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Current Understanding of the Effects of Sun Exposure on Skin Tanning: Mechanisms, Risks, and Protective Strategies

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ABSTRACT:
UV radiation (UV) is designated as a "comprehensive carcinogen" due to its dual nature as a mutagen and a non-specific damaging agent, exhibiting properties of both a tumor initiator and a tumor promoter. UV radiation is the foremost modifiable risk factor for skin cancer and various other environmentally-influenced skin disorders. Nevertheless, UV radiation also plays a beneficial role in human health by facilitating the natural synthesis of vitamin D and endorphins in the skin. Consequently, UV radiation exhibits complex and diverse effects on human health. However, excessive exposure to UV radiation poses significant health risks, including skin atrophy, pigmentary alterations, wrinkling, and malignancy. Epidemiological and molecular evidence establish a clear link between UV radiation and the three most prevalent types of skin cancer: basal cell carcinoma, squamous cell carcinoma, and malignant melanoma, collectively impacting over a million Americans each year. Furthermore, genetic factors contribute to the susceptibility of UV-mediated skin diseases. Notably, specific variations in the melanocortin 1 receptor (MC1R) gene are associated with skin fairness, UV sensitivity, and heightened cancer risk. In light of these findings, our research aims to develop innovative UV-protective strategies by comprehensively understanding the molecular events that occur following UV exposure, with a specific focus on epidermal melanization and the pivotal role played by the MC1R in maintaining the integrity of the genome.
By leveraging this knowledge, we endeavor to devise pharmaceutical interventions that can effectively mitigate the detrimental effects of UV radiation on the skin, reduce the risk of skin cancer, and enhance skin health. Such advancements will not only contribute to safeguarding individuals from the harmful consequences of excessive UV exposure but also pave the way for novel approaches in the field of dermatology and personalized medicine, tailored to the individual's genetic makeup and specific risk factors.

KEYWORDS: UV radiation, dermis, cancer development, genetic mutation, skin pigmentation, malignant tumors, melanin production, MC1R gene.

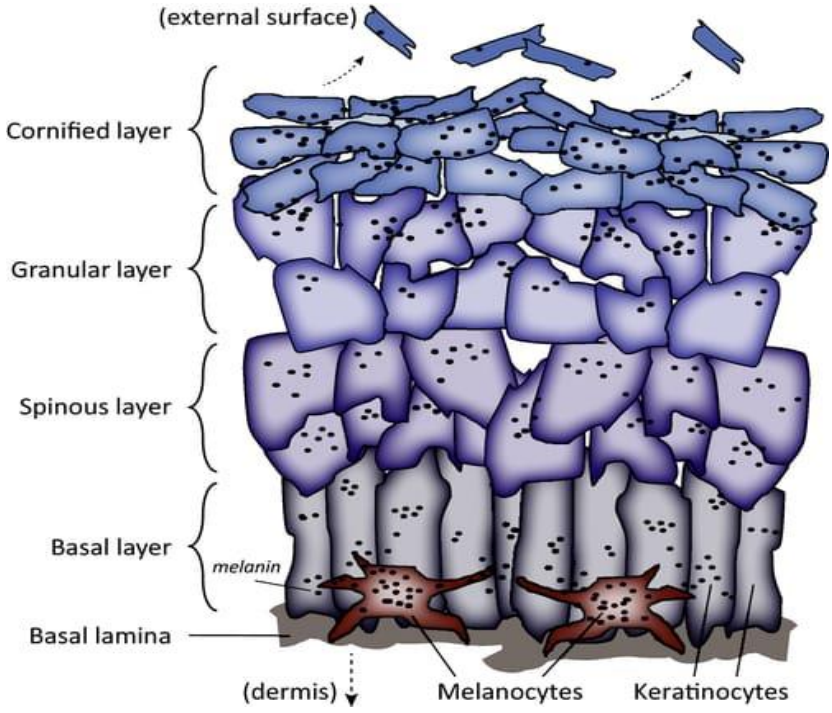
1.THE SKIN :

Comprising roughly 16% of body mass, the skin is the largest organ of the body. Skin is organized into two primary layers, epidermis and dermis, which together are made up of epithelial, mesenchymal, glandular and neurovascular components. The epidermis, of ectodermal origin, is the outermost layer

and serves as the body's point of contact with the environment. As such, epidermal biological and physical characteristics play an enormous role in resistance to environmental stressors such as infectious pathogens, chemical agents and UV[34]. The majority of epidermis cells, known as keratinocytes, express cytokeratins and create desmosomes and tight junctions with one another to build an efficient physicochemical barrier. Dermal features like hair follicles, nerves, sebaceous glands, and sweat glands are found in the dermis, which is derived from mesoderm and sits beneath the epidermis. Fibroblasts and immune cells are also in great abundance in the dermis, and they play an active role in many physiological reactions in the skin. The basement membrane that separates the dermis from the epidermis organises the epidermis into functional layers that are mostly determined by keratinocyte properties like size, shape, nucleation, and keratin expression(Figure1). Corneocytes, tightly-linked dead but intact cells that make up the main barrier of the outermost epidermal layer, are formed by nascent epidermal keratinocytes that migrate outward towards the skin's surface after being produced by cell division by keratinocyte stem cells in the stratum basale[39,42] .

As keratinocytes grow, they also assemble melanin pigments, and epidermal melanin serves to potently block UV ray penetration into the skin in addition to producing a highly effective physical barrier. Although epidermal keratinocytes may contain large amounts of melanin, these cells do not produce it. Melanocytes, which are the second-most numerous cell in the epidermis and are produced from neural crest, are the only cells in the body that can synthesise melanin. Melanocytes are in fact present in both the dermis and the epidermis. The basal layer, which is located atop the basement membrane, is where epidermal melanocytes are typically found. Melanocytes can also be found in hair follicles, where they can give developing hair colour. There are dermal melanocytes in nevi (moles). Since melanocytes are the sole cells that produce pigment in the skin, hereditary melanocytic abnormalities are typically the root cause of inherited pigmentary disorders like albinism. In what is referred to as a "epidermal melanin unit," melanocytes may be in close contact with up to fifty nearby keratinocytes through dendritic extensions[45]. In the epidermal melanin unit, keratinocytes and melanocytes interact often in paracrine and contact-dependent ways. Melanocytic dendrites, which are cellular organelles known as melanosomes, are the means by which the pigment produced by melanocytes is transported to nearby keratinocytes. Actually, keratinocytes are home to the majority of the melanin in the skin, where it builds up to act as a "natural sunscreen" to shield the skin from incoming UV rays. Melanin may have many additional significant physiological impacts in addition to preventing UV rays from penetrating the skin, such as controlling epidermal homeostasis, scavenging free radicals to prevent oxidative damage, and perhaps even having antibacterial action [51].

Figure 1: structure of the epidermis and keratinocyte development. The self-renewing tissue known as the epidermis is mostly made up of keratinocytes that are in various states of terminal differentiation. In the stratum basale (basal layer), keratinocytes are formed. As they progress through the epidermis, they undergo a series of planned differentiation steps that include enucleation, the buildup of cytokeratins, and tight connections with one another. Melanin is also delivered to keratinocytes by melanocytes in the form of melanosomes, which are packaged organelles. The stratum basale, stratum spinosum, stratum granulosum, and stratum corneum are the fundamental layers that extend from the basement membrane outward, and they are individually distinguished by the shape and differentiation state of the keratinocyte as shown by the expression of cytokeratins and other proteins.



2. MELANIN :

The key determinant of skin colour and UV sensitivity is the quantity and type of epidermal melanin. Tyrosine is an amino acid that undergoes oxidation and cyclization to generate melanin, a huge bio-aggregate made up of subunits of many pigment types. **Figure 2:** Intermediates of melanogenesis may have significant regulatory roles in the skin, which is intriguing. The two primary chemical forms of melanin are eumelanin, a dark pigment seen in high concentrations in the skin of people with dark skin, and pheomelanin, a light-colored sulfated pigment produced by the incorporation of cysteines into melanin precursors [10]. Since eumelanin is a considerably more effective UV photon blocker than pheomelanin, the amount of eumelanin in the skin determines how UV-permeable the epidermis is . With minimal epidermal eumelanin, fair-skinned persons—who are nearly always UV-sensitive and have a higher risk of developing skin cancer—"realize" far more UV than people with darker skin tones. Therefore, UV exposure will be more harmful to skin that is fairer[25]. In actuality, pheomelanin levels are comparable in dark-skinned and light-skinned people, and skin tone, UV sensitivity, and cancer risk are all determined by the amount of epidermal eumelanin[11]. According to data, even in the absence of UV I, pheomelanin may encourage oxidative DNA damage and melanomagenesis by producing free radicals in melanocytes that even in the absence of UV, the production of free radicals by pheomelanin in melanocytes may increase oxidative DNA damage and melanomagenesis [26].

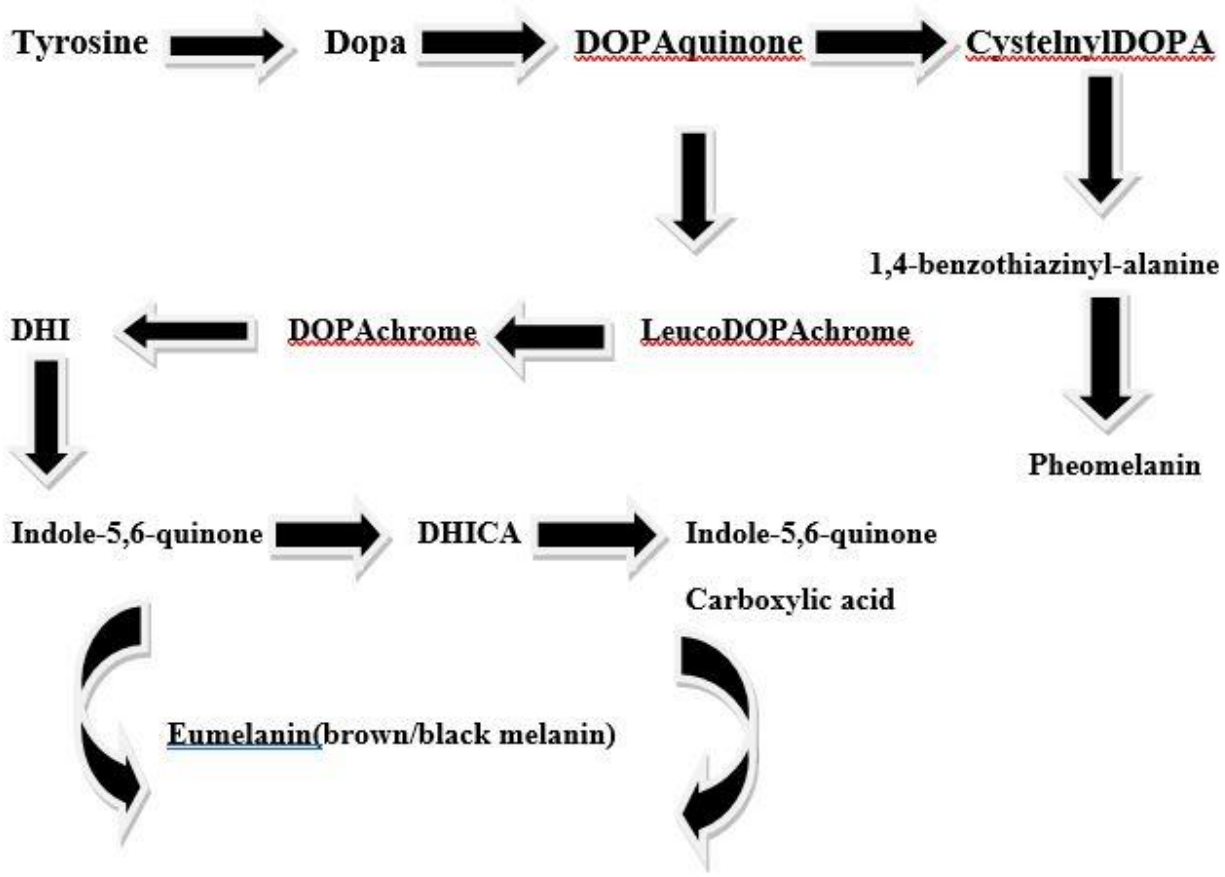


Figure 2: Melanin Biosynthesis. Melanin, a large bioaggregate composed of pigmented chemical species, is found in two major forms: the brown/black highly UV-protective ―eumelanin‖ pigment and the red/blonde UV-permeable ―pheomelanin‖. Both eumelanin and pheomelanin are derived from the amino acid tyrosine. Tyrosinase is the enzyme that catalyzes the rate-limiting synthetic reaction for both melanin species and when defective causes albinism. Incorporation of cysteine into pheomelanin results in the retention of sulfur into the pigment, which yields a light color to the final melanin product and may contribute to oxidative injury in the skin. The melanocyte stimulating hormone (MSH)–melanocortin 1 receptor (MC1R) signaling axis is a major determinant of the type and amount of melanin produced by melanocytes in the skin.

3. SKIN PIGMENTATION :

One of the most significant factors affecting UV sensitivity and skin cancer risk is skin tone[13]. The Fitzpatrick measure, which consists of six phototypes to define skin colour based on basal complexion, melanin level, inflammatory reaction to UV, and cancer risk, is a semi-quantitative measure[14] (Table 1). Using erythema (redness) and edoema (swelling) as endpoints, the minimal erythematous dose (MED) is a quantitative method to determine the amount of UV (especially UVB) needed to cause sunburn in the skin 24-48 h after exposure. The simpler it is for UV to produce irritation (sunburn), the fairer the skin[15]. Dark-skinned people therefore have the highest rates of MED because they require more UV radiation to "burn" their eumelanin-rich skin. Low MEDs are found in people with fair skin whose pheomelanin expression is predominate. Low Fitzpatrick phototype is associated with an increased risk of melanoma and other skin cancers as well as MED [46].

TABLE 1. UV DANGER, FITZPATRICK SCALE, AND SKIN PIGMENTATION

Phototype by Fitzpatrick	Phenotype	eumelanin epidermal	skin's reaction to UV	MED (mJ/cm2) *	cancer threat
1	Bright white exposed skin and normal blue or green eyes British and Northern Europeans frequently feckling	+/−	always peels burns Never suntan	15–30	++++
2	White skin is exposed skin. brown, hazel, or blue eyes Brown, blonde, or reddish hair European/Scandinavian	+	quickly burns lightly peels tans	25–40	+++/++++
3	Fair skin is that which is not exposed. brows eyes Brown hair Central or southern Europe	++	burns a little mediocre tanning skills	30–50	+++
4	Light brown skin is exposed. Brown eyes Brown hair Latino, Asian, or Mediterranean	+++	minimal burning tans quickly	40–60	++
5	Brown skin is exposed skin. Brown eyes Brown hair African, Latino, Asian, or East Indian	++++	Tans rarely burn readily and significantly.	60-90	+
6	Brown skin is exposed skin. Brown eyes Brown hair African, Latino, Asian, or East Indian	++++	Tans rarely burn readily and significantly.	90-150	+/-

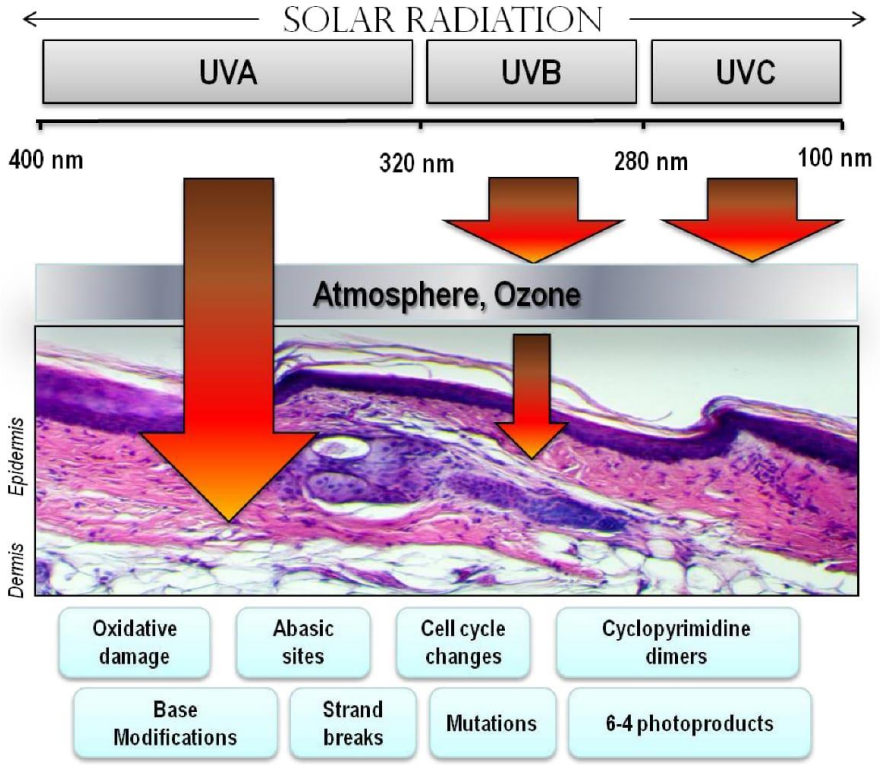
The minimal erythematous dose (MED) is the lowest UVB radiation that results in skin reddening and inflammation 24–48 hours after exposure (i.e., the UV dosage that results in sunburn). The lower the MED of a person's skin, the more UV sensitive they are.

4. ULTRAVIOLET RADIATION (UV) :

UV, which is prevalent in the environment, contributes to a number of skin conditions, including inflammation, ageing and cancer. In the past, exposure to sunlight at work has been the main way that humans have been exposed to UV radiation[8]. However, recreational UV exposure has significantly grown recently due to outdoor activities and the desire to intentionally tan for cosmetic reasons. UV photons are a part of the electromagnetic spectrum and have a wavelength between visible light and gamma radiation. Based on electrophysical characteristics, UV energy can be separated into UV-A, UV-

B, and UV-C components, with UV-C photons having the shortest wavelengths (100–280 nm) and highest energy, UV-A photons having the longest (315–400 nm) but least energetic photons, and UV-B photons falling in the middle (Figure 3). Each UV component has a range of potential impacts on molecules, cells, and tissues[16].

Figure 3 : visible and ultraviolet radiation's electromagnetic spectrum and its biological effects on the skin. Sunlight can be separated into UVA, UVB, and UVC components, but because ozone in the atmosphere absorbs UVC, ambient light is primarily composed of UVA (90%–95%) and UVB (5%–10%) rays. Skin absorption of UV is wavelength-dependent. Longer wavelength UVA reaches well into the dermis and penetrates there. Contrarily, only a small amount of UVB exposure reaches the dermis since it is virtually entirely absorbed by the epidermis. Reactive oxygen species can harm DNA by indirect photosensitizing processes, and UVA is effective at producing these species. Direct UVB absorption by DNA leads to molecular rearrangements that result in the formation of certain photoproducts, like cyclobutane dimers and 6-4 photoproducts. Numerous factors can lead to mutations and cancer.



Geographically, ambient UV exposure varies depending on how much sunlight there is where you are on Earth. Since atmospheric particles can reflect, scatter, and dampen UV radiation, the ambient UV dose varies according to the amount of atmosphere it must pass through[17]. UV doses are therefore higher close to the equator, at higher altitudes, and when there is little cloud or particulate cover. Personal UV exposure is influenced by the intensity of solar radiation, time spent outdoors for work or play, the use of UV-protective clothing, shade, and sunblock, as well as other factors. People who live in equatorial regions tend to wear less clothing, have more contact with ambient sunlight, and typically receive much higher ambient UV doses than people who live in temperate climates because these regions are warm

and conducive to recreational or occupational outdoor activities. Unsurprisingly, the risk of skin cancer often follows this regional trend, especially in fair-skinned people who are sensitive to the sun[29].

5. INDOOR TANNING :

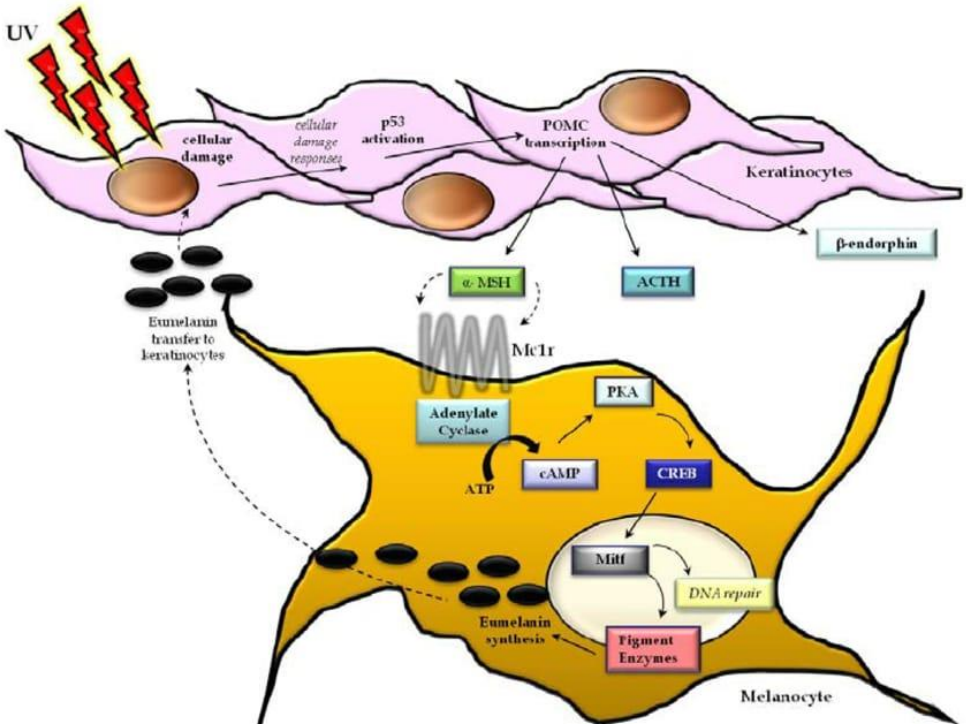
Over the past few years, indoor tanning clinics have grown in both quantity and popularity. In the late 1980s, only 1% of people in America alone had ever used a tanning bed. According to current estimates, more than 25% of Americans have intentionally exposed themselves to artificial UV rays. With about 30 million customers, 100,000 employees, and billions of dollars in yearly revenue, indoor tanning is a significant industry[3]. Machines used for indoor tanning are inadequately regulated and have a wide range of UV content and intensity. Sunlight and tanning bed UV outputs can be up to ten times stronger, making the tanning bed a genuine cancer-causing device. Since tanning frequently appeals to teenagers and young adults, UV exposure history of tanning consumers can be significant for many years. Tanning can be addicting, resulting in frequent and significant UV exposure over time. There is little doubt that indoor tanning raises the risk of skin cancer. If someone tans artificially before the age of 35, their lifetime chance of developing melanoma—the worst of skin cancers—increases by 75%. The number of years of use, sessions, and total UV h exposure all raise the risk of cancer[18]. There does not appear to be a "safe" use of tanning beds because the cellular and DNA damage that causes skin damage and carcinogenesis activates the molecular pathways in the skin that cause UV-induced tanning (Figure 4). In order to further its business interests by downplaying the harmful health implications of UV radiation, the tanning industry has hired a strong political lobby. Instead, the industry educates its customers on the health benefits of UV, emphasising vitamin D synthesis, which occurs naturally in the skin as a result of UVB exposure when 7-dehydrocholesterol is chemically converted to vitamin D3 (cholecalciferol). The amount of UV exposure needed to prevent the symptoms of rickets and vitamin D deficiency is really much less than what is necessary to produce adequate amounts of vitamin D due to the ubiquitous availability of vitamin D in supplements and fortified meals. The hazards of indoor tanning considerably outweigh any potential health benefits, particularly with regard to cancer, according to numerous research. The single best strategy to lower the incidence of melanoma and other skin cancers may be to minimise UV radiation exposure, which includes both natural UV radiation from sunshine and artificial UV radiation from tanning bed use [35].

6. CUTANEOUS RESPONSES TO UV :

UV has a variety of negative impacts on skin physiology, some of which are immediate and others of which are more gradual. Induction of inflammation is one of the most blatant acute effects of UV on skin. In the skin, UVB triggers a chain reaction of cytokines, vasoactive, and neuroactive mediators that combined generate an inflammatory response and "sunburn". Keratinocytes trigger apoptotic pathways and die if the UV radiation surpasses a threshold damage response[24]. Such apoptotic keratinocytes are referred to as "sunburn cells" and can be recognised by their pyknotic nuclei. Additionally, UV causes hyperkeratosis, which is an increase in epidermal thickness. UV harms cells, which causes keratinocytes to activate damage response pathways. Damage signals like p53 activation significantly affect the physiology of keratinocytes, triggering cell cycle arrest, initiating DNA repair, and, if the damage is severe enough, inducing apoptosis. The proliferation of epidermal keratinocytes, however, is mediated by a number of epidermal growth factors several hours after UV exposure and damage response signals have subsided. Following UV exposure, increased keratinocyte cell division causes an accumulation of

epidermal keratinocytes, increasing epidermal thickness. The skin is better protected against UV ray penetration by epidermal hyperplasia [30].

Figure 4 : Mechanisms of the physiologic tanning response are shown in Figure 4. A large portion of the cutaneous melanization response is mediated by hormonal interactions between epidermal keratinocytes and melanocytes. The pro-opiomelanocortin (POMC) gene, which codes for the generation and release of melanocyte stimulating hormone (-MSH), is up-regulated in transcription in keratinocytes after DNA and cellular damage. The activation of protein kinase A, the cAMP responsive binding element (CREB), and the microphthalmia (Mitf) transcription factors is brought on by -MSH binding to the melanocortin 1 receptor (MC1R) on basal epidermal melanocytes, which in turn produces the second messenger cAMP. By increasing amounts of tyrosinase and other melanin biosynthesis enzymes, CREB and Mitf directly increase melanin production. Thus, MSH-MC1R signalling causes epidermal keratinocytes to accumulate melanin and melanocytes to produce more pigment. The skin is better protected against UV harm thanks to this technique. Notably, in addition to the direct effects of UV on melanocytes, other signalling pathways may also cause UV-induced pigmentation, and there is significant debate in the scientific community over the function of epidermal MSH in the adaptive pigmentary response.



Adaptive skin melanization, sometimes referred to as tanning, coexists with epidermal hyperkeratosis. Melanin pigment in the skin is produced and epidermal accumulation is regulated by UV. Defects in this system are associated with a higher risk of developing cancer. This crucial physiological reaction shields the skin from future UV harm. The first skin darkening caused by redistribution and/or molecular alterations to the epidermal melanin pigments causes UV-mediated skin darkening to really be biphasic. Delayed increases in skin darkening start several hours to days after UV exposure, and are mediated by real up-regulation in melanin synthesis and transport to keratinocytes [31]. Adaptive melanization is probably a complicated physiological response that involves a range of interactions between different skin cell types (Figure 4). Along with producing immunological tolerance or immunosuppression and producing vitamin D by converting 7-dehydrocholesterol directly into vitamin D3 (cholecalciferol), UV

also affects the skin in a variety of different ways. The majority of ambient sunshine contains both UVA and UVB rays, however each UV component might have unique effects on the skin. For instance, UVB is a powerful inducer of inflammatory response and DNA photolesion production (such as mutagenic thymine dimers), whereas UVA is much less effective in these processes but is a powerful inducer of oxidative free radical damage to DNA and other macromolecules. Therefore, each could influence carcinogenesis in a unique way [36]. The impact of UVA and UVB on skin physiology is a topic of active research.

7. OXIDATIVE INJURY :

Reactive oxygen species (ROS) such superoxide anion, hydrogen peroxide, and the hydroxyl radical are produced by UV, which in addition to encouraging the creation of photodimers in the genome, results in mutations (Figure 5). The damage caused by free radicals is quite likely to affect nucleotides. Nucleotide base oxidation encourages mispairing outside of the typical Watson-Crick parameters, which results in mutagenesis[4]. For instance, the well-studied mutation known as the transversion guanine-thymine is brought about by ROS oxidising guanine at the 8th position to create 8-hydroxy-2'-deoxyguanine (8-OHdG). Because 8-OHdG prefers to mate with adenines rather than cytosines, this oxidative alteration transforms a G/C pair into an A/T pair. Tumours taken from the skin can have these alterations, indicating that oxidative damage may be carcinogenic. Both the inactivation of reactive species and the repair of the DNA damage they produce are accomplished via cellular maintenance processes. The primary biochemical mechanism by which cells repair free radical damage to DNA to prevent oxidative mutagenesis is the base excision repair pathway (BER). Damage-specific glycosylases that search DNA for certain changes such as deaminated, alkylated, or oxidised bases start this cycle. An enzyme releases the nucleotide base from the sugar and phosphodiesterase backbone by lysing the N-glycosylic link between the base and the deoxyribose after a lesion-specific glycosylase recognises changed or unsuitable bases[5]. In order to maintain fidelity, the complementary strand is used as a template for processing and repairing the DNA's abasic or apurinic/apyrimidinic (AP) site.

A powerful and intricate network of anti-oxidant molecules is also present in cells, detoxifying reactive species to stop free radical damage to DNA and other macromolecules[7]. One of the most significant cellular antioxidant molecules is glutathione (GSH), an oligopeptide composed of the three amino acids cysteine, glycine, and glutamine. GSH serves as a reducing agent to reduce the reactivity of free radicals by providing electrons to molecules that might otherwise be reactive. In the process, glutathione itself is oxidised, but glutathione reductase, which uses NADPH as an electron donor, can decrease glutathione to its baseline state and recycle it. Because glutathione exists in both its reduced and oxidised forms in every cell, changes in the ratio of reduced to oxidised glutathione can be an indication of oxidative stress. Superoxide dismutases (SODs) inactivate superoxide anions, whereas catalase is another important antioxidant enzyme that detoxifies hydrogen peroxide. Since controlling the regulation of these antioxidant enzymes is crucial for defining the skin's reactions to UV radiation, it is a focus of extensive research[19].

8. NUCLEOTIDE EXCISION REPAIR AND XERODERMA PIGMENTOSUM :

UV directly impacts DNA's nucleotide base pairing in addition to free radical production[20]. Pyrimidine bases are highly susceptible to chemical modification caused by UV radiation absorption[21]. Pyrimidines' internal 5–6 double bonds are broken by shorter-wavelength UV photons,

especially UV–B and UV–C. This can result in the formation of aberrant covalent connections between adjacent pyrimidines, which can change the double helix's three-dimensional structure[32]. This predictable formation of two main photolesions—cyclobutane pyrimidine dimers or (6,4) photoproducts—both of which are highly mutagenic—follows UV exposure. One day of sun exposure is thought to cause up to 105 UV-induced photolesions in each skin cell. UV-induced photolesions disrupt transcription, prevent DNA replication, and base pair improperly. They result in distinctive transition mutations called "UV signature mutations," such as TTCC. Numerous primary skin cancer isolates have a high frequency of UV signature mutations in genes that regulate cancer, providing compelling evidence that UV is a cancer-causing factor [37].

Figure 5: Oxidative free radicals are produced by UV. Atomic oxygen and UV photons interact, promoting the production of derivatives of free radicals such superoxide, hydrogen peroxide, and the extremely reactive hydroxyl radical. Intensely attacking macromolecules like protein, lipid, RNA, and DNA, free radicals change their structure and impair their functionality. Enzymes that detoxify and lower the amounts of oxidative species in the cell include glutathione peroxidase, catalase, and superoxide dismutase.

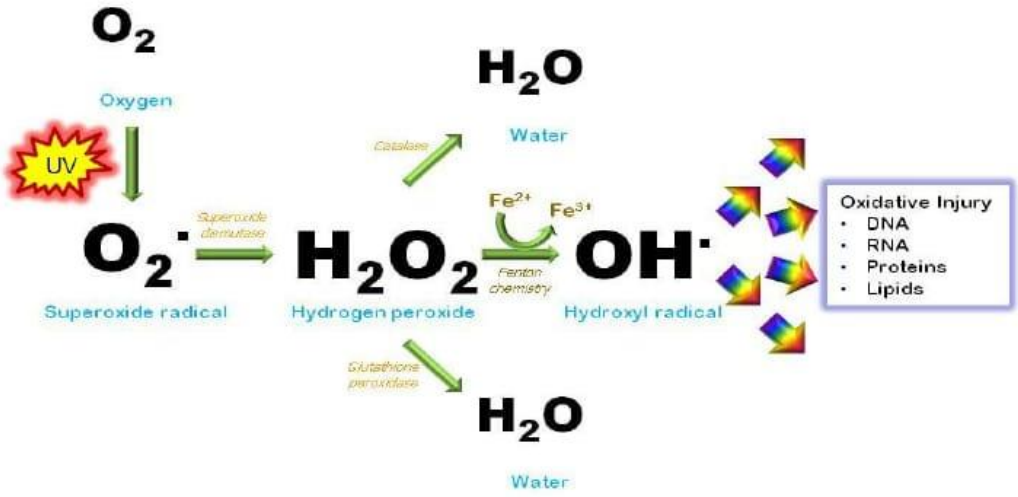
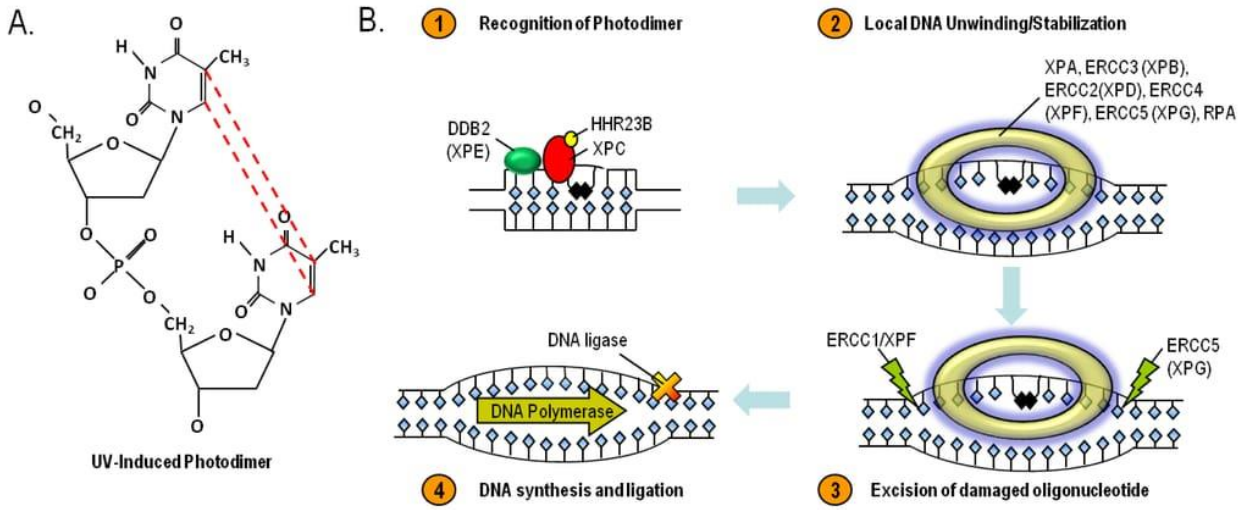


Figure 6 : Shows the structure of UV-induced cyclobutane dimers (A) and their repair via the NER pathway (B). The NER pathway is handled by a minimum of eight enzymes that cooperate to recognise large DNA lesions that alter the double helix's structure, remove the damaged area, and replace it with DNA synthesis controlled by the complementary strand. The clinical disorder known as Xeroderma Pigmentosum (XP) is caused by homozygous impairment in any one of the NER enzymes. The Cockayne syndrome proteins A and B can also play a role in the initiation of NER in the genome's actively transcribed regions, albeit this has not been demonstrated.



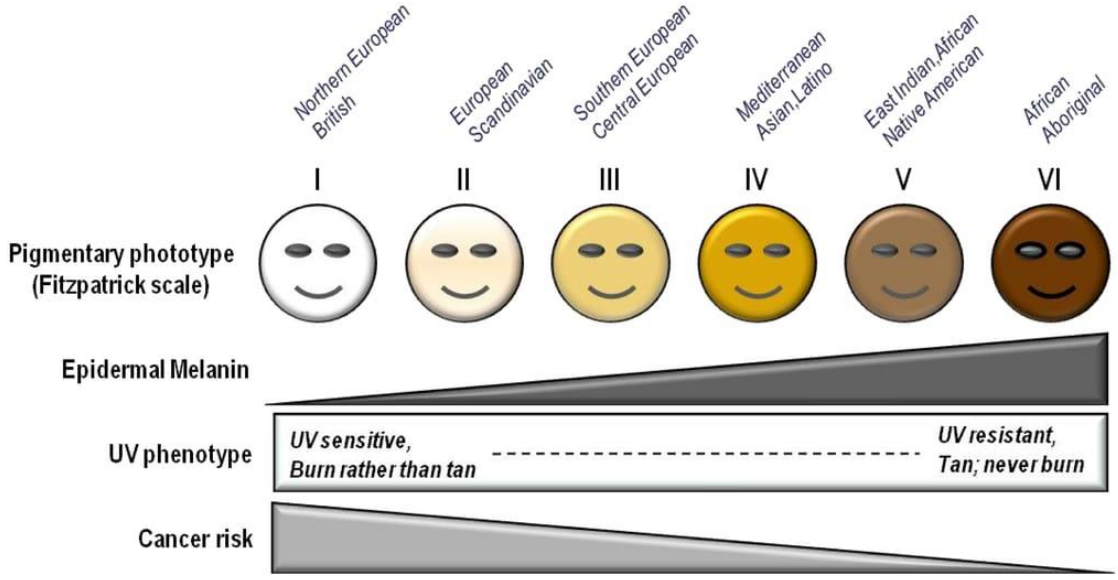
An evolutionary preserved method of mending UV-induced photoproducts and other large DNA damages is called nucleotide excision repair (NER). The importance of NER in cancer resistance is best illustrated by considering the natural history of patients with Xeroderma Pigmentosum (XP), a rare UV hypersensitivity syndrome caused by homozygous defects in any one of at least eight required effector proteins of a common pathway that executes NER: XPA, ERCC1, ERCC3 (XP-B), XPC, ERCC2 (XP-D), DDB2 (XP-E), ERCC4 (XP-F), ERCC5 (XP-G) and POLH. Patients with XP exhibit extreme photosensitivity and, at very young ages, exhibit pigmentary abnormalities, capillary telangiectasias, and atrophy on UV-exposed anatomic areas. Premalignant lesions and skin malignancies appear frequently and manifest themselves more earlier than in people who are not affected. Melanomas, basal cell carcinomas, and squamous cell carcinomas can appear decades before the general population. Additionally, XP-associated skin tumours typically exhibit "UV signature mutations," demonstrating the critical role that NER plays in cancer resistance [44]. The NER pathway is an organised interaction of enzymes that works to fix lesions that change the DNA's three-dimensional structure. The damaged strand is snipped several nucleotides distant on either side of the damaged bases following damage identification and the recruitment of a multiprotein repair complex to the damaged spot. A DNA polymerase uses the non-damaged strand as a template to fill in the gap left by excising the damaged area. in Figure 6. Although only a small number of core components are required and adequate to repair UV-induced DNA damages, a large number of auxiliary components control this genome maintenance system. While the natural history of individuals with XP provides the most compelling evidence of the significance of NER in UV and skin cancer resistance, attention is also being paid to the impact of NER polymorphisms on UV sensitivity and skin cancer incidence in random populations[52].

9. SKIN CANCER :

With well over a million cases identified each year, skin cancers are by far the most prevalent form of cancer in people. About 1 in 5 Americans will get skin cancer at some point in their live. In the United States alone, they are responsible for almost 15,000 fatalities and more than three billion dollars in medical expenses annually. The prevalence of skin cancer rises significantly with age, like many other cancers associated with environmental aetiologies (in this case, UV), perhaps reflecting the lengthy latency between carcinogen exposure and the development of cancer. Based on cell of origin and clinical behaviour, skin cancers are frequently divided into the two main types of melanoma and non-melanoma

skin cancers (NMSC). UV exposure and skin pigmentation have a significant impact on skin cancer risk [33]. (Figure 7).

Figure 7 : Shows how pigmentation affects the risk of skin cancer. People with fair skin and little melanin in their epidermis have a UV sensitive phenotype and tend to burn instead than tan when exposed to the sun. Recent research indicates that DNA repair efficiency in melanocytes may also be impacted by mutations that cause pale skin and tanning impairment, notably signalling deficiencies in the melanocortin 1 receptor (MC1R). Because their skin is less able to block UV photons, MC1R-poor people not only experience higher realised doses of UV radiation, but they may also develop more mutations as a result of UV exposure due to defective DNA repair.



The skin cancer that is most deadly is malignant melanoma. Melanoma, a cancer that is resistant to treatment and is prone to spread, is believed to develop from epidermal melanocytes . Its prevalence has been rising continuously and dramatically over the past few decades. In the 1930s, only one in 1500 Americans received a melanoma diagnosis; today, one in sixty will have the condition[41]. Nearly ten thousand skin cancer-related deaths occur annually in the United States due to melanoma, despite the fact that there are significantly fewer than 10 cases worldwide as a percentage of all skin cancers. Predictably, areas with high populations of fair-skinned residents who live in warm, sunny conditions have the highest melanoma burden. Numerous nevi are another significant risk factor for the disease as most melanomas develop from pre-existing moles. Many melanomas can be treated by surgical excision alone if detected early. However, melanomas spread quickly and have a terrible prognosis for patients with advanced illness. Melanoma is notoriously challenging to treat once it has spread beyond its original site, even with recent advancements in targeted therapy and immunotherapy. Although the cause of the large rise in melanoma incidence over the past few decades is unknown, it is likely multifaceted and includes factors such as increasing UV exposure, environmental and genetic cancer risk factors, better surveillance, and earlier identification [40].

The incidence of non-melanoma skin cancers far outweighs that of melanomas, but luckily, the majority are much more manageable and have much better long-term prognoses. Basal cell carcinomas and squamous cell carcinomas are the two main types, and they are both produced from epidermal keratinocytes. Due to their propensity to contain themselves to the original location of the disease, which

makes therapy considerably simpler, they are less lethal than melanoma. The vast majority of keratinocyte cancers appear on the face, arms, and other parts of the body where UV exposure is greatest. The majority can be adequately treated with local control methods including cryosurgery, MOHS microsurgery, or resection.

All types of skin cancer have a strong epidemiologic and molecular relationship to UV exposure, and it is thought that UV causes about 65% of melanoma and 90% of non-melanoma skin cancers. Strong genetic evidence for a direct mutagenic role of UV radiation in the pathogenesis of melanoma was found by exome analysis of a panel of melanomas, which is well known for its UV-signature mutations in important cancer-relevant genes like the p53 tumour suppressor in squamous cell carcinoma . Resistance to UV-mediated mutagenesis is an important predictor of skin cancer risk since UV-induced DNA mutations represent a key causal factor for melanoma and other skin cancers [41].

10. THE MELANOCORTIN 1 RECEPTOR (MC1R) :

A crucial genetic region implicated in pigmentation, the adaptive tanning response, and skin cancer susceptibility is the melanocortin 1 receptor (MC1R)[22]. The melanocyte surface contains the MC1R, which binds to -melanocyte stimulating hormone (MSH) and sends differentiation signals into the cell by activating adenylyl cyclase and producing cAMP. The protein kinase A (PKA) cascade is activated by cAMP signalling, which increases the levels and/or activity of numerous melanogenic enzymes to improve melanocytes' ability to produce and export melanin. (4 Figures). By improving melanocyte genome maintenance mechanisms, MC1R signalling also reduces UV-mediated mutagenesis[32]. Loss-of-signaling Fair-skinned, sun-sensitive, and skin cancer-prone populations (like Northern Europeans) frequently have MC1R polymorphisms. Due to their correlation with red hair colour, freckling, and a propensity to burn following exposure to UV light, the four most common MC1R mutations (D84E, R151C, R160W, and D294H) are referred to as "RHC" (red hair colour) alleles[37]. RHC mutations, which are loss of signalling MC1R alleles, are linked to a four-fold higher lifetime risk of skin malignancies, including melanoma. The control of eumelanin by POMC generated peptides depends on genetic background, and a large body of evidence implicates MC1R as a major risk factor for skin cancer. The skin is shielded from UV damage by at least two key processes thanks to MC1R signaling. First, the MC1R promotes the formation and accumulation of eumelanin in the epidermis by stimulating pigment synthesis in melanocytes. Epidermal melanization prevents UV rays from penetrating the skin, lowering realised UV dosages as well as the risk of mutagenesis and cancer[38]. By promoting nucleotide excision DNA repair and oxidative resistance, MC1R signalling also has a direct impact on melanocytes' UV resistance. Pharmacologic modification of cutaneous cAMP may be a good strategy to lower UV sensitivity and cancer risk because MC1R signalling is theoretically targetable by substances that affect cAMP levels. Theoretically, increasing the levels of cAMP in the skin can be achieved by either promoting its synthesis (for example, by activating adenylyl cyclase) or preventing its breakdown (for example, by inhibiting phosphodiesterase). Both of these methods have shown considerable promise in raising epidermal melanin levels in animal models, and each is predicted to be efficient even in people with functional loss-of-signaling mutations in MC1R. Alternatives include agonistic MC1R peptide ligands or –MSH[37-38], which are more selective (only acting on melanocytes) but may be less successful in people who have hereditary MC1R signalling abnormalities[52].

11. MEDICATION :

Sun exposure is a well-known cause of skin tanning, which occurs as a result of the production of the pigment melanin in response to UV radiation. The process of tanning is complex and involves a number of mechanisms, including the activation of melanocytes and the subsequent production and transfer of melanin to nearby keratinocytes[48].

However, excessive sun exposure can also lead to a number of risks and health issues, including skin damage, premature aging, and an increased risk of skin cancer. These risks are heightened for individuals with fair skin, as they have less natural protection against UV radiation.

To mitigate these risks, a number of protective strategies can be employed, such as the use of sunscreen, protective clothing, and avoiding peak sun hours[49]. Additionally, regular skin checks and monitoring for any changes or abnormalities can aid in the early detection and treatment of skin cancer.

Pharmaceutical interventions can also play a role in the prevention and treatment of skin damage and cancer, such as the use of topical agents that target specific signaling pathways involved in the development of skin cancer. Furthermore, novel approaches such as the use of nanoparticles and gene therapy may hold promise for the prevention and treatment of skin damage and cancer in the future[50].

Overall, understanding the mechanisms behind sun exposure and skin tanning is crucial for developing effective strategies to protect against the harmful effects of UV radiation and maintain skin health.

12. PROTECTIVE STRATEGY OF UV RADIATION:

UV radiation is a potent environmental stressor that can cause adverse effects on pharmaceutical products. To protect against UV radiation, pharmaceutical companies employ various strategies.

Firstly, packaging materials play a critical role in shielding products from UV radiation. Amber-colored glass or opaque plastic containers with UV-blocking properties are commonly used. These materials limit the transmission of UV light, thus minimizing product degradation.

Secondly, formulation design is crucial. UV-absorbing agents, such as benzophenones or cinnamates, can be incorporated into formulations to absorb or scatter UV radiation. These additives act as a protective barrier, reducing the amount of UV light reaching the pharmaceutical product.

In addition to packaging and formulation, storage conditions are vital for UV protection. Products are stored in cool, dark environments to limit exposure to both UV and visible light. Controlled storage conditions, such as refrigeration or dark storage areas, help maintain product stability and integrity.

Quality control measures are also implemented to ensure UV protection. Regular testing and monitoring of products' UV transmittance or absorbance are conducted to verify the effectiveness of protective measures. If any deviations are detected, appropriate corrective actions are taken.

Lastly, regulatory guidelines provide further guidance on UV protection. Regulatory bodies may specify requirements for UV testing, packaging, labeling, and storage conditions. Compliance with these guidelines ensures that pharmaceutical products meet the necessary standards for UV protection.

Protective strategies against UV radiation in the pharmaceutical industry involve selecting appropriate packaging materials, formulating products with UV-absorbing agents, controlling storage conditions, implementing quality control measures, and adhering to regulatory guidelines. These strategies collectively safeguard pharmaceutical products from UV-induced degradation, ensuring their efficacy, stability, and safety.

13. DISADVANTAGES :

There are several potential disadvantages to writing literature reviews on a topic such as "Sun Exposure and Skin Tanning." These may include:

Limited access to current research: While there is a wealth of research available on sun exposure and skin tanning, new studies are constantly being published. Therefore, it can be challenging to keep up-to-date with the latest findings and to include them in a literature review.

Inconsistent results: Studies on sun exposure and skin tanning often yield inconsistent results, which can make it difficult to draw definitive conclusions. Some studies may find that exposure to UV radiation leads to increased melanin production and a darker skin tone, while others may find no significant effect or even a negative impact on skin health.

Individual differences: The effects of sun exposure on skin tanning may vary depending on individual factors such as skin type, age, and gender. This can make it challenging to generalize findings across different populations.

Confounding variables: Many factors can influence the relationship between sun exposure and skin tanning, such as genetics, diet, and lifestyle factors. These variables can be difficult to control for in studies and can make it challenging to draw clear conclusions.

Health risks: Sun exposure is associated with a range of health risks, including skin cancer and premature aging. Therefore, it is important to balance the potential benefits of tanning with the potential risks to overall health.

Protective strategies: While there are several protective strategies that can help reduce the risks of sun exposure, such as wearing protective clothing and using sunscreen, these strategies may not be effective in all situations or for all individuals. Additionally, some protective strategies may have their own potential risks and drawbacks.

Overall, while literature reviews can provide valuable insights into the current understanding of sun exposure and skin tanning, they may also be limited by inconsistent findings, individual differences, confounding variables, health risks, and limitations of protective strategies.

14. CONCLUSIONS :

Fair skin tone, which is characterised by low amounts of a UV-blocking dark pigment called eumelanin in the epidermis, is one of the biggest risk factors for the development of cutaneous melanoma. Because it is very simple for UV rays to enter the epidermis and harm both keratinocytes and melanocytes in the deeper layers of the epidermis, people with light skin pigmentation experience skin damage from UV considerably more frequently. Fair-skinned people experience higher levels of "realised" UV radiation exposure, and over time, UV-induced mutations that directly contribute to melanoma and other types of skin cancer build up in their skin. By limiting UV exposure, a lot of UV-induced disease, including skin cancer, can be avoided.

In order to influence the carcinogenic process, both we and others are becoming more and more interested in the heritable elements that define melanoma risk. The melanocortin 1 receptor (MC1R), whose activity is crucial to the skin's adaptive pigmentation (tanning) response, is one of the most significant alleles that determines skin cancer risk. In addition to controlling the tanning response, MC1R has a significant impact on the nucleotide excision DNA repair pathway used by melanocytes to repair UV-induced DNA damage. The rational development of pharmaceutical treatments to lessen UV

sensitivity and cancer risk may be made possible by new understanding into how MC1R and other genes function to protect the skin against the damaging effects of UV.

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