen ingredients are considered under cosmetics guidelines, the FDA is required to define sunscreens as drugs since they are advertised to prevent sunburn and, more recently, the risk of skin cancer. In the USA, the FDA has been regulating this industry since August 25, 1978, with the publication of the Advance Notice of Proposed Rulemaking. Sunscreens are considered drugs and cosmetics and therefore must be governed by the FDA-OTC monograph. With the variety of sunscreen agents used in cosmetic and UV protection products, Australia, Canada, and the European Union (EU) have also developed regulatory protocols on safe sunscreen product use. Unlike the USA though, Australia has approved 34 active sunscreen ingredients and the EU has approved 28 of these ingredients. Current FDA regulations allow labeling of sunscreen products to a maximum of 30p, despite the many products currently available with numbers as high as 100. From a cosmetic formulation point of view, increasing the SPF number in a product is governed by simple chemical principles.

Keywords: Melanoma, Carcinoma, Immunosuppression, Retinoids, Tretinoin, Photodamage

Abbreviations: NMSC: Non-Melanoma Skin Cancer; KLF4: Kruppel Like Factor 4; PPARG: Peroxisome Proliferator Activated Receptor Gamma; APC: Antigen Presenting Cell; BBB: Blood-Brain Barrier; EWG: Environmental Working Group; GRASE: Generally Recognized as Safe and Effective; PABA: P-Aminobenzoic Acid; MSS: Mesoporous Silicas; HPCD: Hydroxypropyl-Beta-Cyclodextrin; OMC: Octyl Methoxycinnamate; ROS: Reactive Oxygen Species; PUVA: Psoralen Plus UVA; SAD: Seasonal Affective Disorder; MDD: Major Depressive Disorder; AK: Actinic Keratosis; SCC: Squamous Cell Carcinoma; BCC: Basal Cell Carcinoma; NPs: Polymeric Nanoparticles; BEMT: Bisethylhexyloxyphenol Methoxyphenyl Triazine; SLN: Solid Lipid Nanoparticle; HDPE/LDPE: High-Density Polyethylene/Low-Density Polyethylene; EAE: Autoimmune Encephalomyelitis; MS: Multiple Sclerosis; iNOS: Inducible Nitric Oxide Synthase; TNF- α : Tumor Necrosis Factor Alpha; IARC: International Agency for Research on Cancer; UVAPF: Ultraviolet (UV) A Protection Factor

BACKGROUND

Ra (Re) was the primary name of the sun god of Ancient Egypt. According to Osiris myth, Nut, the mother of Osiris swallowed the setting sun (Ra) each evening and gave birth to him each morning. The Ancient Egyptians were well aware of the dangers of the sun. Their lands were scorched with heat. Women protected their skin, preferring light skin to dark in their cultural hierarchy of beauty. Recent

Corresponding author: Dr. AK Mohiuddin, Assistant Professor, Department of Pharmacy, World University of Bangladesh 151/8, Green Road, Dhanmondi, Dhaka – 1205, Bangladesh, Tel: +8801716477485; E-mail: mohiuddin3@pharmacy.wub.edu.bd

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discoveries written on papyri and the walls of several tombs unearthed ingredients and formulations in use in Ancient Egypt specifically addressing issues of sun damage to the hair and skin. Also, a brief historical review manifests the following interesting things indeed (**Figure 1**):

- Jasmin was used to heal the sun-damaged skin. Recent evidence reveals that Jasmin aids in DNA repair at the cellular level.
- Aloe was used to heal sun-damaged skin.
- Olive oil was used as hydrating oil for both skin and hair damaged by overexposure to the sunlight.
- Almond oil was applied before and after sun exposure to hydrate the sun-damaged skin, improving elasticity and texture.
- Rice bran extracts were used in sunscreen preparations. Today, gamma oryzanol extracted from rice bran has UV absorbing properties.
- Kohl (to darken eyes in order to combat sunlight impairment to the retina in the glare of the desert sun), red ochre (to redden and impart a rosy glow in women's makeup mimicking the effect of the sun on the skin), and henna oil (to dye the lips and nails, darken the color of the hair and skin and protect light skin from the sun). Today, henna is one of the most widely used natural sunscreen with both UVA and UVB protection.
- Lupin extract was used to block the rays of the sun and is still used to date to lighten the color of the skin.
- Calcite powder and clay were used as UV filters similar to the modern-day inorganic particulates zinc oxide and titanium dioxide.
- Aquatic lotus oil was used for protection of the skin from the sun.



Figure 1. Diana, Princess of Wales, Vogue 1981. According to the magazine Longevity, Princess Diana was “scrupulous about using an SPF-8 sunblock.” While the American Academy of Dermatology recommends applying at least SPF 30, protection against UV rays can prevent both sunburn and dangerous skin cancers.

Source: Picard C. *25 Beauty Secrets to Steal from Princess Diana*. Web GoodHousekeeping.com, Mar 7, 2017

INTRODUCTION

Protection from sunlight is often equated with use of sunscreens, but this approach is too narrow, and protection should consist of a package of measures: avoiding overexposure to sunlight, using sunscreens, and wearing protective clothing. Solar ultraviolet (UV) radiation significantly influences the skin, causing aging, sunburns,

precancerous and cancerous lesions and immunosuppression. UV radiation has an immunosuppressive effect on the antigen-presenting cells within the epidermis and contributes to the likelihood of skin cancer. If solar radiation is a primary risk factor for malignant melanoma, it is reasonable to conclude that reducing sun exposure via topical sunscreen use would be associated with reduced disease risk. Melanoma is more

common in Whites than in Blacks and Asians. The incidence of non-melanoma skin cancer (NMSC) is dramatically increasing worldwide, despite the increased use of improved sunscreens. In 2014, the Surgeon General estimated that 2.2-5.0 million people were treated annually for NMSC. As the number of newly diagnosed skin cancers continues to rise, there is a need for additional preventative measures beyond sunscreens. UV radiation is the second most prevalent carcinogenic exposure in Canada, fifth in Switzerland and is similarly important in other countries with large Caucasian populations. Within the UK, Wales has among the highest rates of skin cancer annually and skin cancer diagnosis rates have increased 63% in 10 years. Australia and New Zealand having the world's highest skin cancers. People living in Australia and New Zealand are now advised to apply sunscreen every day when the UV index is predicted to reach 3 or above. Denmark has one of the highest incidences of melanoma in the world, although it is a relatively northern country. Implications for public health: Increased use of sunscreen as part of the daily routine to reduce incidental sun exposure will lead to decreased incidence of skin cancer in the future. There are 3 kinds of UV radiation: UVC, UVB, and UVA. The ozone layer ingests 100% of UVC, 90% of UVB and a negligible measure of UVA. Therefore, exhaustion of the ozone layer expands UV transmission. UVA is related with aging and pigmentation. It enters profound into the skin layer and creates free extreme oxygen species, in a roundabout way damaging DNA. UVA expands the quantity of incendiary cells in the dermis and diminishes the quantity of antigens introducing cells. UVB causes sunburn and DNA strand breaks. It causes pyrimidine dimer changes which are related with non-melanoma skin malignancies. Photo protection includes both essential and secondary protective variables. Essential variables are sunscreens; these incorporate physical barriers which reflect and dissipate light and substance barriers which ingest light. Secondary components incorporate cancer prevention agents, osmolytes and DNA repair enzymes which help to constrain skin harm by exasperating the photochemical cascade that happens by UV sunlight. People with black skin are much less susceptible to sunburn than white-skinned individuals. Black people living in the UK were more likely to use sunscreen as a form of sun protection, whereas sunscreen was the least popular modality in the two African countries with shade being the most common form of limiting sun exposure. A significant benefit from regular sunscreen use has not yet been demonstrated for primary prevention of basal cell carcinoma and melanoma. Concerning the prevention of actinic keratoses, squamous cell carcinomas, and skin aging, the effect of sunscreens is significant, but it remains incomplete. Some organic UV filters (PABA derivatives, cinnamates, benzophenones and octocrylene) have been described to cause photo allergy. Percutaneous absorption and endocrine disrupting activity of small-sized organic and nano-sized inorganic UV filters have been reported.

POSITIVE EFFECTS OF UVR

Exposure to UVR is not always considered bad. In fact, UVR has been found to be particularly helpful in treating vitamin D deficiency, seasonal affective disorders, psoriasis, sarcoidosis, mycosis fungoides and numerous other cutaneous conditions. Within the epidermis, 7-dehydrocholesterol is converted to vitamin D (cholecalciferol) by UVB light. The elderly and young children are the ones who are particularly susceptible to vitamin D deficiency. Vitamin D deficiency can lead to rickets in children, osteomalacia in adults, osteopenia/osteoporosis, and fractures in the elderly. The Institute of Medicine recommends the following vitamin D allowances: 400 IU for 0 to 12 months, 600 IU for 1 to 70 years and 800 IU for greater than 70 years. Light therapy is an inexpensive treatment and can be beneficial in treating certain diseases. Although it has been known for the last 100 years that UV light (particularly UVC with a wavelength range of 240-280 nm) is highly germicidal, its use to treat wound or other localized infections remains at an early stage of development. *Candida auris* is globally emerging yeast, causing severe infections in patients with underlying diseases. This yeast is responsible for several outbreaks within healthcare facilities, where it can be found on hospital surfaces and patient care devices. Spread from these fomites may be prevented by improving the decontamination of hospital surfaces. UV-C decontamination may constitute an effective adjunct to routine room cleaning. Additionally, difficult-to-treat psoriasis patients sometimes find relief with UVR. It is thought that UVR has both anti-proliferative and anti-inflammatory effects through down regulation of T-cell response to antigens. Studies have also shown improvement of the cutaneous effects of sarcoidosis with UVA-1 light and topical psoralen plus UVA (PUVA) therapy. PUVA and narrowband UVB has been shown to induce and maintain remissions of mycosis fungoides. Phototherapy is the use of light for reducing the concentration of bilirubin in the body of infants. However, the exposure to UV in childhood has been established as an important contributing factor for melanoma risk in adults and considering the high susceptibility to UV-induced skin damage of the new-born, related to his pigmentary traits, the UV exposure of the infant during phototherapy should be "as low as reasonably achievable," considering that it is unnecessary to the therapy. Protective eyewear can be necessary during newborn assistance activities carried out in proximity of some sources. Most people judge sun exposure in non-erythemal doses as pleasant. Exposure to sunlight has been linked to improved energy and elevated mood. Seasonal affective disorder (SAD) is a seasonal pattern of recurrent major depressive episodes that most commonly occurs during autumn or winter and remits in spring. The prevalence of SAD ranges from 1.5% to 9%, depending on latitude. Evidence on light therapy as preventive treatment for patients with a history of SAD is limited, preventive

treatment of SAD and the treatment selected should be strongly based on patient preferences. Light therapy, an effective treatment for seasonal affective disorder (SAD), may also be appropriate for MDD which is the second-ranked cause of disability worldwide. Bright light treatment, both as monotherapy and in combination with fluoxetine, was efficacious and well tolerated in the treatment of adults with non-seasonal MDD. The combination treatment had the most consistent effects [77-83].

SUNBURN

Sunburn and sunscreen facts

- Sunburn and sun poisoning are forms of skin damage due to UV ray exposure. The symptoms can range from mild to severe and may require treatment.
- Sunburn might be sun poisoning if there is blisters, hives or rash, fever and chills, nausea, dehydration, headache, pain and tingling, vision problems [1].
- UV rays are most intense at noon and the hours immediately before and after (between 10 AM and 4 PM) [2-10].
- Immediate symptoms of sunburn are hot, red, tender skin; pain when the skin is touched or rubbed; and dehydration; several days after exposure the skin may swell, blister and peel [3].
- Most sunburns are mild and can be treated with home remedies such as applying damp cloths or compresses to reduce the pain, soaking in a tepid bath (with no soap), gently patting the skin dry, applying soothing creams or lotions, OTC pain relievers such as Tylenol or others, and moisturizing the skin [4].
- Sunburn may cause permanent skin damage and skin cancer (malignant melanoma, basal cell carcinoma, squamous cell carcinoma) [5].
- Persons with certain pigment disorders and individuals with fair skin are at most risk of sunburn [6].
- Certain diseases and conditions pose a higher risk of sunburn (for example, albinism, lupus, porphyria, vitiligo and xeroderma pigmentosum) [7].
- Some medications may increase sensitivity to sunburn (photosensitivity) [8,10].
- Sun poisoning is caused by severe sunburn; its symptoms include fever, nausea, chills, dizziness, rapid pulse, rapid breathing, dehydration and shock [9].
- UVA and UVB are mainly responsible for skin pathologies such as sunburns, cutaneous degeneration, photosensitivity, phototoxicity, photo-aging, immunosuppression and skin cancer [11-27].
- Snow reflects up to 80% of the sun's rays, sand reflects 15%, and grass, soil and water reflect 10%. Due to these factors, an individual sitting under a solitary standard beach umbrella can be exposed to up to 84% of the total UV radiation despite feeling adequately covered. For these reasons, it is best to seek deep shade [28].
- Less than 50% of the SPF number claimed on the label is spread on the consumer's skin, meaning that a sunscreen with an SPF 30 will give the real protection of an SPF of 15. Therefore, SPF 60 should be recommended if real protection of 30 is desired. Significant injury, DNA damage, mutations and carcinogenesis can and do occur also with cumulative sub-erythral UV exposure [29].
- The SPF was created in 1956 by Schulze and it reflects the ratio between the lower amounts of UV energy required producing a minimal erythema on sunscreen protected skin and the amount of energy required to produce the same erythema on unprotected skin [30,31].
- Since many of UV filters were shown to cross the blood-brain barrier (BBB), the risk for neurotoxicity also occurs [32-37].
- Sunscreen compounds might block vitamin D synthesis or act as endocrine disruptor and lead to developmental toxicity. The effects of sunscreen on cutaneous synthesis of vitamin D induced by sunlight have been a subject of debate for recent years; however the newest analysis suggests that normal usage of sunscreen by adults do not decrease cutaneous synthesis of vitamin D [38].
- The FDA is notoriously slow in approving sunscreen compounds, requiring exhaustive evidence of their safety. Indeed, FDA has approved only 16 sunscreen ingredients (14 organic filters and two nonorganic filters, including zinc oxide and titanium dioxide), while other areas of the world, like the European Union and Australia, have approved nearly twice as many [39].
- FDA approved sunscreen ingredients are Aminobenzoic acid, Avobenzone, Cinoxate, Dioxybenzone, Homosalate, Meradimate, Octocrylene, Octinoxate, Octisalate, Oxybenzone, Padimate O, Ensulizole, Sulisobenzene, Titanium dioxide, Trolamine salicylate and Zinc oxide [40-44].
- 2 of the 16 main ingredients used in OTC sunblock products are safe, the FDA said. Moreover, the FDA is requesting more information on 12 ingredients among the 16 [45].
- The FDA has changed its guidelines to address broad-spectrum sunscreen use, which involves UV-A and UV-B coverage; water resistance, to indicate the time duration the sunscreen is effective; and sun protection

factor (SPF). SPF-15 or higher is recommended and can be labeled as reducing the risk of skin cancer and early skin aging [40].

- PABA and trolamine salicylate — are not GRASE for use in sunscreens, are no longer permitted for use in OTC sunscreen products. No sunscreens sold in the United States contain PABA or trolamine salicylate [41,42].
- For a decade, Environmental Working Group (EWG) has worked to raise concerns about sunscreens with oxybenzone, which is found in nearly all Americans, detected in breast milk and potentially causing endocrine disruption [43].
- Hawaii recently enacted legislation that will ban the use of two major ingredients -oxybenzone and octinoxate—that have also been implicated in coral toxicity and will be banned. This creates a healthcare dilemma: Will the protection of coral reefs result in an increase in human skin cancers? [46-51].

Sunburn: Pathophysiology

Sunburn is a radiation burn to the skin caused by too much exposure to the sun's UV rays or artificial sources such as tanning beds. Chronic sun exposure creates premature cutaneous aging, decreases immune response to environmental pathogens and increases the risk for developing premalignant and malignant neoplasms [52-77]. The biggest risk factors for sunburn are the amount of time the skin is exposed to UV rays, plus the intensity. Many factors such as time of day, medications, ozone depletion, high altitude, clear skies and skin phototypes influence sunburns [11]. Exposure to solar radiation has the beneficial effects of stimulating the cutaneous synthesis of vitamin D and providing radiant warmth. Unfortunately, when the skin is subjected to excessive radiation in the ultraviolet range, deleterious effects may occur. The most conspicuous is acute sunburn or solar erythema. Initially, UVR causes vasodilation of cutaneous blood vessels, resulting in the characteristic erythema. Within 1 h of UVR exposure, mast cells release preformed mediators including histamine, serotonin and tumor necrosis factor, leading to prostaglandin

and leukotriene synthesis. Within 2 h after UV exposure, damage to epidermal skin cells is seen. Erythema usually occurs 3-4 h after exposure, with peak levels at 24 h [12]. Sunburns are graded as pink, red, and blistering. In contrast, thermal burns are graded by degree (first, second and third), but this classification should not be applied to sunburns because thermal burns have quite different sequelae, such as scarring and death, which are extremely rare consequences of sunburn. Keratoconjunctivitis or ocular sunburn can also be caused by UV radiation, and it follows a similar time course [13]. Studies have shown that UVA impairs the antigen presenting cell (APC) activity of the epidermal cells and thereby causes immune suppression, thus contributing to the growth of skin cancer [30]. In summary, UVA radiation can cause nuclear and mitochondrial DNA damage, gene mutations and skin cancer, dysregulation of enzymatic chain reactions, immune suppression, lipid peroxidation (membrane damage) and photoallergic and phototoxic effects.

On the molecular level, exposure to UV radiation can result in a covalent joining of pyrimidine (usually thymine) dimers. DNA repair mechanisms, such as nucleotide excision repair, base excision repair, or mismatch repair genes, do not recognize dimers; the mutations go uncorrected to the cell cycle. When mutated genes reach the cell cycle, if not repaired by the induction of the p53 pathway, a series of changes can result in malignant transformation and immunosuppression. UV-induced immunosuppression contributes to skin cancer due to damage to DNA and inhibition of protective mechanism within the skin (**Figure 2**). A common type of sun-related skin damage is actinic keratosis (AK). Age, Fitzpatrick skin type 1 or 2 (**Exhibit 1**), and UV light are the major risk factors for developing AK. Most AKs do not progress into invasive squamous cell carcinoma (SCC), but the risk is still present. The risk of malignant transformation of an AK to SCC within one year is approximately 1 in 1,000. However, approximately 60% of invasive SCCs of the skin probably arise from AKs. If not treated or protected against additional sun damage, AKs may eventually progress to invasive SCC. Avoiding sun exposure and daily application of sunscreen statistically decreases the number of AKs [77].

Exhibit 1. Fitzpatrick's Skin Phototypes [14].

- Type I: Pale white skin, burns easily, does not tan
- Type II: White skin, burns easily, tans with difficulty
- Type III: White skin, may burn but tans easily
- Type IV: Light brown/olive skin, hardly burns, tans easily
- Type V: Brown skin, usually does not burn, tans easily
- Type VI: Black skin, very unlikely to burn, becomes darker with UV radiation exposure

* Individuals with Type I to III Fitzpatrick skin phototypes were at increased risk for sunburn

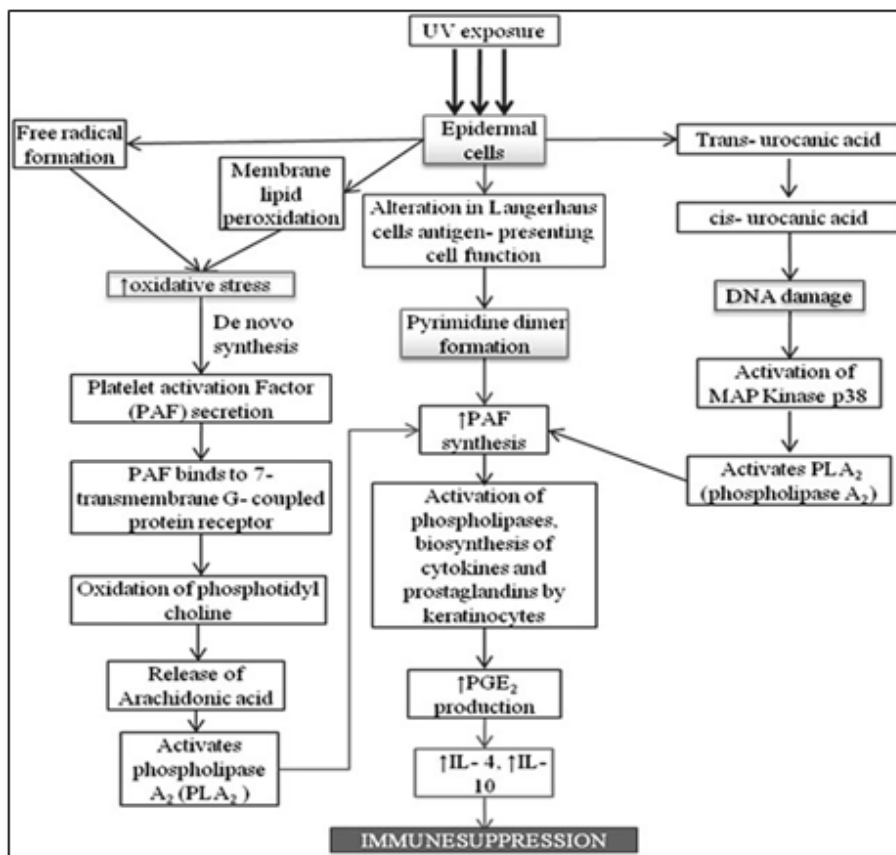


Figure 2. Mechanism of UV induced immunosuppression [130,139-141].

UVR, in particular the UVB range, suppresses the immune system in several ways. UVB inhibits antigen presentation, induces the release of immunosuppressive cytokines and causes apoptosis of leukocytes. UVB, however, does not cause general immunosuppression but rather inhibits immune reactions in an antigen-specific fashion. Application of contact allergens onto UV-exposed skin does not cause sensitization but induces antigen-specific tolerance since such an individual cannot be sensitized against the very same allergen later, although sensitization against other allergens is not impaired. This specific immunosuppression is mediated by antigen-specific suppressor/regulatory T-cells. UVB-induced DNA damage is a major molecular trigger of UV-mediated immunosuppression. Reduction of DNA damage mitigates UV-induced immunosuppression. Likewise, interleukin-12 which exhibits the capacity to reduce DNA damage can prevent UV-induced immunosuppression and even break tolerance. Presentation of the antigen by UV-damaged Langerhans cells in the lymph nodes appears to be an essential requirement for the development of regulatory T cells. Studies addressing the molecular mechanisms underlying UV-induced immunosuppression will contribute to a better understanding how UV acts as a pathogen but on the other hand can be also used as a therapeutic tool.

The diagnosis of SCC has increased over the past 30 years. The most important risk factor for SCC is cumulative sun damage and age; the risk was greatest in those with more than 30,000 hours of cumulative lifetime sun exposure. UVA, UVB, PUVA and tanning beds have been shown to increase the incidence of cutaneous SCC. Prevention of SCC includes protection from the sun, including the use of protective clothing and application of sunscreen. Basal cell carcinoma (BCC) is the most common skin cancer and occurs most frequently on the face and head. In Caucasians, the incidence of BCC has steadily increased and the lifetime risk of developing BCC is 30% [78-86]. BCC arises from the

basal layer of epidermis and its appendages. The most important risk factor is chronic UVR. Other known risk factors include fair skin, light eyes, red hair, chronic arsenic exposure, therapeutic radiation, immunosuppression, basal cell nevus syndrome and various other genetic predispositions. Primary prevention is protection from sun exposure beginning at an early age [77]. Other than UVR, exposure to arsenic, radiation, chronic inflammatory conditions in skin and burns, scars, infections complications or even tattoos are also the contributing factors for BCC [87-96] (Figure 3).

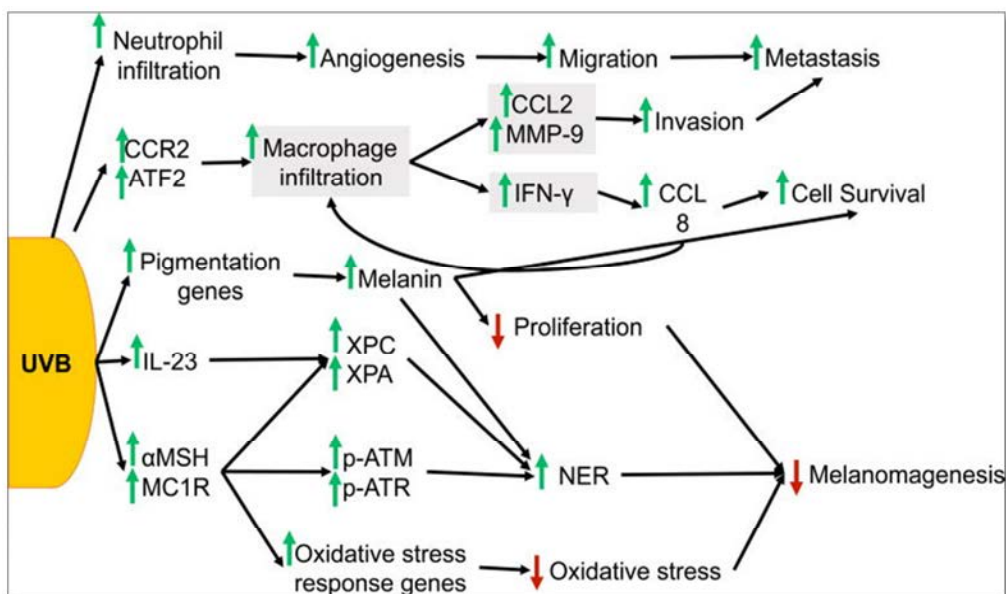


Figure 3. UVB response in melanoma [85].

UVB exposure triggers macrophage and neutrophil infiltration into the skin. Upregulation of CCR2 and ATF2 in melanocytes promotes recruitment of macrophages into the skin, which in turn stimulates production of CCL2, MMP-9 and IFN- γ in macrophages. IFN- γ signaling from macrophages promotes a positive feedback loop between melanocytes and macrophages, in which melanocytes upregulate CCL8, a CCR2 ligand and promotes further recruitment of macrophages. The inflammatory response created by macrophage and neutrophil recruitment promotes angiogenesis, as well as melanoma cell invasion, survival and metastasis. UVB also independently regulates melanin production and MC1R signaling. Induction of pigmentation genes and subsequent increase in melanin production following UVB increases cell survival and NER, but decreases proliferation and ultimately, melanomagenesis. Signaling through MC1R is induced by UVB and activates DNA damage response. Signaling through α MSH and MC1R promotes phosphorylation of ATM and ATR, upregulates XPC and promotes XPA recruitment to stimulate NER. α MSH also activates oxidative stress response genes to reduce oxidative stress in melanocytes/melanoma. UVB-induced expression of IL-23 also activates XPC and XPA to induce NER. IL-23 signaling, melanin production and MC1R signaling can all inhibit melanomagenesis induced by UVB.

Abbreviations: ATF2: Activating Transcription Factor 2; CCR2: Chemokine (C-C Motif) Receptor 2; CCL2: Chemokine (C-C Motif) Ligand 2; MMP-9: Matrix Metalloproteinase-9; IFN- γ : Type II Interferon; IL-23: Interleukin-23; NER: Nucleotide Excision Repair; MC1R: Melanocortin 1 Receptor; ATM: Ataxia-Telangiectasia Mutated Gene; α MSH: α -Melanocyte-Stimulating Hormone; ATR: Ataxia Telangiectasia and Rad3-Related; XPC: Xeroderma Pigmentosum Group C; XPA: Xeroderma Pigmentosum Group A

Epidemiological analysis reveals that annually in the United States alone, ~5 million skin cancer patients are treated, and that between 40 and 50% of Americans are susceptible to develop skin cancer at least once by the age of 65 [96]. More than 90% of melanoma cases in the United States are attributed to skin cell damage from UV radiation exposure. Skin cancer is the most common form of cancer, representing 40-50% of all cancers diagnosed in the US. Melanoma is the most serious form of skin cancer. Melanoma is responsible for the most skin cancer deaths, with about 9,000 persons dying from it each year [84]. Despite early screening and detection programs, the overall mortality rate from melanoma has remained stable or continues to rise. The incidence of melanoma has more than tripled in the Caucasian population in the United States over the past 30 years. An estimated 60-70% of cutaneous malignant melanomas are thought to be caused by UV

radiation exposure. Two types of UV radiation are primarily responsible for causing carcinogenic skin damage: UVA (315 nm-400 nm) and UVB (280 nm-315 nm) [85]. Intense and intermittent sun exposure at a young age increases a patient's risk of melanoma. Individuals with five or more severe sunburns in childhood or adolescence have an estimated twofold greater risk of developing melanoma. Melanoma is commonly found on areas sporadically exposed to UVR, such as the back of the legs in women and the backs of men. UVB, UVA and PUVA therapy all have been proven to increase the risk of melanoma. Appropriate UVR protection decreases the risk of developing a melanoma or having a secondary melanoma. Studies indicate that decreasing recreational sun exposure following the diagnosis of primary melanoma can significantly decrease the chance of developing a second melanoma [77] (**Exhibit 2**).

Exhibit 2. Environmental factors that influence ultraviolet radiation [32-36].

- **Ozone layer:** The main absorber of UVR is produced for the most part in the terrestrial stratosphere of the equatorial region of the planet. Ozone layer is the name given to the region with high concentration of this gas in the Earth's atmosphere, located at a height between 15 and 30 km. This layer contains between 80 and 90% of the total ozone in the terrestrial atmosphere and is responsible for the intensive absorption of UVB radiation and part of the extinction of UVC radiation.
- **Altitude:** The higher the altitude of a location, the thinner is the atmosphere above it and, consequently, the larger the quantity of UVR reaching the surface. In situations of clear and cloudless skies, the UVR flux may increase between 5 and 10% for each 1000 m altitude. Nevertheless, this altitude-related increase in UVR may vary to values close to 20% per kilometer, as it depends on a series of other factors, such as the quantity of ozone in the lower layers of the atmosphere, the type of surface that reflects UV radiation, the particulates present in the atmosphere and even the position of the sun.
- **The time of day:** In a clear sky situation, the "higher" the Sun is in the sky, the higher the levels of UV radiation are. This means that the farther the Sun is from the horizon, the shorter the optical pathway the radiation has to cross in the atmosphere.
- **The season of the year:** In the summer, the Sun reaches higher positions in relation to the horizon than in the winter and, consequently, the UVR flux is more intense. The differences between the seasons of the year become more relevant as the latitude becomes higher.
- **Clouds:** Clouds can both attenuate and enhance UVB radiation, although attenuation is generally the case. Completely overcast clouds always attenuate UVB rays, even up to 99% of UVB radiation in extreme cases. Up to 50% enhancement of UVB radiation can occur from broken clouds [39] or at elevated sites above clouds.
- **Suspended particles:** Polluted environments or those with suspended dust may show UVR attenuation in relation to clear sky situations. Some studies demonstrate that polluted locations, such as São Paulo or Mexico City, may present situations with around 20% of the incident UVR.
- **Surface reflection (albedo):** The term 'albedo' is used to express the relationship between the radiation reflected by a surface and the radiation such surface receives from the Sun. Very light colored surfaces, such as freshly fallen snow, may reflect up to 90% of the incident radiation; therefore, wearing adequate protection for the eyes and skin is required in environments like mountains and ski tracks.
- **Outdoor vs. indoor working:** Outdoor workers can get three to nine times as much solar UVR exposure as indoor workers. Paradoxically, outdoor workers have a lower incidence of cutaneous malignant melanoma compared to indoor workers. It is supposed that indoor solar UVA exposure, which causes mutations, depletes vitamin D3 in the skin. Behavior includes the time spent outdoors and the use of photoprotective agents. In adult life, a British indoor worker in the UK might typically receive 30% of his or her annual UV exposure from sun-seeking holidays, 40% from summer weekends, 20% from casual weekday exposure between April and September and just 10% from sun exposure during the 6 months period October to March.

Photoaging

Every organ experience aging in various ways. Skin aging can be categorized into three groups, intrinsic, photo and hormonal aging. The consequences of photo-aging are usually characterized by morphological changes including wrinkle formation or by histological changes in connective tissues. In order to generate more wrinkles, vasculature structures are needed to develop. Numerous reports

suggested that angiogenesis plays a significant role in inducing wrinkle formation in photo-damaged skin [97-142]. Among harmful environmental factors that contribute to extrinsic aging, long-term effects of repeated exposure to ultraviolet light are the most significant and are referred to as photoaging. Premature skin aging and development of malignant cutaneous tumors, melanoma and non-melanoma, are interrelated issues that are increasingly important

problems in the field of dermatology. Skin aging is important aesthetically, whereas skin cancer is a direct threat to the health of the patient [143]. Photoaging is a multisystem degenerative process that involves the skin and skin support system. It is a cumulative process and depends primarily on the degree of sun exposure and skin pigment. The epidermis and dermis are both affected by UVB, but the dermis is also affected to a significant extent by UVA. It has long been thought that the majority of human photo-lesions due to UVB rays, now it is believed that UVA play a substantial role in photoaging. Photoaging affects the sun-exposed areas and is characterized clinically by fine and coarse wrinkling, roughness, dryness, laxity, telangiectasia, loss of tensile strength and pigmentary changes [144]. These changes are more severe in individuals with fair skin and are further influenced by individual ethnicity and genetics. Photoaging may be prevented and treated with a variety of modalities, including topical retinoids, cosmeceuticals, chemical peels, injectable neuromodulators, soft tissue fillers, and light sources [145]. There is also an increase in development of benign and malignant neoplasms on photoaged skin. During the years the progress has been made in understanding the photoaging in human skin. UV irradiation invokes a complex sequence of specific

molecular responses that damage skin connective tissue [146]. In severely damaged skin, there is loss of epidermal polarity (orderly maturation) and individual keratinocytes may show atypia, especially the lower epidermal layers. More profound changes occur in the dermis, where photodamage is characterized by degeneration of collagen and deposition of abnormal elastic material, reflected by wrinkles, furrows, and yellow discoloration of the skin. The greater the photodamage, the more the accumulation of thickened, tangled and degraded elastic fibers [147-153]. The application of topical growth factors after microneedling can be useful to reduce visual signs of facial photoaging by improving skin texture and minimizing the appearance of fine lines and wrinkles [151]. Amongst retinoids, tretinoin is the most potent and best-studied retinoid. However, its irritation potential has prompted dermatologists to switch over to less irritating but comparably effective retinoids like adapalene and to some extent retinol and retinaldehyde [154]. Bakuchiol (functional analogue of topical retinoids, as both compounds have been shown to induce similar gene expression in the skin) is a phytochemical that has demonstrated cutaneous anti-ageing effects when applied topically. Bakuchiol is promising as a more tolerable alternative to retinol [152] (Figure 4 and Exhibits 3 and 4).

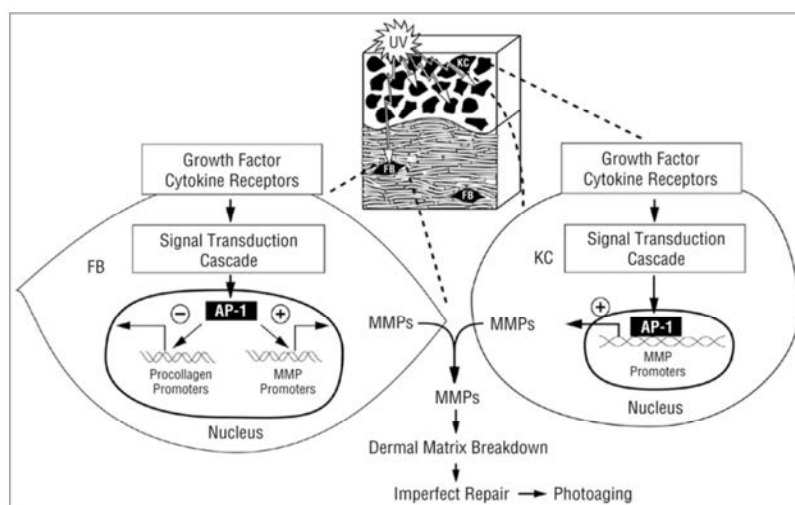


Figure 4. Mechanisms of photoaging and chronological skin aging [143,147-150].

Photodamaged skin displays variable epidermal thickness, dermal elastosis, decreased/fragmented collagen, increased matrix-degrading metalloproteinases, inflammatory infiltrates and vessel ectasia. The main effects of acute and chronic exposure to UV radiation are DNA damage, inflammation and immunosuppression. These effects are direct as well as indirect due to ROS production. The ROS are particularly harmful in that they destabilize other molecules and promote chain reactions that damage biomolecules rapidly, such as telomere shortening and deterioration, mitochondrial damage, membrane degradation and oxidation of structural and enzymatic proteins. Collagen and elastin are the structural proteins of the ECM. The deterioration/remodeling of the collagen and elastin fibers facilitates angiogenesis and metastasis, and the damaged collagen and elastin proteins serve as additional sensitizers of photooxidative stress. Accumulation of collagen fragments, which occurs with chronic UV exposure and the passage of time, impairs the mechanical and functional properties of the dermal extracellular matrix. Elastic fibres, such as oxytalan fibres in papillary dermis, are associated with not only skin resilience, but also skin surface texture, and elastic fibre formation by fibroblasts is facilitated by increased expression of fibulin-5. Thus, induction of fibulin-5 expression is a damage-repair mechanism, and fibulin-5 is an early marker of photoaged skin

Exhibit 3. Comparison between photoaging and intrinsic aging [130].

Particular	Photoaging	Intrinsic aging
Epidermal changes	Thickness increases, acanthropic in early phase and atrophy in later stages	Thin epidermis
	Proliferative rate is higher than normal	Proliferative rate is lower than normal
	Non-uniform and random distribution of keratinocytes, polarity of cells is lost, frequent enlargement	Uniform and defined distribution of keratinocytes, polarity is maintained, usually atrophied
	Diversified melanosomes	Uniformly distributed melanosomes
	Increased number of stratum corneum (SC) cell layer	Normal cell layer
	Vitamin A content is destroyed by sun exposure	Plasma content of retinol increases
Dermal changes	Marked elastogenesis followed by massive degeneration	Elastogenesis followed by elastolysis
	Massive increase in elastic fibers	Gradual decline in production of dermal matrix
	Increased lysozyme deposition on elastic fibers	Modest lysozyme deposition on elastic fibers
	Decrease in amounts of mature collagen	Mature collagen more stable in degradation
	Increased mast cells	Decreased mast cells
	Vessels become dilated	Micro vessels decrease
	Pronounced inflammation	No inflammatory response
	Marked increase in glycosaminoglycans	Slight decrease in glycosaminoglycans
Common signs and symptoms	Mild (age 28-35 years): Few wrinkles, no keratoses	Fine wrinkles, thin and transparent skin
	Moderate (age 35-50 years): Early wrinkling, sallow complexion with early actinic keratoses	Loss of underlying fat leading to hollowed cheeks and eye sockets with noticeable loss of firmness on the hands and neck
	Advanced (age 50-60 years): Persistent wrinkling, discoloration of the skin with telangiectases and actinic keratoses	Bones shrink away from the skin as a result of bone loss, which causes sagging of skin, dry skin with pruritus
	Severe (age 65-70 years): Severe wrinkling, photo aging, gravitational and dynamic forces affecting the skin, actinic keratoses with or without skin cancer	Inability to sweat sufficiently to cool the skin, faster graying of hair

Exhibit 4. Exogenous antioxidants with photoprotective or damage protective effects [154].

Antioxidants	Outcome of the study
Ascorbic acid	Topical vitamin C 5% cream applied for six months led to clinical improvement in the appearance of photoaged skin
	Topical vitamin C stimulates the collagen-producing activity of the dermis
	Magnesium ascorbyl phosphate administration immediately after exposure in hairless mice significantly delayed skin tumor formation and hyperplasia induced by chronic exposure to UV radiation
	Ascorbic acid was a photoprotectant when applied to mice and pig skin before exposure to ultraviolet (UV) radiation
Vitamin E	UV-induced vitamin E depletion
	The interaction of vitamin E with the eicosanoid system may result in an anti-inflammatory effect and thereby complement the photoprotective effects of other antioxidants in the skin
	Vitamin E has skin barrier-stabilizing properties
Lycopene	UV light decreased skin lycopene concentrations more so than skin β -carotene concentrations
	Lycopene protects against UV-induced erythema in humans
Carotenoids (carotene, β-carotene and carotenoid mix)	Supplementation with carotenoids contributes to basal protection of the skin but is not sufficient to obtain complete protection against severe UV irradiation
	Dietary beta-carotene has effect on wrinkles and elasticity, procollagen gene expression, and ultraviolet (UV)-induced DNA damage in human skin
	Erythema-protective effect of a carotenoid mix inhibited serum lipid peroxidation
	Pre-supplementation with β -carotene before and during sunlight exposure provides protection against sunburn
	Inhibition of UV-induced epidermal damage and tumor formation in mouse models
Tretinoin	Topical tretinoin ameliorates the clinical signs of photoaging
	The treatment of photodamaged skin with tretinoin increased collagen I formation
	Topical tretinoin is safe and effective in the treatment of photodamage
	Improvement in photodamaged skin
	Topical tretinoin reduced the effects of photoaging
	Topical tretinoin in combination with sun protection as a useful approach to the treatment of sun-damaged skin
Coenzyme Q10 (CoQ10)	Topical application of CoQ10 has the beneficial effect of preventing photoaging
	Coenzyme Q10 protects against oxidative stress-induced cell death and enhances the synthesis of basement membrane components in dermal and epidermal cells
	CoQ10 was shown to reduce UVA-induced MMPs in cultured human dermal fibroblasts
Glutathione	Glutathione is a photoprotective agent in skin cells

Zinc	Zn-treated fibroblasts were more resistant to UVR than cells grown in normal medium
	Zn can positively influence the effects of oxidative stress on cultured human retinal pigment epithelial (RPE) cells
Resveratrol	Application of resveratrol to the skin of hairless mice effectively prevented the UVB-induced increase in skin thickness and the development of the skin edema
Green tea	Green tea polyphenols were shown to reduce UV light-induced oxidative stress and immunosuppression
	Topical treatment or oral consumption of green tea polyphenols (GTP) inhibits chemical carcinogen- or UV radiation-induced skin carcinogenesis in different laboratory animal models
Green tea or caffeine	Oral administration of green tea or caffeine in amounts equivalent to three or five cups of coffee per day to UVB-exposed mice increased levels of p53, slowed cell cycling, and increased apoptotic sun burn cells in the epidermis
Silymarin	Silymarin strongly prevents both photocarcinogenesis and skin tumor promotion in mice
	Skin cancer chemopreventive effects
Genistein	Antioxidant and anticarcinogenic effects on skin
Cocoa	Dietary flavanols from cocoa contribute to endogenous photoprotection, improve dermal blood circulation, and affect cosmetically relevant skin surface and hydration variables
	Photoprotection against UV-induced erythema

Sunburn home remedies and treatment

Certain medical treatments have been tried and studied to treat sunburn. However, in general, most remedies have not shown any clinically proven benefit as far as speeding the recovery or reversing the damage. Therefore, most of the treatments available are only used to treat symptoms.

- **Non-steroidal anti-inflammatory drugs (NSAIDs):** Systemic and topical non-steroidal anti-inflammatory drugs, when used at dosages to achieve optimal serum levels for anti-inflammatory effect, only result in an early and mild reduction of ultraviolet B-induced erythema [15]. In oral (ibuprofen, Motrin, Naprosyn, Advil, etc.) or topical diclofenac 0.1% gel (Solaraze) forms have shown to reduce redness if applied before or immediately after UVB exposure. This benefit may be diminished after 24 h. These medications may also help relieve the symptoms of sunburn such as pain and discomfort [4].
- Topical steroid creams have not shown any significant improvement in sunburn symptoms. Oral steroids such as prednisone have not proven to be beneficial and have been associated with some significant side effects. Treatment with topical moderate-potency or high-potency corticosteroids does not provide a clinically useful decrease in the acute sunburn reaction when applied 6 or 23 h after UV exposure [16].

- **Applying Aloe vera gel:** Topical application of *Aloe vera* is not an effective prevention for radiation-induced injuries and has no sunburn or suntan protection [17]. The *Aloe vera* cream was continuing applied at the test sites twice daily for the next three weeks. The results showed no sunburn or suntan protection and no efficacy in sunburn treatment when compared to placebo. The *Aloe vera* cream has no bleaching effect too. However, this may be beneficial in treating the symptoms [18].
- **Topical anesthetics:** Advertised remedies such as topical anesthetics (benzocaine) may help with symptoms of sunburn; however, very little clinical data is available to substantiate their effectiveness. LMX is a topical liposomal formulation containing 4% or 5% lidocaine. LMX 4% is available OTC and is FDA-approved for temporary relief of pain and itching associated with minor cuts, minor burns, sunburn, and insect bites [19].
- **Vitamin D preparations:** Vitamin D enables anti-inflammation to promote tissue repair in response to injury. Mechanistically, vitamin D signaling activated M2-autophagy regulators Kruppel like factor 4 (KLF4), peroxisome proliferator activated receptor gamma (PPARG) and arginase 1. Analysis of UV-exposed human skin biopsies detected a similar increase in macrophage autophagy following vitamin D intervention, identifying an essential role for autophagy

in vitamin D-mediated protection of skin from UV damage [25].

- **Sunscreens:** Sunscreens represent a practical approach to photoprotection for skin. The importance of beginning sun protection at a young age cannot be overstated. In humans, the regular use of sunscreens has

been shown to reduce AKs, solar elastosis, UV-induced immunosuppression and photosensitivities. Sunscreens also prevent the formation of SCCs in animals. A thorough understanding of the mechanism of action of sunscreens, different sunscreen vehicle choices, and adverse effects can help educate patients on their choice of sunscreens [77] (Figure 5).

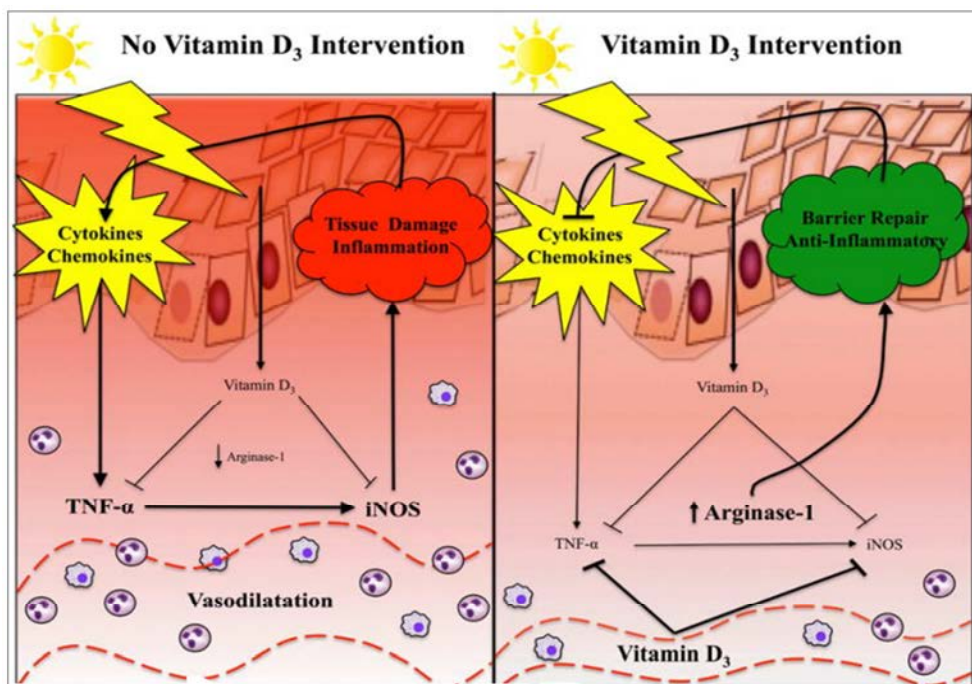


Figure 5. The effect of oral vitamin D3 intervention on skin inflammation [26].

As depicted in panel A, levels of vitamin D3 are at baseline levels in the absence of high dose oral vitamin D3 intervention. In this context, exposure to erythemogenic doses of UVR results in sunburn and the release of pro-inflammatory cytokines and chemokines in the skin, including TNF-α** and iNOS*, which further propagate tissue inflammation. Increased skin redness and thickness are mediated by vasodilation, an influx of inflammatory cells, and vascular congestion within the skin. The gene expression profile of skin at this time is characterized by increased expression of various pro-inflammatory genes. As depicted in panel B, levels of vitamin D3 rapidly rise within the serum after high dose oral vitamin D3 intervention. Arginase-1 is up regulated within the skin, and production of the pro-inflammatory mediator's TNF-α and iNOS are attenuated after sunburn. Reduced skin erythema and thickness are observed clinically. The gene expression profile of skin at this time is characterized by increased expression of skin barrier genes, which help to repair the epidermal barrier and attenuate the inflammatory insult. *iNOS is the synthase isoform most commonly associated with malignant disease. **TNF-α is a primary cytokine that can be induced in keratinocytes and in dermal fibroblasts by UVB, synthesized in adipose tissue by adipocytes and other cells in the tissue matrix. TNF-α is mainly secreted by activated macrophages immediately postburn. The host immune response is activated by TNF-α, as is the subsequent release of cytokines following trauma and infection

Medication responsible for increase skin sensitivity to sunlight

A large number of medications are known to increase skin sensitivity to sunlight and are called photosensitive drugs or medications. Photo-sensitizing chemicals usually have a low molecular weight (200 to 500 Da and are planar, tricyclic or polycyclic configurations, often with heteroatoms in their structures enabling resonance stabilization. All absorb UV and/or visible radiation, a characteristic that is essential for

the chemical to be regarded as a photosensitizer. Some of the common ones include (Figure 6 and Exhibits 5 and 6):

- NSAIDs (Non-steroidal anti-inflammatory drugs)
- **Antibiotics:** Tetracyclines (tetracycline, doxycycline (Vibramycin)), Quinolone (ciprofloxacin (Cipro), levofloxacin (Levaquin)), Sulfonamides (sulfamethoxazole and trimethoprim; cotrimoxazole (Bactrim, Septra), sulfamethoxazole (Gantanol)).

- **Diuretics (water pills):** Thiazides (hydrochlorothiazide (Hydrodiuril), furosemide (Lasix))
- **Cardiac medications:** Amiodarone (Cordarone), quinidine
- **Diabetes drugs:** Sulfonylureas such as chlorpropamide (Diabinese), glyburide (Micronase, DiaBeta, Glynase)
- **Psychiatric drugs:** Chlorpromazine (Thorazine), tricyclic antidepressants such as desipramine (Norpramin) and imipramine (Tofranil)
- **Acne medications:** Isotretinoin (Accutane) [20-24,34].



Figure 6. Use of sun protective [178].

Public guidelines for sun protection have been updated as stakeholders warn that Australians are using sunscreen as a “suit of armour”. Heather Walker, chair of Cancer Council Australia’s National Skin Cancer Committee, said that recent research shows 85% of people do not apply sunscreen correctly. The Australasian College of Dermatologists and Cancer Council updated the guidelines following concerns that many Australians only use sunscreen to protect their skin. By not using clothing, a broad-brimmed hat, shade, sunglasses and sunscreen correctly when the ultraviolet index reaches three or above, they are putting themselves at risk, the organizations say

Exhibit 5. Cosmetic ingredients and cancer risk [34].

Cosmetic substances	Risks
DEA (diethanolamine) TEA (triethanolamine)	Can result in formation of carcinogenic nitrosamines
Bronopol (2-bromo-2-nitropropane-1,3-diol)	May break down into formaldehyde and also cause the formation of nitrosamines
1,2-Dioxane in surfactants/detergents	Contaminated with carcinogenic 1,4-dioxane
Artificial colors (as Blue 1 and Green 3)	Carcinogenic
Hair dyes	Dark colors ingredients are carcinogenic
Cosmetic lanolin	Can be contaminated with carcinogenic pesticides such as DDT, dieldrin, and lindane, in addition to other neurotoxic pesticides
Talc	Carcinogenic
Silica	May be contaminated with carcinogenic crystalline quartz

Exhibit 6. Endocrine disrupting effects of the commonly used UV filters [74].

UV Filters	Endocrine Disrupting Effects	
Benzophenones	Estrogenic disrupting effects	Activation of ER α , ER β ; Inhibition of the activity of 17 β -Estradiol; Induction of proliferation of MCF-7 cell; Induction of VTG in fathead minnows; Reduce of the uterine weight in immature Long-Evans rats
	Androgenic disrupting effects	Antagonists of human AR transactivation; Repression of 4,5-dihydrotestosterone-induced transactivational activity; Inhibition of testosterone formation in mice and rats
	Disrupting effects toward other nuclear receptors	Inhibition of human recombinant TPO; Interference with THR; Inhibition of TPO activity in rats; Antagonists of PR
Camphor derivatives	Disrupting effects toward estrogen receptor	Activation of ER α , ER β ; Inhibition of the activity of 17 β -Estradiol; Induction of proliferation of MCF-7 cell; Induction of pS2 protein in MCF-7 cells; Reduce of the uterine weight in rats; Induction of VTG in fish
	Disrupting effects toward androgen receptor	Repression of 4,5-dihydrotestosterone-induced transactivational activity; Inhibition of testosterone formation in HEK-293 cells; Antagonists of Human AR
	Disrupting effects toward progesterone receptor	Antagonists of PR; Increase of PR mRNA levels in rats; Inhibition of the expression of PR protein in rats; Disturbance of the expression of membrane-associate PR in insects
Cinnamate derivatives	Disrupting effects toward estrogen receptor	Activation of ER α ; Inhibition of the activity of 17 β -Estradiol; Induction of proliferation of MCF-7 cell; Reduce of the uterine weight in rats; Induction of VTG in fish
	Disrupting effects toward thyroid hormone receptor	Decrease of T4 level; Inhibition of the conversion of T4 to triiodothyronine in rats
	Disrupting effects toward other nuclear receptors	Antagonists of PR and AR; Inhibition of 4,5-dihydrotestosterone activity; Reduce of the prostate and testicular weight in rats

*AR: Androgen Receptor; ER: Estrogen Receptor Alpha; PR: Progesterone Receptor; T4: Thyroxine; THR: Thyroid Hormone Receptor; TPO: Thyroid Peroxidase; VTG: Vitellogenin

Tanning/pigmentation with or without sun exposure

Some Africans and Asians avoid sun and use bleaching products to lighten skin, while many Caucasians seek the sun for tanning to achieve a bronze skin to “look good.” UV radiation from the sun or from artificial sources increases skin pigmentation. Sunlight and indoor UV induced tanning is a common behavior, especially among adolescents, young adults and individuals with lighter skin. Several health

benefit claims such as improved appearance, enhanced mood and increased vitamin D levels have been attributed to tanning. The Indoor Tanning Association claims that a base tan can act as “the body’s natural protection against sunburn. Sunless tanning products may serve as a sensible, safer alternative for those who desire tanned skin [155]. There are three phases of tanning: immediate pigment darkening (IPD), persistent pigment darkening (PPD) and delayed tanning (DT). IPD occurs during the first minutes of

exposure to UVA and then fades within few hours. PPD appears within hours of higher doses of UVA exposure and persist up to several days or weeks. DT develops over 3-7 days after UVB exposure and then remains for weeks. The mechanisms of UVA- and UVB-induced pigmentation are different. UVA induces IPD and PPD through oxidation of pre-existing melanin or melanogenic precursors. IPD is oxygen dependent, and reactive oxygen radicals are considered to be responsible for this process. PPD is also due to the upward movement of melanosomes toward the surface of the skin. Persons with lightest skin (skin type I) do almost not tan, while IPD and PPD are strongest in moderately and darkly pigmented skin. DT results from synthesis of melanin in the melanocytes, followed by melanin distribution to neighboring keratinocytes [156]. UVA (320-400 nm) causes immediate pigment darkening (IPD) as well as persistent pigment darkening (PPD) of skin within hours via photooxidation and/or polymerization of existing melanin or melanogenic precursors due to the generation of reactive oxygen species. In contrast, UVB (280-320 nm) induces a slower but more stable type of pigmentation termed delayed tanning (DT) which requires the increased synthesis of melanin following the stimulation of tyrosinase activity and the entire melanogenic cascade [157]. UVB-induced DT is photoprotective (it is estimated to have a SPF of 3) while DT induced by UVA is not

considered to be photoprotective. DT is maximal from 10 days to 3-4 weeks, depending on the UV dose and the individual's skin color. It may take several weeks or months for the skin to return to its base constitutive color. UVA-induced DT is 2-3 orders of magnitude less efficient per unit dose than UVB and has an earlier onset, often directly after IPD [158]. The IPD method can also be used as an appropriate endpoint in the determination of UVA protection. It is time saving, and thus considerably lowers the risk of UV exposure, particularly when testing sunscreen products with higher UVAPF [159]. IPD typically appears grey to black while PPD is brown. Both IPD and PPD do not require any new pigment synthesis and are thought to result from oxidation and/or polymerization of pre-existing melanin or melanogenic precursors and metabolites. Melanosomes have also been shown to redistribute within both keratinocytes and melanocytes during the IPD/PPD response. PPD is protective against neither UVB-induced erythema nor UVB-induced DNA lesions [160]. Exposure to ultraviolet radiation from indoor tanning device use is associated with an increased risk of skin cancer, including risk of malignant melanoma and is an urgent public health problem. By reducing indoor tanning, future cases of skin cancer could be prevented, along with the associated morbidity, mortality and healthcare costs (**Figure 7 AND Exhibits 7 and 8**) [161-175].



Figure 7. Give me a tan! - Megan Fox [176,177].

Megan Fox comes up the most when searching online for pale vs. tan photos. She demanded a sun bed be delivered to the set of Transformers: Revenge of the Fallen, because she was feeling self-conscious about her pale skin, according to Fox News. But they didn't have one available so offered to send an expert to give Megan a customized spray tan. However, Megan turned down the offer, saying she wanted a sun bed instead

Exhibit 7. Common tanning methods [171-174].

UV tanning: Tanning salons offer an indoor method of UVR with tanning beds and booths. These salons expose people to man-made UV light. Tanning beds were introduced in North America in 1978 and gained considerable popularity in the 1980s. Indoor tanning salons are a common choice among those who tan as they do not require people to spend hours outside in the sunlight. At any given tanning salon, there are typically three to five different types of beds. They are classified as level 1 through 6. In general, increasing levels correspond to increasing concentrations of UVA relative to UVB. Increasing the bed level also increases the pressure and number of lamps, resulting in a deeper tan that appears faster and fades slower than lower level beds. In tanning salons, the user has the option to stand (e.g. in a booth) or lie supine (e.g. in a bed). The time spent in a bed is limited by the strength of lamps used and ranges from 8 to 20 min. One of the most important differences between beds is the percent of UVA versus UVB light.

Tanners for topical use: Topical sunless tanners are products that are applied to the skin to give the appearance of a tan. These products come in many forms including lotions, gels, mousses, sprays, wipes, creams and powders. Temporary bronzers are one type of topical self-tanner. Bronzers come in creams, lotions, and powders. When a bronzer is applied to the skin, it coats the outer layers of the epidermis. Bronzers are considered temporary because they only last until they are washed off by normal soap and water use. The use of a bronzer is similar to putting on make-up every day. Commonly used ingredients for temporary bronzers include caramel, walnut oil extract and jojoba extract. DHA formulations have become popular among the public due to their relative ease of application and longer lasting tan when compared to temporary color bronzers, which wash off readily with soap and water. The temporary color bronzers also have a higher tendency to cause blotchiness, an uneven tan, and a less natural looking color. DHA is not approved for use on non-skin areas, such as the eyes, lips, and mucous membranes. As a result, DHA has not been approved in the use of spray tanning booths due to the potential exposure to non-FDA approved sites, even when taking precautions, such as wearing nose plugs, goggles, or applying petroleum jelly to the lips.

Tanning pills: The FDA has banned canthaxanthin-containing tanning pills due to their significant adverse effects when ingested in large quantities. Some of the side effects include gastrointestinal disturbance, urticaria, hepatitis, retinopathy, and potentially fatal aplastic anemia. Tanning pills are non-prescription formulations that are readily available to customers for purchase over the Internet. The most common active ingredient is canthaxanthin. Another common ingredient in tanning pills is beta-carotene, a different carotenoid. Beta-carotene is obtained through the dietary consumption of fruits and vegetables and it contributes to the yellow pigment found in human skin. Its deposition in the skin is thought to contribute to photoprotection, guarding against the deleterious effects of both natural and artificial UV light exposure, and raising the minimum amount of UVR exposure required causing sunburn.

Alpha-melanocyte stimulating hormone analogues: Afamelanotide is a subcutaneous implant administered once a month. It has been approved for erythropoietic protoporphyria in Europe. Other analogues of alpha-MSH, Melanotan I and II, are available and unregulated to enhance skin pigmentation for cosmetic tanning. They are not equivalent to afamelanotide. They have been reported to cause side effects, such as satiety, hypertension, and penile erections. Other risks include the potential to transmit blood-borne infections, rhabdomyolysis, encephalopathy, and renal dysfunction. These side effects have not been reported with the controlled-release subcutaneous afamelanotide implant that is undergoing clinical trials.

Exhibit 8. Future research opportunities to inform efforts to reduce indoor tanning in the US [175].

Individual-level strategies
<ul style="list-style-type: none"> • Continue to develop and evaluate tailored and targeted messaging strategies. • Evaluate the long-term impact that messages have on indoor tanning behaviors. • Test the efficacy of behavioral counseling among groups other than female undergraduate tanners.
The roles of parents, clinicians and schools
<ul style="list-style-type: none"> • Assess parents’ perceptions of the risks associated with indoor tanning. • Assess parents’ awareness of their children’s use of indoor tanning devices. • Examine the prevalence of the practice of parents doing indoor tanning with their children. • Evaluate strategies for engaging parents in prevention efforts targeting children. • Identify ways to disseminate information about and tools for behavioral counseling to clinicians. • Monitor clinicians’ behavioral counseling practices. • Develop and evaluate educational, systems and environmental interventions in school settings.
Mass media campaigns
<ul style="list-style-type: none"> • Develop and evaluate the efficacy of mass media campaigns. • Engage celebrities and other public figures in mass media campaign efforts.
Legislation
<ul style="list-style-type: none"> • Track the development and implementation of new indoor tanning legislation. • Compare the effects of various types of indoor tanning legislation on behaviors. • Develop informational resources for decision makers. • Monitor public support for indoor tanning legislation.
Assessment, monitoring and evaluation
<ul style="list-style-type: none"> • Continue surveillance efforts at the national level to track indoor tanning device use. • Increase surveillance efforts at the state and local levels to track indoor tanning device use. • Collect data on the prevalence and use of unsupervised indoor tanning devices. • Monitor indoor tanning attitudes and beliefs among the U.S. population and among indoor tanners. • Monitor trends in outdoor tanning (i.e., sunbathing). • Conduct economic analyses to quantify the impact on morbidity, mortality, productivity and health care costs. • Monitor trends within the indoor tanning industry over time (e.g. industry size and pricing). • Continue surveillance of melanoma incidence and mortality rates. • Collect data on basal and squamous cell carcinomas using electronic medical records. • Conduct modeling studies to estimate trends in the incidence of basal and squamous cell carcinomas.

The sun care industry

The U.S. sun care market size was estimated at USD 1.95 billion in 2016. The growing consumer awareness regarding the ill-effects of over exposure to ultraviolet (UV) rays on

the undefended skin is expected to propel growth. Furthermore, rising utilization of organic sun care products owing to absence of synthetic chemicals in the formulation is expected to drive growth over the forecast period. The sunscreen manufacturers are actively using these

formulations as it increases the endurance of skin cells against UV rays and enhances the self-defence mechanism. Enhanced standard of living coupled with increasing disposable income of the middle-class working population in economies of North America, including the U.S., is expected to propel sun care market growth over the forecast period. The industry players including L'Oréal are using nanotechnology by manipulating the materials at an atomic or molecular in order to enhance the efficiency of the product. Over the past five years, the Sunscreen Manufacturing industry has grown by 1.6% to reach revenue of \$407m in 2018. In the same timeframe, the number of businesses has grown by 3.9% and the number of employees has grown by 1.5% [178-180].

CLASSIFICATION OF SUNSCREENS

Sunscreens are classically divided into physical or chemical sunscreens. Chemical sunscreen absorbs into the skin and then absorbs UV rays, converts the rays into heat and releases them from the body. Physical blockers are inorganic and reflect, scatter and/or absorb UVR. Physical UV absorbers like titanium dioxide and zinc oxide have been considered as highly protective agents against UVR. ZnO and TiO₂ combinations are particularly valuable because of their ability to filter both UVA and UVB radiations, providing broader UVR protection than that observed with individual component [95]. They are used in sunscreens as nanoparticles, which denotes a size <100 nm. The smaller size of these mineral particles increases their cosmetic acceptability by users as they are much less visible after application. ZnO has a broad UVA-UVB absorption curve, while TiO₂ provides better UVB protection. Overall, the human health risks with inorganic filters are extremely low given a lack of percutaneous absorption; however, there is potential risk when exposed via inhalation, prompting recommendations against spray sunscreen products with nanoparticles [111]. UV-A rays heavily contribute to both premature skin aging and skin cancer, while UV-B rays cause sunburn. Hence, the use of sunscreen is strongly encouraged by many healthcare practitioners in order to minimize or possibly eradicate the harmful effects of UV rays on our skin, keeping in mind, that about 90% of all skin cancers are associated with exposure to the sun's harmful radiation. Protection against both UVB and UVA radiation is advocated. Most sunscreens combine chemical UV absorbing sunscreens and physical inorganic sunscreens, which reflect UV, to provide broad-spectrum protection. The correct use of sunscreens should be combined with the avoidance of midday sun and the wearing of protective clothing and glasses, as part of an overall sun protection regimen [94,95]. Unfortunately, inaccurate information is currently roaming the media and the Internet regarding the safety, toxicity, and acute side effects of the active ingredients currently used in sunscreens, therefore discouraging people from using sunscreens [92]. Chemical sunscreens are organic and generally aromatic compounds

conjugated with a carbonyl group. They are designed to absorb high-intensity UVR, produce excitation to a higher energy state, and, with the return to the ground state, result in conversion of the absorbed energy into a longer, lower energy wavelength. Chemical sunscreens can be classified based on their portion of UV coverage. Commonly known ingredients for UVB sunscreen protection are Padimate O, octinoxate, octisalate, octocrylene and ensulizole. Commonly known Studies reveal that Persistent Pigment Darkening (PPD) to be a stable end point inducible by all the UVA wavelengths, not affected by fluence rate, i.e., a reliable endogenous UVA dosimeter in the skin [89]. Problems associated with chemical sunscreens are: (i) Requires about 20 min after application before it starts to work; (ii) Chemical sunscreens may cause side effects, such as erythema, edema and irritation (especially for those who have dry skin with a damaged moisture barrier) due to the multiple ingredients combined in order to achieve broad spectrum UVA and UVB protection; (iii) The higher the SPF (such as formulas of SPF 50 or greater), the higher the risk of irritation for sensitive skin types; (iv) The protection it offers gets used up more quickly when in direct UV light, so re-application must be more frequent. (v) Increased chance of redness for rosacea-prone skin types because it changes UV rays into heat which can exacerbate flushing; (vi) May clog pores for oily skin types [93]. The importance of adequate UVA protection has become apparent in recent years. The United States and Europe have different standards for assessing UVA protection in sunscreen products. The majority of tested sunscreens offered adequate UVA protection according to US Food and Drug Administration guidelines for broad-spectrum status, but almost half of the sunscreens tested did not pass standards set in the European Union. UVA sunscreen ingredients are oxybenzone, meradimate, avobenzene and tetraphthalidine dicamphor sulfonic acid [90,91]. Broad spectrum is a term designed to mean protection from both UVA and UVB. Problems associated with physical sunscreens are: (i) Can rub off, sweat off and rinse off easily, meaning more frequent re-application when outdoors as needed; (ii) The physical sunscreen agents impart high opacity to the topical preparation, which makes the formulated creams cosmetically unacceptable and leave a whitish layer on the skin, making some formulas incompatible for medium to dark skin tones; (iii) Can be less protective if not applied and re-applied generously and accurately since UV light can get between the sunscreen molecules and get into the skin [93]. There are few reports available on the application of Polymeric Nanoparticles (NPs) of physical and chemical sunscreen ingredients (titanium dioxide, zinc oxide, octyl methoxycinnamate, oxybenzone, octocrylene and luteolin) to improve sun protection efficacy. UV-absorbing agents must accumulate within the upper skin layers in order to provide a dense light-absorbing layer and guarantee water resistance. Incorporation of antioxidants could provide additional benefit by scavenging free radicals. Natural

polyphenols are attractive in this respect, due to their potential activity as photoprotectants and antioxidants [95].

FDA APPROVED SUNSCREEN INGREDIENTS: LITERATURE REVIEW

Aminobenzoic acid

Aminobenzoic acid is a Vitamin B Complex Member. The chemical classification of aminobenzoic acid is Vitamin B Complex Compounds. In 1943, p-aminobenzoic acid (PABA) was patented. Red petrolatum was used by the United States military as a sunblock during World War II. The initial compounds were primarily ultraviolet B radiation (UVB) blockers as it was to blame for the most observable effect, sunburn [48]. When exposed to light, aminobenzoic acid (para-aminobenzoic acid or PABA) absorbs UV light and emits excess energy via a photochemical reaction that may cause damage to DNA. Because DNA defects contribute to skin cancer, aminobenzoic acid is no longer widely used in sunscreen formulations. Aminobenzoic acid may also increase oxygen uptake at the tissue level and may enhance monoamine oxidase (MAO) activity to promote the degradation of serotonin, which in excess, may lead to fibrotic changes [46]. Aminobenzoates are the most potent UVB absorber but do not absorb UVA. Their use has declined due to para-aminobenzoic acid (PABA) sensitivity. PABA is a very effective UVB filter; however, it was reportedly the most common photoallergen and contact allergen (Figure 8) [47].

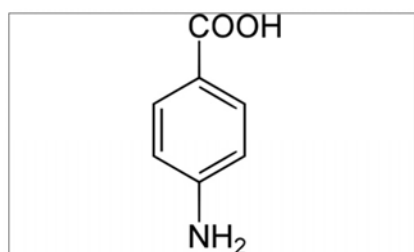


Figure 8. p-aminobenzoic acid (PABA).

Avobenzene

UVA blockers, considered broad spectrum and have a high efficacy against UVA I (>380 nm); however, they are very photounstable and lose from 50% to 90% of their particles after 1 h of UV exposure. It is also reported that they degrade the UV filter octinoxate [40,59]. Avobenzene is the most widely used UVA filter in sunscreen lotion and it is prone to degradation in the presence of sunlight/UV radiation, they show a significant skin penetration [56]. 30% HPCD-Avobenzene system was the most photostable following UVA exposure at various regimens and also enabled photoprotective efficiency *in vivo*, evidenced by lower levels of sunburn cells and skin edema induction [60]. To overcome the photo-instability of avobenzene, various photostabilizers have been used as additives, including

antioxidants such as vitamin C, vitamin E and ubiquinone. The dual role of glutathione as a skin whitening agent and a photostabilizer of avobenzene may be useful for the development of multipurpose cosmetic lotions [49]. Avobenzene is dibenzoyl methane derivative. It is oil soluble crystalline solid [50,58]. Mesoporous silicas (MSs) containing avobenzene or oxybenzone effectively ameliorated UVA-induced skin disruption and reduced the possible toxicity elicited by percutaneous penetration [56]. Photosensitization by drugs is a problem of increasing importance in modern life. This phenomenon occurs when a chemical substance in the skin is exposed to sunlight. Photosensitizing drugs are reported to cause severe skin dermatitis, and indeed, it is generally advised to avoid sunbathing and to apply sunscreen. In this context, the NSAID diclofenac is a photosensitive drug, especially when administered in topical form. Avobenzene provides partial photoprotection to diclofenac from photocyclization to carbazole derivatives [52]. Avobenzene is widely used in various personal care products, is present in swimming pools, and is toxic to aquatic organisms. Avobenzene induces mitochondrial dysfunction-mediated apoptosis leading to abnormal placentation during early pregnancy [53]. Avobenzene was more unstable/toxic than octyl p-methoxycinnamate (an organic UV-B filter originally developed in the 1950s, has been one of the most widely used sunscreens for decades) [54,55]. Octocrylene helps stabilize avobenzene, which is good, but it is a known endocrine disruptor that also releases free radicals (Figure 9) [57].

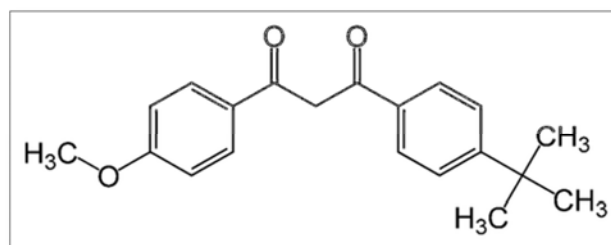


Figure 9. Avobenzene.

Oxybenzone

Oxybenzone is a benzophenone derivative used as a sunscreen agent. Oxybenzone absorbs UVB and UVA II rays, resulting in a photochemical excitation and absorption of energy [116]. Oxybenzone (Benzophenone-3) is an emerging human and environmental contaminant used in sunscreens and personal care products to help minimize the damaging effects of ultraviolet radiation. The Center for Disease Control (CDC) fourth national report on human exposure to environmental chemicals demonstrated that approximately 97% of the people tested have oxybenzone present in their urine, and independent scientists have reported various concentrations in waterways and fish worldwide. Oxybenzone can also react with chlorine,

producing hazardous by-products that can concentrate in swimming pools and wastewater treatment plants. Moreover, adverse reactions could very well be increased by the closed loop of ingesting fish contaminated with oxybenzone and/or washing the ingredient off our bodies and having it return in drinking water as treatment plants do not effectively remove the chemical as part of their processing protocols. In humans, oxybenzone has been reported to produce contact and photocontact allergy reactions, implemented as a possible endocrine disruptor and has been linked to Hirschsprung's disease. Environmentally, oxybenzone has been shown to produce a variety of toxic reactions in coral and fish ranging from reef bleaching to mortality (Figure 10) [117].

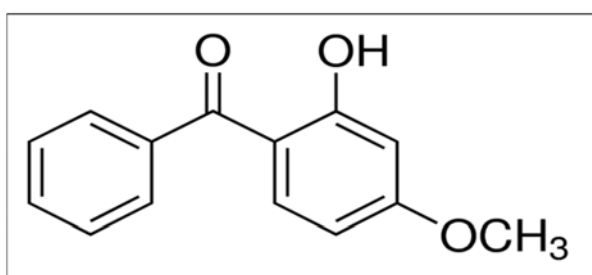


Figure 10. Oxybenzone.

Dioxybenzone

Dioxybenzone is an approved sunscreen ingredient in concentrations up to 3% [67]. The benzophenone sunscreens, octabenzone (UV-1) and dioxybenzone (UV-2) were found to exhibit significant chemopreventive activity against mouse skin carcinogenesis which correlated with their antioxidant potency [63]. In a study aimed to qualify photo-safety screening, benzophenone derivatives and ketoprofen exhibited significant reactive oxygen species (ROS) generation upon exposure to simulated sunlight; however ROS generation from sulisobenzone and dioxybenzone was negligible [68]. Polymerization with natural polymer pullulan not only provides a long polymer backbone to dioxybenzone, but also keeps the distance between benzene rings of the dioxybenzone and prevents reduction of photoabsorption intensity. UV/Vis spectrophotometry confirmed that dioxybenzone-pullulan polymer and dioxybenzone demonstrated similar UV absorption. Dioxybenzone showed higher plasma concentration after multiple applications compared to that of dioxybenzone-pullulan polymer [64]. Chlorine is used as a chemical disinfectant in swimming pools. Its reactivity suggests sunscreen components might be chlorinated, altering their absorptive and/or cytotoxic properties. Chlorinated oxybenzone and dioxybenzone caused significantly more cell death than unchlorinated controls. In contrast, chlorination of sulisobenzone actually reduced cytotoxicity of the parent compound. Exposing a commercially available sunscreen product to chlorine also

resulted in decreased UV absorbance, loss of UV protection, and enhanced cytotoxicity [65]. Bromal hydrate was also detected as one of the byproducts generated by oxybenzone and dioxybenzone, which is highly toxic; the "positive halogen" properties of bromal hydrate are responsible for its high toxicity [66]. In addition to allergic reactions, concerns have been raised about the relative ease of which benzophenone is absorbed into the skin and may promote generation of potentially harmful free radicals (Figure 11) [69].

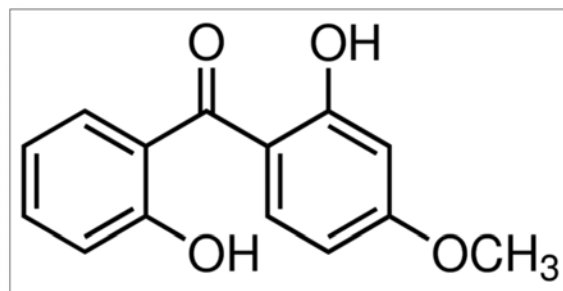


Figure 11. Dioxybenzone.

Cinoxate

Ester derivatives such as ethylhexyl methoxycinnamate (octinoxate), isoamyl p-methoxycinnamate (amiloxiate), octocrylene and cinoxate are used in cosmetics all over the world as UV filters. However, their maximum concentrations in cosmetic products are restricted due to their adverse effects, which include contact and a photocontact allergies, phototoxic contact dermatitis, contact dermatitis, estrogenic modulation and generation of reactive oxygen species. 4-hydroxycinnamic acid, which is currently indexed as a skin-conditioning cosmetics ingredient, has been widely tested *in vitro* and *in vivo* as a new drug candidate for the treatment of hyperpigmentation [61]. Cinnamates have replaced PABA as the next most potent UVB absorber and include octinoxate (OMC) and cinoxate (2-ethoxyethyl-methoxycinnamate). Cinoxate is less commonly used [62]. Major Key players with cinoxate are Major Key Players are Parchem (US), Carbosynth Limited (UK), Synchem UG & Co. KG (DE) (Figure 12) [110].

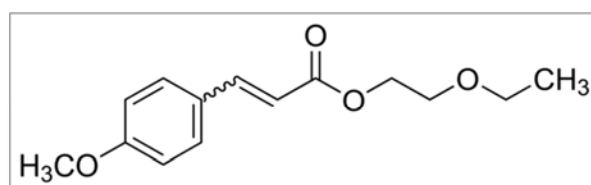


Figure 12. Cinoxate.

Octinoxate

Octinoxate (Octyl Methoxycinnamate, OMC) is a cinnamate ester and common ingredient in sunscreen and other skin care products to minimize DNA photodamage. It was

originally developed in 1950's as an organic UV-B filter that absorbs UV-B rays from sun. It is often combined with nanoparticles or other water-resistant liposomes in formulations to increase the localization at the epidermis and decrease the risk of percutaneous absorption [105]. OMC is the most commonly used UVB filter in the US. It is not as potent a UVB absorber as padimate O; for this reason, other UVB absorbers are used in combination to increase the SPF. OMC is not very photostable and degrades in the presence of sunlight after a short period of time. OMC is a potent UVB absorber and is the most frequently used sunscreen ingredient. The efficacy of OMC can be further increased when encapsulated in polymethyl methacrylate microsphere [62]. Due to low water solubility (<1 mg/L), OMC is suitable for most waterproof sunscreen formulations [106]. Hawaii legislature passed a bill that outlaws products that contain Oxybenzone and OMC, effective January 2021. The bill is based on studies that show that oxybenzone may harm coral larvae and that both compounds may "bleach" coral, causing it to lose symbiotic algae [107-109]. OMC has been detected in human urine, blood and breast milk, which indicates that humans are systemically exposed to this compound. OMC is an endocrine disruptor that mimics estrogen and can disrupt thyroid function (Figure 13) [112,113].

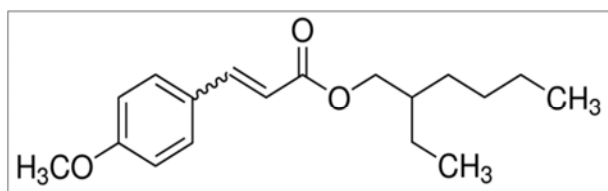


Figure 13. Octinoxate.

Homosalate

Homomenthyl salicylate or 3,3,5-Trimethylcyclohexyl Salicylate. After topical application of gel, the bioavailability of HMS was 5.4 ± 1.1 and $4.2 \pm 0.6\%$ for high and low doses (10 and 20 mg), respectively. Homosalate (HMS) is an UV filtering agent used in sunscreens and other cosmetics for skin protection purposes. It is a viscous or light yellow to slightly tan liquid or oil, derives from salicylic acid [70,71]. Salicylates are weak UVB absorbers and they are generally used in combination with other UV filters. Both octisalate and homosalate are water insoluble that leads to their high substantivity, which is the ability to retain its effectiveness after exposure to water and perspiration [72]. HMS does not have endocrine disruptor effects on thyroid function and the pubertal development of female and male rats [73]. Another study says HMS is a potential endocrine disruptor and studies in cells suggest it may impact hormones. In addition to direct health concerns following homosalate exposure, the chemical may also enhance the absorption of pesticides in the body [75]. Homosalate suppressed the ear edema

response to dinitrobenzene; a possible mechanism of action of the salicylates is suppression of COX (Figure 14) [114].

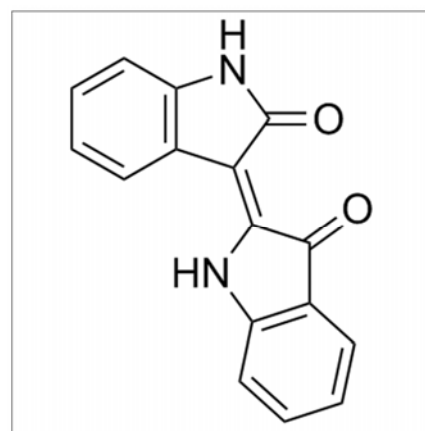


Figure 14. Homosalate (Homomenthyl salicylate).

Octisalate

Also, Ethylhexyl salicylate, a benzoate ester and a member of phenols. It derives from a salicylic acid. Salicylates are weaker UVB absorbers. It has an approved usage level of 3 to 5% in both US and EU and is a good solubilizer for benzophenone 3. In suntan lotions, it is used as a preservative and antimicrobial. This salicylate salt is found in wintergreen leaves [115]. They have a long history of use but were supplanted by the more efficient PABA and cinnamate derivatives. They are generally used to augment other UVB absorbers. With the trend to higher SPFs, more octisalate or octyl salicylate (ethylhexyl salicylate) is being used followed by homosalate or homomenthyl salicylate. Both materials have the ability to solubilize oxybenzone and avobenzene [97]. Both homosalate and octisalate were found to suppress experimental autoimmune encephalomyelitis (EAE), a widely used animal model of Multiple sclerosis (MS). Thus, salates may be useful new insight into mechanisms of controlling autoimmune disease (Figure 15) [114].

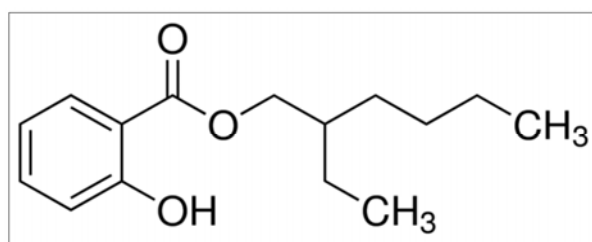


Figure 15. Octisalate (Ethylhexyl salicylate).

Meradimate (menthyl anthranilate)

Meradimate, before known as menthyl anthranilate, is used in a maximal concentration of 5% in different products as a UV filter. It is currently required to be named as meradimate in all FDA approved OTC products. Meradimate is approved

by the FDA and Health Canada to be used as an ingredient in sun blocking products Meradimate is a monoterpenoid, a broad-spectrum ultraviolet absorber used as a chemical filter in commercial sunscreens [76]. A moderately effective UVA protector not permitted for use in Europe or Japan. Its protective effective action does not cover completely the UVA rays as it only reaches 336 nm. This has been proven even though meradimate has a theoretical protective coverage range between 200-380 nm. Its function is related to the intrinsic structure of meradimate which is an ortho-disubstituted aminobenzoate. This structure allows easy electron delocalization and shifts in the maximum absorption. Poor photoprotection reported by Rodrigues et al. [76] makes it a poor choice for an efficient, efficacious sunscreen chemical filter (**Figure 16**).

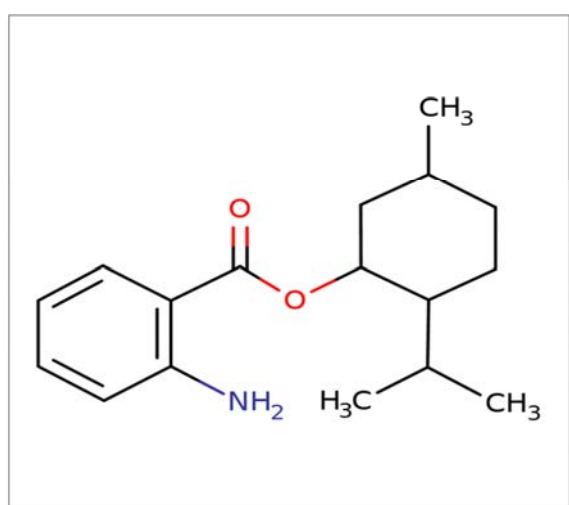


Figure 16. Meradimate (menthyl anthranilate).

Octocrylene

2-Ethylhexyl-2-cyano-3,3 diphenylacrylate or octocrylene is chemically related to cinnamates. It can be used to boost SPF and improve water resistance in a given formulation. Octocrylene is photostable and can improve the photostability of other sunscreens. It is expensive and can present difficulties in formulation [97]. The absorption profile of octocrylene spans from 290 to 360 nm with peak absorption at 307 nm. The compound has an excellent safety profile with low irritation, phototoxicity, and photoallergic potential. Octocrylene may be used in combination with other UV absorbers to achieve higher SPF formulas and to add stability. [62]. Photostability refers to the ability of a molecule to remain intact with irradiation. Photostability is potentially a problem with all UV filters. This issue has been raised specifically with avobenzone. This effect may degrade other sunscreens in a formulation, including octyl methoxycinnamate. Octocrylene and some of the newer sunscreens, including BEMT, stabilized avobenzone [97]. Chlorination reactions showed that only octocrylene was stable in chlorinated seawater [66]. UVA and UVB

screening potentials of octocrylene and zinc oxide formulations were compared in the 290-400 nm wavelength region. Zinc oxide loaded SLN suspensions were found to be more effective in the UVA region while octocrylene loaded ones performed better in the UVB region [98]. Octocrylene appears to be a strong allergen leading to contact dermatitis in children and mostly photoallergic contact dermatitis in adults with an often-associated history of photoallergy from ketoprofen. Patients with photoallergy from ketoprofen frequently have positive photopatch test reactions to octocrylene. These patients need to be informed of sunscreen products not containing octocrylene, benzophenone-3, or fragrances [99,100]. The clinical studies show that octocrylene is both a photocontact allergen and a contact allergen [103]. Octocrylene's ability to cause contact allergy is probably attributable to its reactivity towards lysine [101]. A reduction of the UV filter in the formulation packed in HDPE/LDPE material can occur over time, reducing the protective effect of the product when applied to the skin [102]. Wide application in cosmetics leads to contamination of the aquatic environment, mainly affects transcription of genes related to developmental processes in the brain and liver as well as metabolic processes in the liver (bioaccumulation study in male zebrafish) (**Figure 17**) [104].

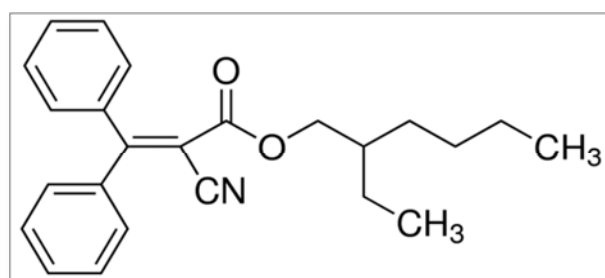


Figure 17. Octocrylene (2-ethylhexyl-2-cyano-3,3 diphenylacrylate).

Padimate O

Padimate A and Padimate O were introduced as substitutes for PABA to reduce the number of reactions seen with PABA. Ethylhexyl dimethyl PABA is also known as padimate O, OD-PABA or octyl dimethyl p-aminobenzoate. It is a viscous liquid tends to retain on the surface of the stratum corneum with little penetration. It has a very low potential for sensitization. Ester derivatives of PABA became more popular with greater compatibility in a variety of more substantive vehicles and a lower potential for staining or adverse reactions. Padimate O is an active sunscreen agent in cosmetics and over-the-counter sunscreen drug products in concentrations up to 8%, as regulated by the FDA. No irritation was reported when both eyes are washed and left unattended. 5% ethylhexyl dimethyl PABA mixed with mineral oil applied to rabbit skin did not cause irritation and no skin sensitization in guinea pigs with the

same. High concentrations of padimate O may be toxic to the epididymis and caution should be exercised when administering this substance to infants younger than six months of age due lack of understanding of its metabolism and absorption. It is widely used as an ingredient in many cosmetics at an average concentration of 1.25% (0.5-2.0%) in Korea. It is toxic to the following four organs: testis, epididymis, spleen, and liver. In addition, experiments using human keratinocytes found that ethylhexyl dimethyl PABA inhibits cell growth and DNA synthesis at low concentrations, and halted the cell cycle of malignant melanoma cell line (MM96L) at the G1 phase. According to the EWG database, it is used in many products including lipstick, conditioner, shampoo, anti-aging agents, hair spray, and sunscreen. No significant reproductive toxicity, genotoxicity, carcinogenicity, skin sensitization, skin irritation or phototoxicity was observed in response to Padimate O administration (limited studies there, requires further investigations) (Figure 18) [97,118,119].

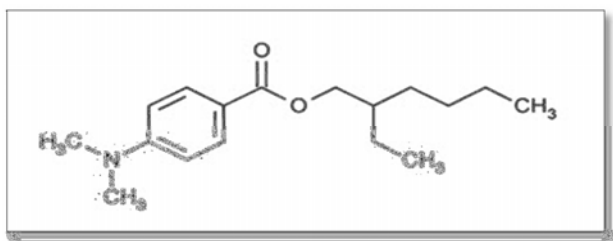


Figure 18. Padimate O (ethylhexyl dimethyl PABA).

Ensulizole

2-phenylbenzimidazole-5-sulfonic acid/Phenylbenzimidazole sulfonic acid or ensulizole is a water-soluble UVB absorber that can be used in the water phase of emulsion systems. It is commonly found in cosmetic products and sunscreen formulas in combination with other UV filter compounds due to its minimal protection against UV-A wavelengths, indicated to be used as an UV-B-absorbing molecule in sunscreen formulations. In contrast to most oil-soluble sunscreen ingredients, allowing for a less-greasy, more aesthetically pleasing formulation such as a daily use moisturizer containing sunscreen. Phenylbenzimidazole sulfonic acid boosts the SPF of organic and inorganic sunscreens. It can also be used in clear gels owing to its water solubility. Due to its water solubility, ensulizole is commonly used in products formulated to feel light and less oily. It was demonstrated by studies that ensulizole treatment provided protection against cyclobutane pyrimidine dimers and photosensitized the formation of oxidized guanine bases after UV-A or UV-B exposure. According to the FDA, the maximal approved concentration of ensulizole is 148 mM although concentrations ranging between 74 and 148 mM can be found in commercial sunscreen products. Ensulizole is capable of generating reactive oxygen species, including singlet oxygen upon photoexcitation. Based on the findings *in vitro* and in

cellulo, ensulizole induces damage on the DNA, causes DNA strand breaks and photosensitizes the formation of oxidized guanines via type I and II photosensitization mechanisms following UV-A or UV-B irradiation (Figure 19) [87,120-125].

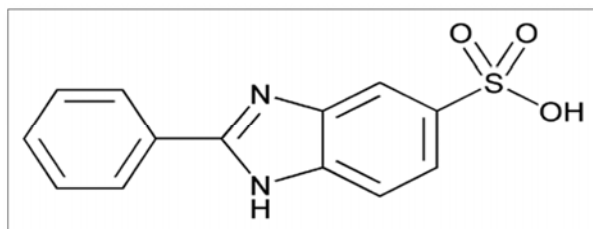


Figure 19. Ensulizole (Phenylbenzimidazole sulfonic acid).

Sulisobenzone

A benzophenone does not undergo decomposition to an inactive form if it does not couple to target molecules. Instead, it degrades from the photo-excited state back to its initial state, so it can be once again photolyzed to an active state. This process increases the likelihood that the benzophenone will couple to a target molecule during the photoreaction. Benzophenones are used as photoinitiators, fragrance enhancers, ultraviolet curing agents, and, occasionally, as flavor ingredients; they are also used in the manufacture of insecticides, agricultural chemicals, and pharmaceuticals and as an additive for plastics, coatings, and adhesives. The UV-filter substance Sulisobenzone (BP-4) is widely employed in sunscreens and other personal care products. Sulisobenzone is approved by the FDA in concentrations of up to 10% and in Canada, is approved by Health Canada at the same concentrations. It works to filter out both UVA and UVB rays, protecting the skin from sun UV damage. The benzophenones are a group of aromatic ketones that have both pharmaceutical and industrial applications. Benzophenones may be found organically in fruits such as grapes, used primarily as a UVA absorber, but boosts SPF values in combination with other UVB absorbers. Sulisobenzone water soluble, somewhat unstable, and used with less frequency. It can cause skin and eye irritation. Does not penetrate the skin to a large degree, but enhances the ability of other chemicals to penetrate. Safety use in sunscreen is questionable (Figure 20) [88,126-130].

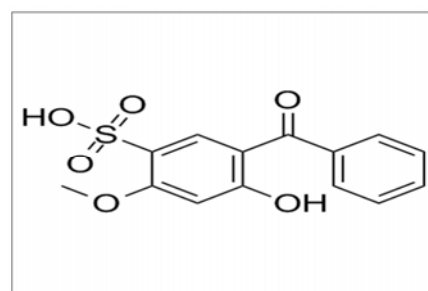


Figure 20. Sulisobenzone (benzophenone-4/BP-4).

Trolamine salicylate

Trolamine salicylate is an organic compound or a salt formed between triethanolamine and salicylic acid. Triethanolamine neutralizes the acidity of the salicylic acid. It is a topical analgesic used for temporary relief of minor pain associated with arthritis, simple backache, muscle strains, sprains, and bruises. Unlike other topical analgesics, trolamine salicylate has no distinct odor which improves patient acceptability. Trolamine or triethanolamine salicylate has good water solubility. It is mostly used for water soluble sunscreens to help increase the SPF of cosmetics owing to their substantivity to the skin. It also displays low systemic absorption upon dermal or topical administration and has low skin irritant properties. Approved in both the US and Canada, trolamine salicylate is used in concentrations of up to 12%. It filters UVB rays, but has no effect on UVA rays, which means it cannot be relied on alone as a sunscreen. It has found to cause photocontact dermatitis (**Figure 21**) [106,131,132].

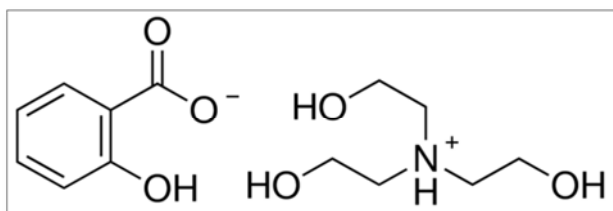


Figure 21. Trolamine salicylate.

Titanium dioxide

TiO₂ occurs naturally in three crystalline structures: rutile, anatase and brookite. Rutile is the most common and stable form of this pigment. Important optical properties of this birefringent crystal are its refractive indices in the UV and visible wavelength range. The USP classifies it as a topical protective. The protection is primarily for its opacity due to high refractive index (2.7). However, the high refractive index is not the only property that determines how well a substance blocks light. The film thickness in which the substance is suspended as well as the size of the individual particles also affects the efficacy of the sunscreen. Advantages offered by sunscreens based on inorganic compounds comprise absence of skin irritation and sensitization, inertness of the ingredients, limited skin penetration, and a broad-spectrum protection. As a solar ray protective, it is used in a conc. 5% to 25% in ointments and lotions. Since it is not absorbed into the skin, this effect may not be an issue in topical use on unbroken skin. It is also used as a white pigment in cosmetics and paints. According to the US FDA, the protection factor against UVA should be at least one-third of the overall sun protection factor. Previously, TiO₂ had a suboptimal cosmetic profile, appearing thick and white on application. Current formulations are micronized or nanoparticle formulations, which blend in with the skin tone and attain better cosmesis.

As micro-sized TiO₂ is the most effective in UVB and micro-sized ZnO in the UVA range, the combination of the two oxides assures the required broad band UV protection. The particle sizes that result, within human SC, in higher UV absorption and scattering and lower UV transmission improve the UV attenuation. Emulsions are generally unstable, often change from water-oil to oil-water or break down during application on the skin, and may increase the cutaneous permeability. It has been demonstrated that sunscreen TiO₂ particles penetrate deeper into human skin from an oily than from an aqueous dispersion. The International Agency for Research on Cancer (IARC) has recently classified TiO₂ as an IARC group 2B carcinogen, possibly carcinogenic to humans. The IARC conclusions are based on evidence showing that high concentrations of pigment-grade and ultrafine TiO₂ dust cause respiratory tract cancer in rats. Intrinsic cyto- and genotoxicity of both TiO₂ and ZnO NPs (<100 nm) has been frequently reported. Coating the NPs does reduce the toxic effects, especially when silica-based coatings are used, but cannot completely prevent these effects. TiO₂, however, has currently attracted more scientific attention than ZnO [40,133,134].

Zinc oxide

Sunscreens containing metal oxide nanoparticles appear transparent on the skin and provide excellent protection against sunburn caused by UV radiation. Zinc oxide is a widely used broad-spectrum sunscreen, repeated application of ZnO-NPs to the skin, as used in global sunscreen products, appears to be safe, with no evidence of ZnO-NP penetration into the viable epidermis or toxicity in the underlying viable epidermis. It was associated with the release and penetration of zinc ions into the skin, but this did not appear to cause local toxicity. In the past two decades, ZnO NPs have become one of the most popular metal oxide nanoparticles in biological applications due to their excellent biocompatibility, economic, and low toxicity. ZnO NPs have emerged a promising potential in biomedicine, especially in the fields of anticancer and antibacterial fields, which are involved with their potent ability to trigger excess ROS production, release zinc ions, and induce cell apoptosis. In addition, ZnO NPs have superior antibacterial, antimicrobial, and excellent UV-blocking properties. ZnO NPs-exposed HepG2 cells presented higher cytotoxicity and genotoxicity, which were associated with cell apoptosis mediated by the ROS triggered mitochondrial pathway. In the brain, the oxidative stress and inflammation reaction were found after ZnO NP exposure and more remarkable changes were identified in aged individual. These kinds of neurotoxicity might due to the destruction of the BBB integrity caused partly by ZnO NPs-induced systemic inflammation [135-138].

SUNSCREEN FORMULATION

On the surface, sunscreen products are pretty simple. They consist of a delivery vehicle containing one or more

sunscreen active ingredients. When applied to the skin, these sunscreen actives intercept solar UV rays before they can damage the underlying skin. However, while conceptually simple, a detailed analysis reveals that sunscreen

formulations are quite complex, requiring careful selection of sunscreen active and vehicle components to control multiple performance and in-use parameters (Exhibit 9) [164].

Exhibit 9. Aqueous, non-aqueous and clear sunscreen lotion formulation.

Aqueous Lotion		Non-Aqueous Lotion		Clear Lotion	
Ingredients	(%)	Ingredients	(%)	Ingredients	(%)
Filtrosol B	7	Giv-Tan F/Cinoxate	1.5	Isobutyl PABA	5
Methyl Cellulose	0.5	Denatured ethyl alcohol	65	Tween 20	9
Glycerin	2	Oleyl alcohol	10	Alcohol SD 40	45
Ethyl alcohol	10	Water	23	Water	41
Water	80.5	Perfume	q.s.		
Perfume	q.s.				

Alpha-Tocopherol (Filtrosol) has many protective actions, such as decreasing immunosuppression, erythema, photoaging, and photocarcinogenesis [40]. Naturally occurring vitamin E is not a single compound; instead, vitamin E is a group of molecules with related structures, some of which may have unique properties in skin. After topical application, vitamin E accumulates not only in cell membranes but also in the extracellular lipid matrix of the stratum corneum, where vitamin E contributes to antioxidant defenses. However, much of a topically applied dose of vitamin E alone will be destroyed in the skin following exposure to UV light. This suggests that although vitamin E is working as an antioxidant, it is unstable on its own and easily lost from the skin. Thus, improving the stability of topical applications with vitamin E is important [165]. Methyl Cellulose (Methylester of cellulose) is used as an emulsifying, suspending and thickening agent in cosmetics, pharmaceuticals and the chemical industry. It's a non-ionic polymer, is highly hydrophilic and thus easily dissolves in cold and hot water [166]. Ethyl alcohol is antimicrobial preservative; disinfectant; skin penetrant; solvent. Cetyl and cetearyl are both derived from coconut and are fatty alcohols. Typically, fatty alcohols are used as emollients and thickeners in skin-care products. Fatty alcohols are not irritating and, in fact, can be beneficial for dry skin. If LMW alcohols are high up on the ingredients list on a bottle of sunscreen then they are going to dry out skin. However, Topical application of 10% ethanol stimulates the proliferation of peritoneal tissue explants – a semi *in vivo* wound model – which can be interpreted as positive influence for stimulation of wound healing by ethanol [167,168]. Oleyl alcohol is mainly used in topical pharmaceutical formulations and is generally regarded as a nontoxic and non-irritant material at the levels employed as

an excipient. However, contact dermatitis due to oleyl alcohol has been reported. It's an antifoaming agent; dissolution enhancer; emollient; emulsifying agent; skin penetrant; sustained-release agent. SD alcohol 40 is a type of denatured alcohol used in cosmetics and personal care products as an anti-foaming agent, astringent, antimicrobial agent and a solvent. In addition to SD alcohol 40, the specially denatured alcohols acceptable for use in cosmetics are SD Alcohol 23-A and SD Alcohol 40-B. As an astringent, SD alcohol 40 causes biological tissue to contract or draw together. After topical application, astringents work on proteins called keratins, which function to hold skin cells together to form a barrier. The bonds between keratins are affected by temperature and pH, forming only when skin is slightly acidic or cool. If the bonds break, the keratin molecules will separate, causing the outer layer of skin to swell. Astringents cool the skin and cause the bonds to reform. It is this process that produces the temporary toning effect associated with astringents [169]. 2-Ethoxyethyl-p-Methoxycinnamate (Giv Tan® F/Cinoxate) used as sunscreen. The most common moisturizing ingredients are occlusive agents which create a barrier that blocks water from escaping the skin. Ingredients like Petrolatum, Mineral Oil and Dimethicone can all be used as occlusive agents. Humectants, which are ingredients that attract water, are also added to lotions. Glycerin is the most commonly used humectant. Finally, emollients are added to improve the feel of the lotion on the skin. They can reduce the tackiness and greasiness caused by the other moisturizing ingredients. Common emollients include coconut oil, cetyl esters, and certain silicones. Sunscreen formulations are typically thinner in viscosity than standard skin lotions (Exhibit 10) [170].

Exhibit 10. Sunscreen formulations with Avobenzone, TiO₂ and ZnO NPs [95].

Ingredients	Quantity (% w/w)							
	SC1	SC2	SC3	SC4	SC5	SC6	SC7	SC8
Oil phase	25.05	25.05	25.05	25.05	25.05	25.05	25.05	25.05
Preservative	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Aqueous phase	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
Plain morin	-	-	0.05	-	-	-	0.05	-
Avobenzone	-	-	-	-	-	2.66	2.66	2.66
Nano titanium dioxide	-	4.55	4.43	4.55	4.55	4.43	4.43	4.43
Nano zinc oxide	-	4.55	4.43	4.55	4.55	4.43	4.43	4.43
Morin nanoparticles	-	-	-	-	0.05	-	-	0.05
Plain nanoparticles	-	-	-	0.05	-	-	-	-
Water (solvent)	to 100	to 100	to 100	to 100	to 100	to 100	to 100	to 100

Morin is a yellow chemical compound that can be isolated from *Maclura pomifera* (Osage orange), *Maclura tinctoria* (old fustic) and from leaves of *Psidium guajava* (common guava) [161]. Morin is a pentahydroxyflavone that is 7-hydroxyflavonol bearing three additional hydroxy substituents at positions 2' 4' and 5. It has a role as an antioxidant, a metabolite, an antihypertensive agent, a hepatoprotective agent, a neuroprotective agent, an anti-inflammatory agent, an antineoplastic agent, an antibacterial agent, an EC 5.99.1.2 (DNA topoisomerase) inhibitor and an angiogenesis modulating agent. It is a pentahydroxyflavone and a 7-hydroxyflavonol [162]. ZnO and TiO₂ combinations are particularly valuable because of their ability to filter both UVA and UVB radiations, providing broader UVR protection than that observed with individual component

[95]. In 2018, the EWG reported that a large increase in these inorganic filters with ~41% of sunscreens in the United States designated as mineral only. This figure has more than doubled (from 17%) since 2007 [111]. Only two sunscreen active ingredients approved in the US, avobenzone (butylmethoxydibenzoylmethane) and zinc oxide (ZnO), provide true broad-spectrum protection against UVA wavelengths >360 nm. Although effective against shorter UVR wavelengths <360 nm, titanium dioxide TiO₂ is also often believed to confer broad-spectrum protection and is substituted for ZnO or avobenzone. Use of proper formulation strategies can ensure that avobenzone losses are minimized to the extent that they have no impact on a product's ability to deliver sustained protection, even over periods of prolonged exposure to UVR (Figure 22) [163].



Figure 22. Colorful reefs are a major draw for tourists. But chemicals in sunscreen and ocean warming pose serious threats to them [183].

Studies have shown that oxybenzone and octinoxate are found in over 3,500 sunscreen products, including household names like Tropicana, Banana Boat and Coppertone. When corals absorb these chemicals, they have a similar reaction as they would if surrounding water temperatures were to get too warm. In addition, the presence of these chemicals in sea water allows viruses to thrive, putting corals at high risk of catching an infection that could lead to bleaching and death

SUNSCREEN VS. CORAL REEF

While covering less than 1% of the ocean surface, coral reefs provide habitat for nearly one third of marine fish species as well as 10% of all fish captured for human consumption. Coral reefs also provide major essential benefits to people, like food production, tourism, biotechnology development, and coastal protection. There is strong evidence that some sunscreen ingredients, especially oxybenzone, are harmful to corals if the concentration in water is high. In some situations, primarily related to the number of swimmers and the geography of the shoreline, concentrations of oxybenzone far exceed the levels shown to be harmful to corals [181]. In 2015, the non-profit Haereticus Environmental Laboratory surveyed Trunk Bay beach on St. John, where visitors ranged from 2,000 to 5,000 swimmers daily, and estimated over 6,000 pounds of sunscreen was deposited on the reef annually. The same year, it found an average of 412 pounds of sunscreen was deposited daily on the reef at Hanauma Bay, a popular snorkeling destination in Oahu (Hawaii) that draws an average of 2,600 swimmers each day. Over the past three years, one-fifth of the world's coral reefs have died off — and there is a growing awareness that sunscreen is playing a role. From 6,000 to 14,000 tons of sunscreen slide off of humans into coral reef areas each year, exposing the gorgeous underwater ecosystems to chemicals that can kill them. Global warming is the main reason that coral reefs are dying — but sunscreens play a role, too [182]. Danovaro et al. [184] revealed that sunscreens, by promoting viral infection, potentially play an important role in coral bleaching in areas prone to high levels of recreational use by humans. Coral bleaching has negative impacts on biodiversity and functioning of reef ecosystems and their production of goods and services. This increasing world-wide phenomenon is associated with temperature anomalies, high irradiance, pollution, and bacterial diseases. Hard-coral bleaching and the increase in viral abundance in seawater were also seen after coral treatment with mitomycin C, an antibiotic commonly used to induce the lytic cycle in latent viral infections [184]. Unfortunately, the World Conservation Institute estimates that 20% of coral reefs are already destroyed, another 25% are in great immediate threat, and another 25% will be threatened by 2050 [185].

Epilogue

The skin stratum corneum acts as a barrier that isolates the organism from the environment and avoids water loss from tissues. Such a sealed sheath is essential for the physiological processes of the skin and of the entire body, but poses problems for the topical delivery of substances to the tissues. This kind of hindrance has been known since ancient times and has been empirically approached, e.g. by the use of greasy or oily materials in skin care applications. Technological achievements in the topical administrations of medicaments and in skin care products have led to the

development of vehicles and penetration enhancer and to the design of technologically advanced formulations. Although synthetic chemical structures have been abundantly used in this field, traditional practices and scientific studies have shown through the years that botanical sources can provide all kinds of elements for vehiculating drugs and active compounds and for enhancing their permeation through the skin. There is wide variability in price, SPF protection, and product claims among commercially available sunscreens. Cosmetic elegance is one of the most important positive features, followed by product performance. Dermatologists should counsel patients that sunscreen products come with numerous marketing claims and varying cosmetic applicability, all of which must be balanced with adequate photoprotection. In addition, consumers should be advised to select a product with broad-spectrum coverage, an SPF of 30 or higher, and water and/or sweat resistance in the setting of water activities or high ambient temperatures. UV filters are analyzed in their pure form by ingredient suppliers and also by cosmetic companies that purchase those filters for incorporation into their finished products. Once these UV filters are included into cosmetic finished products, they also need to be analyzed for both quality control and regulatory compliance. Use of sun screening agents is beneficial in minimizing the occurrence of skin cancers in people with fair skin. However, the same effect on Asian skin is debatable, as this skin type is considered to be resistant to skin cancers. Sunscreen use is advisable in young adults to prevent and minimize other photodamaging effects. Affordability and proper application techniques are the challenges that must be addressed in order to achieve regular sunscreen usage.

ARTICLE SUMMARY

Promoting sunscreen use is an integral part of prevention programs aimed at reducing UV radiation-induced skin damage and skin cancers. Protection against both UVB and UVA radiation is advocated. Despite the efforts of physicians and regulatory authorities to spread awareness regarding sunburn, skin cancer, and the benefits of regularly using sun screening agents, treatment adherence is low. Providing cosmetically acceptable preparations and educating people about following the application instructions, is a challenge often faced by treating physicians. Pricing sunscreens reasonably and making them water resistant and non-sticky are a few of the challenges faced by manufacturers. Manufacturers must also consider sensitization reactions, especially in those having eczema or photo dermatoses. Sun protection factor (SPF) is affected by application density, water resistance and other factors. An adequate SPF for an individual should be balanced to skin phenotype and exposure habits. The correct use of sunscreens should be combined with the avoidance of midday sun and the wearing of protective clothing and glasses, as part of an overall sun protection regimen. The FDA approved sunscreen ingredients are extensively

reviewed. A clear and straightforward recommendation on their safety and efficacy still remains a big challenge.

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