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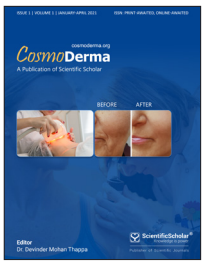

Review Article

Trust your sunscreen with caution: A literature review on the side effects of sunscreen

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ABSTRACT

Sunscreen use has grown significantly in recent years due to its ability to block harmful ultraviolet (UV) rays and reduce skin problems such as sunburn, aging skin, and immunosuppression. This review examines the ingredients in sunscreen and the effects they have. Substances including oxybenzone, avobenzone, homosalate, octisalate, enzacamene, and benzophenone enter the systemic circulation. The discovery of these substances in plasma and urine sparked concerns about their safety and the requirement for additional study into the long-term consequences they produce. The adverse effects of benzophenone, ecamsule, zinc oxide, titanium oxide, methylisothiazolinone, homosalate, octinoxate, aluminum oxide, and cinnamate derivatives such as octyl methoxycinnamate and octocrylene are also covered in this research. The mechanism of action of UV filters, as well as methods for assessing the effectiveness of sunscreens such as the sun protection factor, persistent pigment darkening, and immune protection factor, is elaborated. This literature review will also discuss the safety and effectiveness of the compounds used in sunscreen formulation as well as any potential health risks and toxicities.

Keywords: Sunscreen, Adverse reaction, Side effects, Absorption, Toxicities, Benefits

INTRODUCTION

Sunscreen use is currently becoming a global trend. This topical formulation has gained more acknowledgment in recent years as our population has recognized the risks posed by the sun's rays on our skin. There is evidence that prolonged exposure to ultraviolet (UV) light might cause skin problems. Sunscreens reportedly help to reduce the frequency of skin conditions due to their ability to absorb, reflect, and scatter UV light. UV radiation with shorter wavelengths is more likely to cause biological damage.[1,2]

This research provides a valuable assessment of the literature on overall adverse reactions of sunscreen use, benefits, risks, and absorption of this formulation into our circulation and evaluation techniques of sunscreen to assist doctors in providing patient counseling. Over time, sunscreen technology has made significant progress in terms of accessibility, consumer acceptance, safety, and effectiveness. Nonetheless, there is still an opportunity for more study and innovation to formulate an ideal sunscreen.

MATERIAL AND METHODS

In literature, search databases such as Google Scholar and PubMed, terms like "sunscreen," "adverse effects," "absorption," and "toxicities" were used. We researched over 30 articles that had been published in the previous 5 years and analyzed them.

RESULTS

According to the results of the literature review, there is enough data to encourage the future study of the ingredients used in a sunscreen formulation. These compounds have been found to be absorbed by systemic circulation and produce potential toxicities. Hence, to increase the safety and efficiency of sunscreen technology, it is crucial to keep researching and developing it.

DISCUSSION

Sunscreen is a commercial product designed to shield the skin from UV rays. The Food and Drug Administration defines broad-spectrum sunscreens as those that offer UV A protection proportionate to its UV B protection. They contain UV filters and a variety of other ingredients such as emulsifiers, perfumes, coloring agents, preservatives or stabilizers, and emollients [Figure 1].[3]

Sunscreen classification

According to how they are administered, sunscreens can be broadly divided into topical and systemic categories[1] [Figure 2]. A multi-component sunscreen includes both active chemicals to block UV radiation and common coatings to prevent bleaching and color fading.[4] The formulation of sunscreen can contain a variety of UV filters. They are divided into two groups: synthetic or organic and inorganic or mineral filters. To maximize sunscreen effectiveness, UV filters should typically stay on the surface or in the stratum corneum upper layers.[5,6] Organic sunscreens fall roughly into three categories: sunscreens that block UV B (290–320 nm), UV A (320–400 nm), and broad-spectrum sunscreens (290–400 nm).[1]

Aromatic ketones, Benzophenones 1, 2, 3, and 4 are only efficient against short-wave UV A radiation and are the most popular UV A organic filters, while sulfur and sodium atoms are components of the benzophenones 4, 5, and 9. Cinnamates are a class of UV B filters; they are present in 90% of sunscreens. Other significant classes of UV B filters include p-aminobenzoic acids and their derivatives, salicylates, camphor derivatives, octocrylene, ensulizole, and urocanic acid. Other frequently used filters include ecamsule, avobenzone, and meradimate.[5]

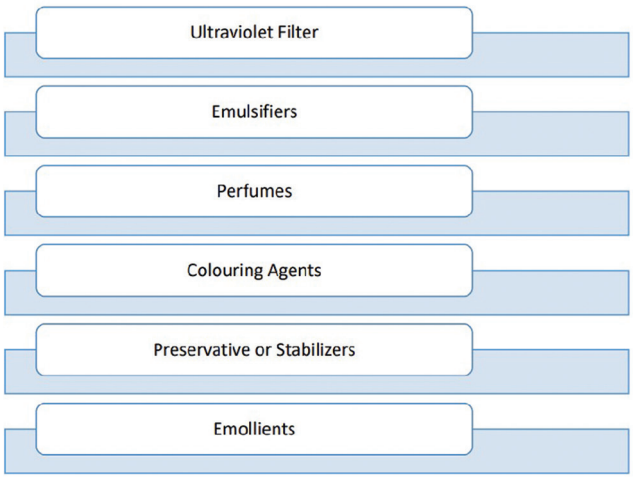

Figure 1: Ingredients present in sunscreen.

Inorganic sunscreen shields the skin by scattering and reflecting UV rays. The size and dispersion of the particles affect their effectiveness.[1] Inorganic sunscreen filters that can also be found as nanoparticles include titanium dioxide and zinc oxide. Nanoparticles have photocatalytic characteristics resulting in their photo passivation, which prevents any oxidative stress on the skin or from losing its protective features. Typically, an inert mineral coating of aluminum hydroxide or silica is precipitated on the surface of these nanoparticles. Moreover, sunscreen also has preservatives such as methylisothiazolinone. Systemic sunscreens are rarely used, even though they provide UV protection.[1,5,7]

Evaluation of a sunscreen's effectiveness

Sun protection factor, persistent pigment darkening, and immune protection factor are the three basic measures used to assess the efficacy of sunscreen. A sunscreen's sun protection factor measures how well it can prevent erythema from developing after exposure to UV rays. Sun protection factor ratings measure the effectiveness of protection and specify how long they will shield the user from UV rays. Undoubtedly, the sun protection factor numbers are often between 6 and 10, 15 and 25, and 30 and 50 and 50+, respectively, denoting poor, medium, high, and extremely high protection.[1,8]

However, the Japan Cosmetic Industry Association developed the *in vivo* persistent pigment darkening method in 1996 to evaluate the UV A effectiveness of sunscreen. Sunscreens with a PA+ grade offer little protection, especially because they only have two to four UV A filters. PA++-rated sunscreens that display significant UV A blocking have four to eight sunscreen ingredients present in them. On the other hand, the PA+++ and PA++++ classifications signify products with a high level of sunscreen effectiveness and more than eight UV A filters.[8]

Immune protection factor describes a sunscreen's capacity to stop UV-induced immunosuppression. It is evaluated using sophisticated techniques such as the capacity of a sunscreen to block either the sensitization or elicitation arm of immediate or delayed-type hypersensitivity reactions to allergens such as nickel and dinitrochlorobenzene, respectively.[1]

Sunscreen benefits

Sunscreen is essential for reducing the prevalence of UV-induced skin issues in individuals, such as the

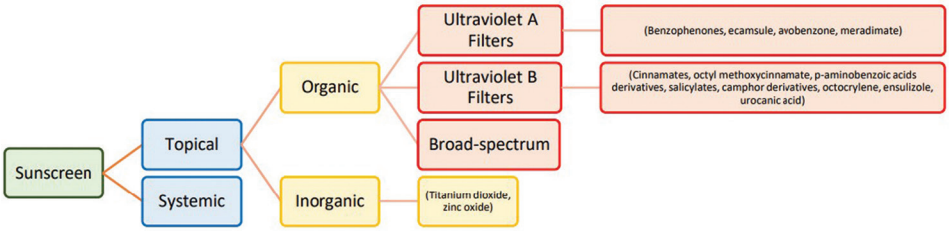

Figure 2: Classification of sunscreen.

production of reactive oxygen species, erythema, edema, inflammation, premature skin aging, dryness, sunburn reactions, photosensitivity, pigmentation, skin cancer, and other adverse effects[3,8-11] [Figure 3].

UV A is the main cause of photoaging because it has a longer wavelength and hence has deeper dermal penetration than UV B, which is mostly absorbed by the skin's epidermis. The dermis of the skin is exposed to 9–14% of solar UV B radiation. Skin photoaging, which includes wrinkles, laxity, blister, roughness, and loss of skin tone, is largely caused by radiation[11,12] [Figure 4]. Two sunscreen components, photolyases, and antioxidants have also been shown to prevent and possibly even reverse the effects of photoaging.

Sunscreen has been shown to reduce melanoma and non-melanoma skin cancers. Sunscreens usage evidence also indicates a reversal of extrinsic aging. In comparison, sunscreens' benefits in preventing skin cancer outweigh any short-term changes to the epidermal barrier.[2,12,13]

Emerging technologies such as Sunsphere and Microencapsulation have led to further advancement of sunscreen. Sunspheres are sun protection factor enhancing vehicles. They are created using water-filled, UV radiation-resistant styrene/acrylate copolymers. It is a hollow capsule that scatters the light that enters it. It increases the sun protection factor by 50–70% and seemed to have improved spreadability, *in vitro* sun protection factor, and water resistance.[10,14]

Microencapsulation helps us to reduce the adverse effects of UV filters by preventing direct contact with skin and transcutaneous entry. By microencapsulating, the organic UV filters like octyl methoxycinnamate and butyl-methoxydibenzoylmethane into a microporous zeolitic imidazole framework were able to produce sunscreens that are long-lasting, safe, fluorescent, and stable. We consider their use to be crucial given all the potential uses mentioned above.[15]

Sunscreen risks

Despite sunscreen being beneficial, its use poses risk to humans. Some sunscreen ingredients are potential carcinogens

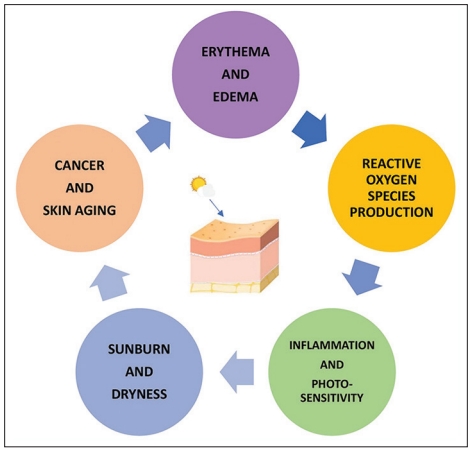

Figure 3: Damage caused by ultraviolet rays on skin.

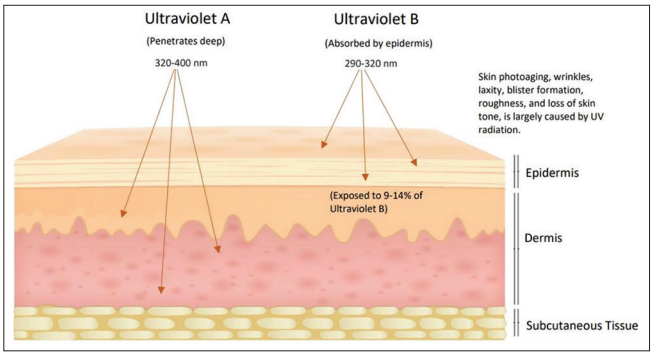

Figure 4: Action of ultraviolet rays.

and endocrine-disrupting chemicals such as benzophenone-3 which is harmful to developing embryos and fetuses as they can interfere with hormones, neurotransmitters, and growth factors crucial for normal development. It has been found to penetrate the blood-placenta barrier which causes worry in pregnant women. Male fertility may be at risk since it can imitate progesterone's effect on human spermatozoa. Another ingredient, octocrylene, may operate as a barrier to the calcitriol's function, leading to abnormal vitamin D production in the body.[16,17]

There is growing evidence that certain endocrine-disrupting chemicals can affect renal function and cause cumulative

renal damage too. In addition, studies have shown that some UV filters can be discovered in urine. Sunscreen compound, octinoxate, has antiandrogenic action, which indicates a risk to reproductive organs exposed *in utero*. The importance of benefits and risks associated with sunscreen use plays a critical role in creating awareness in the population[6,18,19] [Figure 5].

Absorption of sunscreen ingredients

The possibility that UV filters could pass through the skin and enter circulation sparked questions about the potential harm that UV filters might do to the human body. Even low penetration rates may result in a significant amount of sunscreen entering the systemic circulation. Benzophenone-3, camphor, and octyl-methoxycinnamate exhibit this effect and could produce allergies or phototoxic results.[20,21] For instance, clinical trials have shown sunscreen ingredients such as oxybenzone, octocrylene, and ecamsule to have high systemic absorption than advised standards. [2] 0.5 ng/mL in the blood was approved as the regulatory threshold for sunscreen active ingredients by the Food and Drug Administration.[22]

Researchers also found that oxybenzone was absorbed at a level of 258.1 ng/mL when it was applied to the skin every 2 h as directed on the bottle, this was 516 times more than the advised limit when it was applied to the skin every 2 h as directed on the bottle.[6] Bloodstream absorption by ingredients depends on a number of factors, such as the active ingredient's physicochemical properties, the formulation's features, and the stratum corneum's thickness and structure.[22]

After applying sunscreen containing 4% benzophenone-3 for 48 h, the average amount of benzophenone-3 excreted in urine was 11 mg/mL, demonstrating significant skin permeability. Avobenzone and octocrylene were found in more than 20% of urine samples, and the lipophilic UV filter octocrylene and its metabolite 2-cyano-3, 3-diphenylacrylic acid showed substantially slower clearance.[22] Physical sunscreens are not absorbed into the body like chemical sunscreen components.

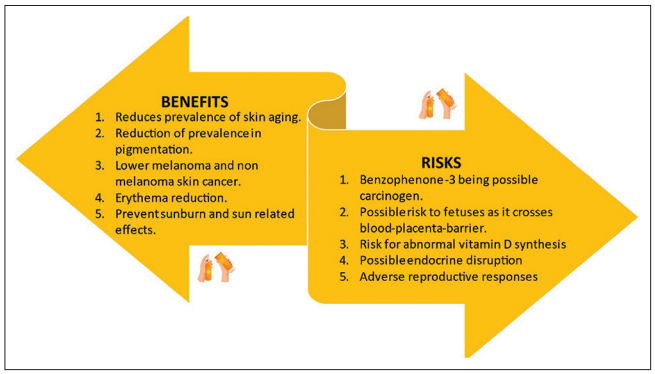

Figure 5: The risks and benefits of sunscreen.

Less than 0.03% of zinc nanoparticles, according to an *in vitro* investigation, entered the stratum corneum's top layer.[2] It is vital to consider how encapsulation techniques, in addition to formulation components, may affect how well sun filters are retained and absorbed by the skin.[23]

Each ingredient and their related adverse reactions

Sunscreens help in protecting our skin, but there are reports of adverse reactions due to certain compounds in them which are being researched. There are concerns about its safety as cellular damage and biological changes challenge its potency on a daily basis. Their toxicities include hormonal imbalances, allergic reactions, increased oxidative stress, and phototoxic events.[6] These UV filters and their coating compounds have been observed to cause a varying spectrum of clinical manifestations which have been reviewed in this literature review.

Benzophenone – chemical formula: $C_{13}H_{10}O$

Benzophenone enters blood plasma at levels 339–419 times higher than the toxicological concern level after passing through human skin.[24] Its residues have been discovered in human urine, breast milk, and seminal fluid as well as cause estrogen and androgen-disrupting effects.[25] Oxybenzone is the most widely known benzophenone in sunscreens, as well as the most common photo allergen, causing both photoallergic and allergic contact dermatitis.[26] However, contact urticaria and even contact-mediated anaphylaxis are present, though it is uncommon.[27] Furthermore, it can yield reactive oxygen species, increase lipid peroxidation, decrease mitochondrial membrane potential, release death protein, and activate caspase-3.[18] There is evidence that it causes DNA damage too.[24]

Ecamsule – chemical formula: $C_{28}H_{34}O_8S_2$

Ecamsule is a topical agent used in sunscreen; hence, it should not be ingested. Human systemic exposure to Ecamsule in actual exposure settings is <0.1%. Side effects such as dermatitis, dry skin, acne, itching, redness, and skin irritation were the most common reactions observed.[10]

Zinc oxide and titanium oxide – chemical formula: ZnO and TiO

These compounds are present in inhaled nanoparticles that are difficult to expel from the lungs, can penetrate through bloodstream, and can be pulmonary carcinogens. Nanoparticles in the bloodstream can cause organ damage through oxidative stress and/or proinflammatory pathway activation.[3]

Methylisothiazolinone – chemical formula: C_4H_5NOS

Methylisothiazolinone is a highly allergenic preservative found in many personal care products, including sunscreens. This compound in sunscreen can cause allergic contact dermatitis, which can mimic photoallergic contact dermatitis. Furthermore, it can cause photoaggravated contact dermatitis, even after avoiding the allergen.[7]

Homosalate – chemical formula: $C_{16}H_{22}O_3$

Homosalate is a chemical that is frequently found in sunscreens and sun-protective skin care products. It has the potential to be an endocrine disruptor and may enhance pesticide absorption in the body. Its exposure tends to result in 3.5 times more cell growth and multiplication in human breast cancer cells.[19]

Octinoxate – chemical formula: $C_{18}H_{26}O_3$

Octinoxate is an UV filter found in hair color and shampoos, as well as sunscreen, lipsticks, nail polish, and moisturizers. Octinoxate increases cell proliferation in estrogen-responsive cells, which can increase the risk of breast cancer.[19]

Aluminum oxide – chemical formula: Al_2O_3

Alumina (aluminum oxide) is added to sunscreens to improve spreadability and it functions as a pigment carrier, absorbent, anticaking, and bulking agent. In a study article by Hoffmann *et al.*, the application of this compound containing sunscreen caused erythema and papules covering approximately 50% of the test area in one child out of sixteen, granuloma itch in seven, and rest were unaffected.[28]

Cinnamate derivatives

Cinnamate derivatives, such as octyl methoxycinnamate and octocrylene, are frequently used in sunscreens, even though they absorb both UV-A and UV-B rays, particularly in the 305 nm range.[25]

Octocrylene – chemical formula: $C_{24}H_{27}NO_2$

Octocrylene absorbs primarily UV B and short UV A wavelengths. Cutaneous side effects such as skin irritation, sensitization, and photosensitization are seen. However, in humans, the irritant reactions to octocrylene are uncommon, whereas sensitization and photosensitization are more prevalent. Photoallergic contact dermatitis to octocrylene is much more frequent in adults than in children.[29]

Adverse reactions on use of sunscreen could result in irritant contact dermatitis, allergic contact dermatitis, phototoxic, and photoallergic reactions on the face, anterior neck, and dorsum of hands [Figure 6].[26] The severity of the clinical

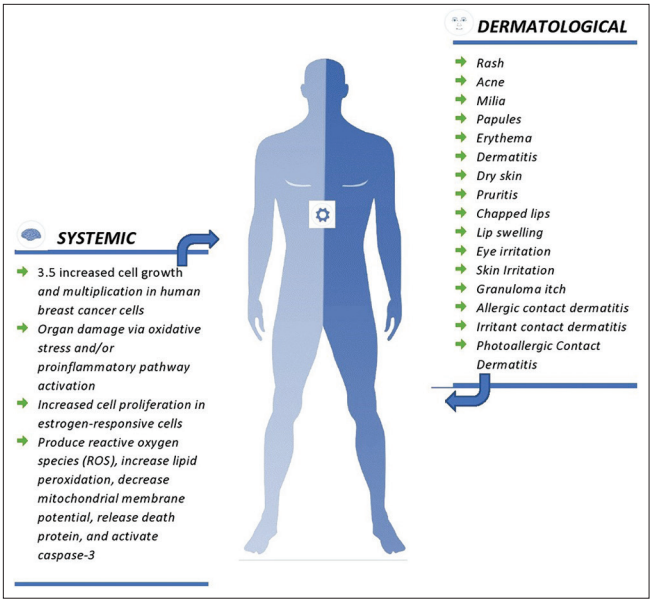

Figure 6: Side effects of sunscreen.

reaction depends partly on the area of exposed skin.[27] A study done by Matta *et al.*, showed that the active constituents (avobenzone, oxybenzone, octocrylene, and ecamsule) of four commercially available sunscreens indicated side effects that were rash, milia, lip swelling, pruritus, chapped lips, and eye irritation.[29] Since occlusive mask donning for healthcare workers during COVID- 19 was mandatory, a letter to editor, Kaul *et al.* (2020) have supported the potency of topical applications such as sunscreens to become an irritant to cause side effects such as contact irritant dermatitis due to the chemical agents present in them. Furthermore, it can cause changes in skin flora and potential of hydrogen, which can aggravate preexisting dermatoses such as atopic dermatitis and predispose to bacterial folliculitis.[30] Sunscreen use is currently widespread to the face on a regular basis and causes sensitivity issues when it comes into contact with the eyes. Furthermore, there is still a scarcity of ocular sunscreen products.[31] Many natural compounds, such as lignin, flavonoids, aloe vera, shea butter, and others are effective in protecting our skin from these rays. They also have high antioxidant capacities and a variety of other advantages over synthetic ones.[32] Hence, it is important for us to take the aspects of formulation and effectiveness into account as it holds significant benefits if generated in an optimal manner with organic or low-risk damage-causing ingredients.

Limitation

This overview may be subject to a number of restrictions such as only two main electronic databases, PubMed, and Google Scholar which were used. Hence, further important studies might have gone unnoticed. Second, we considered most of the literature reviews that looked into the adverse reaction,

side effect, toxicities, absorption, and safety of sunscreen and took only those that had free full texts that were also available in EN languages. However, papers featuring animal experiments and those without a free full-text option were not included as we have focused on side effects occurring in humans following the sunscreen use. Evidence indicates not many toxicity studies on humans or earlier study investigations on this subject which points to lack of research evidence as well as statistical analysis data not being readily available.

CONCLUSION

Sunscreen now plays a crucial role in our lives, its awareness and usage are more prominent among the current generations than before. Despite its benefits, sunscreen is associated with certain risk factors. Certain ingredients in sunscreen can be carcinogenic and endocrine disrupting chemicals, and not all consumers react well to certain ingredients, leading to side effects. Despite these associated risks and side effects, the use of sunscreen is still very crucial to prevent diseases associated with UV damage. Consumers should select sunscreens with ingredients that best suit their skin and provide maximal protection from UV rays.

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Ethical approval

Ethical approval was not required for this study.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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