ABSTRACT

One of the major concerns affecting the human skin is the exposure to ultra-violet radiations (UVR) causing photo-damage and skin cancers. In order to provide preventive measures against such incidences, there is an increased demand for sun-protectants. Sunscreening agents have shown beneficiary effects on the skin by reducing the exposure of UVR and its associated symptoms. Although various constituents have been recognized to have sun protecting activity, their safety and efficacy is still a concern. The United States Food and Drugs Administration (USFDA) and European Guidelines (EU) guidelines have made the sun protecting factor (SPF) and other such indices compulsory on the labels of such formulas to guide the consumers for better selection. The various ranges of radiations and skin types influence the mechanism of photoreaction and subsequent choice of the formulation. Apart from existing agents, certain novel sunscreening agents and technologies are now available to provide better protection to human populations.

Keywords: Sun protection, UVA and UVB, Sunscreen agents, COLIPA

INTRODUCTION

The body, in general, undergoes aging with time. On a molecular level, several intrinsic and extrinsic factors trigger aging resulting in malfunctioning of various activities in the body. These result in the cutaneous changes associated with aging. Intrinsic aging is due to the natural aging process of the body which may be genetic in nature affected by hormonal and vascular changes. When intrinsic changes get accelerated due to environmental conditions, significantly due to over-exposure to UVR, it results in the extrinsic photo-aging [1].

If the skin is exposed to the harmful UVR for a long period of time, it may result in severe damage to the skin by producing free radicals, DNA breakdown, etc. causing sunburn, pigmentation, wrinkles, dermatitis, urticaria, ageing, immune-suppression and ultimately skin cancer [2-4]. Therefore, although complete avoidance of the solar radiations is not possible and not advisable, the exposure needs to be balanced for preventing the skin from the deleterious effects of the rays [5, 6]. Sunscreens and UV filters have proved to be an excellent choice over the years [7-9]. This review incorporates search criteria based on the keywords mentioned in the manuscript and articles from major scientific resources like scopus, pubmed, science direct and google scholar were cited. The articles up to the year 2018 have been referred, but certain very old articles were also brought into use for demonstrating the historical importance of the facts.

The human skin

The skin is a complex and the largest organ in the human body with a surface area of about 2 m² covered with wrinkles, lines, dents, furrows etc [1, 10]. The thickness of the skin varies from part to part depending upon the function of the part it is covering. The major functions of the skin are protection, communication, and control. There are three distinct layers of the skin-the epidermis, dermis and the hypodermis/subcutaneous layer. Apart from the different layers, there are various cells which are associated with the production of melanin (melanocytes) and cells associated with defence (Langerhans' cells) [11].

Melanogenesis

The melanocytes produce the pigment melanin which is responsible for the colour of the skin, eyes, and hair. During the process of keratinisation, melanin is transferred to the keratinocytes. The main function of the melanin is to protect the skin from the UVR. The melanin pigment is classified into two types, particularly into Eumelanin and Pheomelanin [12]. The schematic representation of melanin synthesis has been depicted in fig. 1.

Penetration capacity and effects of UVR on skin

When the skin is exposed to the solar radiation, these interact with the biological molecules causing temporary/permanent changes in the molecules. There are several chromophores (molecules capable of absorbing light) in the layers of the skin, and this absorption leads to photo-damage. The solar radiations affecting the skin are widely divided into UVR (UVA, UVB) and visible light.
UVB radiations (280-320 nm) affect the basal layer of the epidermis and the upper margin of the dermis. These radiations are absorbed by the chromophores present in the proliferating cells of the epidermis, mainly the DNA causing sunburn.

UVA radiations (320-400 nm) have a deeper penetration capacity than UVB. These radiations penetrate to the dermal layer and interact with collagen and elastin, which are considered to be the structural components of the skin (fig. 2). These photochemical reactions cause premature ageing of the skin resulting in the formation of wrinkles and loss of elasticity. These radiations also cause immediate tanning of the skin due to excess release of melanin [13].

Mechanism of photoreaction

Exposure to UVR has various deleterious effects on the skin. The acute effects of UVR include inflammation induction. Cytokines and various mediators in the skin are induced by UVB that causes sunburn [14]. In response to sunburn, causing cell injury, several damage response pathways are induced in the keratinocytes such as p53 activation, DNA repair activation or apoptosis induction if the damage is severe [15]. This causes proliferation of keratinocytes mediated by epidermal growth factors which result in up-regulation and building up of melanin pigment on the skin.

Although UVA and UV B are potent mediators for carcinogenesis; they cause damage to the skin through different pathways [16]. UV B stimulates inflammation and formation of photolesions whereas UV A stimulates damage to DNA and other macromolecules [17]. Various reactive oxidative species are formed due to mutation-initiated by UVA [18].

There are several cellular maintenance pathways to inactivate oxidative species and repair DNA damage [19]. Cells have a complex inbuilt network of anti-oxidant molecules which inactivate ROS to prevent damage to DNA and other macromolecules. Glutathione (GSH) is an antioxidant composed of three amino acids–cysteine, glycine, and glutamine. GSH acts as a reducing agent by donating an electron to the antioxidant  activity [23].

Sunscreens act by preventing and blocking the damaging effects of UVR of sunlight. These are generally applied over the skin which is exposed to the sun primarily to absorb or scatter the rays before it penetrates into the body. These cause damage to the integrity of the cells causing premature ageing of the skin which can be associated with sagging, wrinkling, pigmentation, hyperplasia, etc. Sunscreens to an extent have controlled the deleterious effects of the UVR.

Ideal properties of sunscreens

There are various characteristics which are required by the sunscreens to categorize as the ideal sunscreen. Since these agents are both complex organic and inorganic in nature, the biodegradability of these molecules needs to be noted as it may pose a threat to the environment in which it is synthesized and formulated.

An ideal sunscreen must absorb the rays causing sunburn, typically in the range of 2900-3300 A˚ and be stable in the presence of sunlight to which it is expected to show its efficacy. If the molecule is not stable and gets degraded, the by-product should have an absorption capacity of 2900-3300 A˚. The decomposed products should not be toxic and irritating. It should be neutral in nature and should not be affected by the presence of an acid or a base and also should have a good solubility in the ointment base in which it is formulated and should not be easily washed away with water or during perspiration. A non-volatile agent will be ideal so that evaporation does not take place during application.

Although all the ideal characteristics cannot be obtained from a single agent, a combination of sunscreen agents are used together to formulate a sunscreen formulation.

Classification of sunscreen agents

Sunscreen agents can be broadly classified based on their capacity to absorb, scatter or reflect sunlight. High energy UVR is absorbed by chemical sunscreens while physical sunscreens scatter and reflect the rays [21]. Chemical agents can be organic compounds, and a combination of organic and inorganic compounds can be incorporated into a formulation for obtaining broad spectrum formulation (fig. 3).

Mechanism of action

The mechanism of action of various sunscreens can be understood by the type of molecule incorporated into the formulation. Inorganic agents act by scattering the micro-particles in the upper skin layers which may enhance the efficiency of the sunscreen compound thereby increasing the sun protection factor [22]. The use of certain sunscreens causes a reduction in the generation of free radicals in the skin due to its antioxidant activity [23].
Organic molecules, on the other hand, absorb the radiations instead of scattering them. Thus, this distinct feature makes them the target for degradation in the presence of sunlight and therefore these molecules can lead to the generation of free radicals. Organic sunscreens also have the ability to cause photo-irritation and photosensitizing reactions.

Inorganic molecules also have certain disadvantages due to their dispersion nature of the molecules which require an additional requirement of surface coating the molecule. This, in turn, reduces the photoreaction of the molecules upon exposure to UVR thus free radical generation does not take place.

**Factors determining the efficacy of sunscreens**

1. **SPF**
2. **Substantivity**

The sun protection factor is a number representing the ratio of the time required for a given irradiation to produce minimal perceptible erythema (MED: minimum erythemal dose, the UVR dose necessary to produce the minimal sunburn or minimal perceptible erythema 16 to 24 h after exposure) in sunscreen-protected skin to the time required in unprotected skin [24-26].

The UV-dose/time is used to calculate the SPF using:

\[
\text{SPF} = \frac{\text{MED protected skin}}{\text{MED unprotected skin}}
\]

MED protected skin-minimum erythemal dose for protected skin after application of 2 mg/cm² or 2 µl/cm² of the final formulation of the sunscreen product MED unprotected skin-minimum erythemal dose for unprotected skin, i.e. Skin with no sunscreen

Another factor by which the efficacy of the sunscreen is measured is by the Persistent Pigment Darkening (PPD) Protection Factor. One of the major disadvantages of this method is that it is not applicable to skin type 1 (table 1) and its clinical significance is not clear [27].

Immediate pigment darkening response is calculated as the dose of UVA required to produce the effect with the sun screening agent to that produced without an agent [28]. In this method, the clinical significance is unknown, the results obtained are not accurately reproducible. This method is applicable to skin types 3 and 4 [29].

**Table 1: Classification of skin types based on the degree of tanning**

<table>
<thead>
<tr>
<th>Skin type</th>
<th>Hair</th>
<th>Eye</th>
<th>Response to solar rays</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>White, very fair</td>
<td>Red, blond</td>
<td>Blue</td>
<td>Always burns, never tan</td>
<td>11</td>
</tr>
<tr>
<td>White, very fair</td>
<td>Red, blond</td>
<td>Blue, green, hazel</td>
<td>Usually burns, tans with difficulty</td>
<td>11</td>
</tr>
<tr>
<td>Cream white</td>
<td>Not particular</td>
<td>Not particular</td>
<td>Mild burn gradually tans</td>
<td>11</td>
</tr>
<tr>
<td>Brown</td>
<td>Not particular</td>
<td>Not particular</td>
<td>Rarely burns, tans with ease</td>
<td>11</td>
</tr>
<tr>
<td>Dark brown</td>
<td>Not particular</td>
<td>Not particular</td>
<td>Very rarely burns, tans easily</td>
<td>11</td>
</tr>
<tr>
<td>Black</td>
<td>Not particular</td>
<td>Not particular</td>
<td>Never burns, tans easily</td>
<td>11</td>
</tr>
</tbody>
</table>

**Formulation aspects**

Although the idea of formulating a sunscreen seem pretty simple, with the concept of selecting two or more suitable sunscreen agents and incorporating them in a vehicle base which when applied topically will obstruct the UVR before causing damage to the skin, the formulation of sunscreen, in itself, is a big challenge-starting from selection of an appropriate agent, its compatibility with the vehicle base and other additives, its stability under prescribed conditions of storage and also on exposure to sunlight and its efficacy and efficiency is a big challenge. Thus sunscreen formulation takes a lot of research and understanding of the components used for obtaining a better and effective formula [30].

The most commonly used sunscreen agents are the inorganic, physical agents such as TiO₂ [31] and ZnO. These are widely used because of lower penetration capacity into the skin, a scattering of the UVR, reduced skin irritation and sensitivity and they provide a broad spectrum of protection in combination [32]. Nanoparticles (NPs), less than 100 nm are more often used than micronized form (0.1-10 um) of these molecules because NPs provide lower opacity without reducing their efficacy [33].

There are several sunscreen products which contain NPs of titanium dioxide (TiO₂) and zinc oxide (ZnO) or a combination of both. These provide a broad spectrum against UVR along with a transparent product. The products containing NPs have better texture, spreadability and increased UVR protection [34]. There are several factors which affect the efficiency of NPs such as NP size, NP coating and the vehicle base in which the NPs are suspended and applied on the skin. A general formulation strategy is to coat the NP in a silicone-based material ZnO which is uncoated, are amphoteric in nature and are generally incorporated into the aqueous phase of the formulation. But, the silicone coated ZnO NPs are hydrophobic in nature and are majorly exposed to these dust during the manufacturing of these ultrafine molecules. Ultrafine ZnO comparatively is safer to use.

biodegrabilidad. It may also cause potential vitamin D₃ deficiency on prolonged use. Also, TiO₂ is also categorized as a potential carcinogen. According to studies, it has been observed that ultrafine particle dust of TiO₂ causes respiratory tract cancer as manpower is majorly exposed to these dust during the manufacturing of these ultrafine molecules. Ultrafine ZnO comparatively is safer to use.

**Regulatory bodies**

Several guidelines have come into play due to the ever-increasing number of sunscreen agents in the recent past. These regulations are to maintain and monitor the quality along with safety and toxicity profile of the sunscreen molecules both in regards to the human and environmental aspects, the main aim being providing adequate protection against the harmful UVR.

**USFDA guidelines**

Earlier, the FDA had specified rules for the molecules protecting the skin against the UV B radiations. When research and development took place for molecules protection against UV B, more rules and regulations were put forth for providing the completely monitored production and release of sunscreen molecules [37].

When misleading and false statements started preacing the market, US FDA revised to more stringent guidelines thus preventing the use of claims such as ‘broad spectrum’, ‘water and sweat proof’, ‘water resistant’ without proper investigation and test reports. Therefore, products claiming broad spectrum has to provide adequate documents proving its effect against UVA and UV B radiations. A product indicating ‘water resistant’ on its label should provide its duration of action [38].

Any claim which suggests immediate sun protection or sun protection prevailing for longer than two hours should not be mentioned without direct reapplication. Supporting documents need to be provided to FDA for approval in case any statement which suggests any of the above claims.

Drug fact is an integral part of the product label. SPF value is of utmost importance for sunscreen agents as it decides the category of the sunscreen to be used for maximum and effective protection.
**EU guidelines**

EU also provides a minimum level of protection against UVA in terms of SPF. PPD (in vivo) or COLIPA (in vitro) are the measures by which UVA protection is measured, and it must be at least one-third of the SPF (in vivo) value. As per the guidelines, products are divided into low, medium, high and very high according to the SPF of the products ranging from SPF 6 to SPF 50+. Star system is also employed for consumer understanding and ease which denotes that 1 has least sun protection and 5 has the ultra-sun protection [39, 40].

**Other countries guidelines**

Other countries such as Japan, Australia [41] and New Zealand have similar guidelines though some of the regulations may differ. Statements claiming drug facts without proper documents are prohibited as it may mislead the consumers.

**Indian guidelines**

There are only two combination approved products as per the Official website of Industrial Regulatory Agency due to lack of guidelines in the standardization of sunscreen agents and approved ingredient list. The products available are a combination of octinoxate + avobenzone + oxybenzone + octocrylene + zinc oxide lotion and cinoxate + avobenzone + oxybenzone + titanium oxide lotion. Several others sunscreens agents are widely used such as camphor derivatives and UV broad spectrum active agents.

**New developments in sunscreens**

New molecules with broad spectrum efficiency are being identified from various biological sources like herbs, minerals and various oils from fish, etc. These chemicals constituents are responsible for their activity against solar radiations because of their anti-oxidant property to deactivate the free radical generation. These agents have shown greater and better protection against the radiations when compared to the synthetic molecules as these are bio-degradable causing less harm to the health and the environment.

**Herbal formulations**

Herbs have been in the dictionary of treating ailments from centuries. They have known to contain certain phytoconstituents which relieve many diseases without causing adverse reactions as compared to synthetic molecules. Many molecules from natural sources have shown good photo-protecting efficacy, like anti-oxidants, due to which formulations are being made from these sources.

Turmeric, vitamin E and C, aloe vera, quercetin are some of the molecules which have shown great efficacy against harmful UVR. Some of them are discussed in detail below.

**Phytoconstituents with photo protectant characteristics**

Quercetin is a molecule obtained from various biological sources like wine, apples, and blueberries. It is a flavonoid and has good anti-oxidant and anti-inflammatory properties which are the prerequisite characteristics required for sunscreen formulations. Due to its poor solubility in the aqueous phase, it has lower efficacy when applied topically. Various measures like liposomal formulation, lipid nanocapsules, and smart crystals are taken to increase its solubility and thus increase its delivery to the skin. The formulations proved to be safe as no toxicity profile is observed. The liponanocapsules formulations delivered quercetin in optimum quantity on the surface of the skin which resulted in promising anti-inflammatory and free radical scavenging property. Thus, quercetin is a molecule which has the desired property of a competent sunscreen agent [42-43].

*Moringa oleifera* is observed to have various cosmetic advantages along with being a food supplement. The phytoconstituents present in *Moringa oleifera* has been proved to be used as a sun-protecting agent. The extracts of *Moringa oleifera* have many photoprotective properties along with a significant SPF. When formulated, there were no signs of any significant irritation [44].

*Marcelia taxifolia* (ethanolic extract) shows a broad spectrum UVR protection as it is rich in flavonoids which have anti-oxidant property. Formulations of varying concentrations of extracts were formulated and evaluated for significant SPF. After evaluation, it was found to be of greater than 6 which show that it can be used as a sunscreen agent [45].

**Mineral sources and vitamins**

Minerals have been identified as an excellent source of protection against harmful sun radiations. Some minerals are an integral part of the body for functioning in several roles, especially as biocatalysts. One of the most important minerals under observation is magnesium. Magnesium is abundantly found in various fruits, nuts and vegetables like spinach, peanuts, pumpkin, banana, etc. In the bone, magnesium is found in the bones, muscles, and brain and is considered as a catalyst for many enzymatic reactions in the body. One major factor affecting magnesium absorption is vitamin D production. Vitamin D production is enhanced by sun exposure which in turn increases Magnesium absorption. This magnesium is responsible for protecting the skin against solar radiations by strengthening the epidermis, accelerating healing of the outer layer of the skin.

Vitamins also play an important role in protecting the skin. These vitamins have anti-oxidant properties which are rich in leafy vegetables, cod liver oil, raspberry seed oil, etc. Vitamin A and beta-carotene in carrot have an anti-oxidant and anti-inflammatory activity that shield the skin from generating free radicals. Raspberry seed oil has the capacity to protect the skin against both UVA and UV B. This has shown equivalent efficacy to that of titanium dioxide which is the most widely used sunscreen agent in the market. It is known to protect the skin from inflammation and pain from sunburn.

**Hydroxyapatite** is a mineral present in the bones and teeth of the human body, present in various forms by substituting the hydroxyl group of the molecule. These form 70% of the bone structure. It can combine with several monovalent and divalent ions like fluoride, chloride, carbonates, calcium, etc. to form various crystaline structures of the molecule [46]. Pharmacologically, it is found to have photoprotective properties as, when evaluated against a placebo, it showed a significant increase in the SPF of the formulation. It has the capacity to block broad spectrum UVR when a combination of an ascobic acid with hydroxyapatites was prepared [47, 48]. When measured against TiO2 it showed as equivalent sun screening activity thus proving hydroxyapatites to be a competent physical photoprotective agent [49, 50].

**Challenges in formulating sunscreen agents**

Even though the main aim of formulating an effective sunscreen is to protect the naked skin against various effects of the sun rays, there are many challenges that regulate the effective use of sunscreen all over the world. These challenges may be due to the geographical location, lifestyle diversification, environmental safety concerns and also the regulatory authorities controlling and regulating the use of certain ingredients in the cosmetic product due to their adverse reactions. Due to these differences, cosmetic sunscreen products are always under the scrutiny of the regulatory bodies regarding their safe use and efficacy; and amidst all these controversies, the demand for a better sunscreen is high as it not only protects the skin from acute skin damages but also from various high-risk damage like DNA damage resulting in premature ageing, wrinkling and ultimately skin cancer [51-53].

The safety and efficacy of sunscreen agents are because of the fact that most of the sunscreen agents used in the market are synthetic chemical entities which may be toxic when applied to the skin as it gets absorbed into the deeper layers of the skin and cause several undesired side effects [54]. The increased amount of use of sunscreen can also cause a reduction in the formation of vitamin D due to blockage of UVR penetrating the skin [55-57]. Even though physical sunscreen agents like TiO2 and ZnO do not penetrate into the skin, the is evidence where these particles, both in nano-particulate or non-nano-particulate form have to cause melanoma formation in mammalian cells [58, 59].

The solubility of such molecules remains to be yet another challenge during formulating a sunscreen product. Some agents are dissolved
in the oil phase while some are dispersed in the aqueous phase. Aqueous based formulations give less water resistance, while oil-based formulations have higher water resistance and safety but aesthetic elegance is low because of the oily appearance [60, 61].

Another challenge is the environmental safety and toxicity. As the sunscreen agents are washed off to the water bodies, the aquatic animals are the ones which are affected because of the accumulation of such toxic substances in the water. Degradation of aquatic flora and fauna is a major concern as its contamination may directly or indirectly affect several species in the food chain [62-64].

CONCLUSION

Sunscreen lotion may absorb or reflect some of the ultraviolet radiations and protects against sunburn. All sunscreens are graded with a Sun Protection Factor number. Skin protection also achieved through some of the cosmetic ingredients used in the formulation. SPF tells how long you may be exposed to UVB light before you burn. Sunscreen lotions or gels consists of a delivery vehicle containing one or more sunscreen active ingredients. When applied to the skin, these sunscreen actives divert ultraviolet rays before they can hurt the underlying skin. However, a thorough study reveals that sunscreen formulations are quite complex, needs careful selection of sunscreen agent and vehicle components to control multiple performance and in-use limitations.

AUTHORS CONTRIBUTIONS

All the authors have contributed equally

CONFLICT OF INTERESTS

The authors have no conflict of interests to declare

REFERENCES

The authors have no conflict of interests to declare


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