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***Corresponding Author**
Tanveer Hussain
E-mail
tanveer.hussain@vu.edu.pk

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UV radiations from sunlight as a potential carcinogen for the development of skin malignancy: A review of the current status and future prospects

Afifa Zaeem[1], Muhammad Sultan Abbasi[1], Ayesha Maqbool[2], Masroor Ellahi Babar[2], Tanveer Hussain[2*]

[a] Department of Biotechnology, Virtual University of Pakistan, Lahore-Pakistan
[b] Department of Molecular Biology, Virtual University of Pakistan, Lahore-, Pakistan

Abstract

Sunlight filtered ultraviolet (UV) radiations are one of the most expected reason of skin malignancy. The intensity of photo-damage to skin, caused by the UV radiations varies with their type (UVA, UVB, and UVC). Human skin has developed a natural defense mechanism for protection against harmful UV radiations by producing vitamin D but climatic change and ozone depletion are the top most factors contributing towards excessive UV filtrations into the earth surface. These excess UV radiations result in two main types of skin cancers, melanoma and non-melanoma skin cancers (NMSCs). Additionally, UV radiations mainly contribute towards immunosuppression by inhibiting immune system. Photo-aging and photo-carcinogenesis are the consequences of immunosuppression. Other major effects of UV exposure include DNA damage and deregulation of p53 protein. Oxidative DNA damage by UV rays can result in the formation of pyrimidine dimers by photochemical reactions. The most common photoproduct is cyclobutane pyrimidine dimers (CPDs) and 6-4 photoproducts, which are primary cause of skin malignancies. Nucleotide excision repair mechanism is used to repair DNA damages by excising CPDs in surrounding regions. Lastly, various remedies and preventive measures are introduced in market for skin protection to avoid DNA damages, especially nanotechnology-based sunscreens. Nanoparticles of zinc oxide (ZnO) and titanium oxide (TiO_2) have unique properties to filter the UV radiations, thus act more efficiently for skin protection as compared to their conventional particles. Therefore, public awareness about harmful effects of UV radiations and use of nanoparticles containing sunscreens should be promoted to prevent the cases of skin anomalies. This review is aimed at summarizing all the aspects of UV radiations related to skin cancer including the types of UV, resulting DNA damage, photo-immunology and preventive measures.

Introduction

Skin cancer is one of the most abundant of cancer types in fair-skinned population. The mortality and morbidity rates of skin cancer are increasing considerably. The causative factors for skin cancer may be intrinsic and/or environmental. One of the top most physical risk factor responsible for skin cancer is ultraviolet (UV) radiations [1]. In the end of nineteen century, it was for the first time reported that the solar radiations are a major environmental carcinogen for human skin cancers [2]. Sunlight acts as a potential carcinogen to which every human is exposed. The UV component of sunlight is the main epidemiologic risk factor for malignancy. There is a general perception that each of the three main types of skin cancer (squamous cell carcinoma (SCC), basal cell carcinoma (BCC) and melanoma) are triggered by solar radiations. The UV radiations play a key role in DNA damage in the initiation of skin cancer. When DNA damages are left unrepaired and apoptosis do not occur, DNA lesions code for their mutagenic properties. Thus, resulting in the stimulation of proto-oncogenes or inactivation of tumor suppression genes [3]. Nevertheless, UV may also assist human health by a natural mechanism of synthesizing vitamin D in skin cells. Therefore, it could be said that the UV has both complex and mixed effects on humans. Individuals with less fair complexion are at increased risk of skin cancer because UV radiations can penetrate deep inside their epidermis. In the past, the source of UV for skin was only occupational exposure but now outdoor leisure activities and intentional tan for cosmetic purposes, have added to UV exposures. Thus, increasing the rate of skin cancer [4]. The purpose of this review is to outline the different aspects of UV radiations reaching earth because of climatic changes, UV penetration into the skin, vitamin D production in the presence of UV radiations, cancerous consequences at molecular level and potential remedies for the purpose of control.

1. Types of UV radiations

Sunlight is a major form of energy for all planets of solar systems. It is basically transmitted and delivered in the form of continuous spectrum of different wavelengths composed of electromagnetic radiations [5]. Moreover, this continuous spectrum of electromagnetic radiations is composed of various types, including ultra-violet (UV), visible, and infra-red radiations [6]. Selectively, UV radiations which are a major cause of cancer can be subdivided into UVA, UVB and UVC of varying wavelength of 315-400nm, 280-315nm and 100-280nm, respectively [7].

1.1. UVA

UVA radiations are electromagnetic radiations with a specific wavelength range and a band width of 80nm, which means they possess low energy. This larger wavelength and low energy properties makes UVA rays directly compatible for penetration to the skin. Moreover, recent research studies demonstrated that the radiations with the greater wavelength are most probably not filtered by the ozone layer of the stratosphere. As a result, 90-99% of these radiations reach earth. Thus, the chances of skin damage and aging are tremendously enhanced because of over pigmentation and tanning [8, 9]. Excessive and long-term exposures of UVA act as precursor in causing skin cancer because oxygen free radical species are generated through a process of photo-sanitized reaction which directly results in DNA damage [10]. Moreover, in previous studies, Wenczl et al. (1998) has also reported that DNA damage is catalyzed by UVA [11]. In his experiment, single stranded DNA breaks were observed in cultured human melanocytes after UVA exposure. Epidemiologic and clinical studies also provided evidence to the role of the UVA with pathogenesis of melanoma [8, 12-15]. Similarly, stem cells have also reported to face DNA damage resulting in carcinogenesis because one-minute exposure of UVA [16].

1.2. UVB

UVB are the radiations with the intermediate wavelength as compare to the other types of UV rays. 1-10% of total UVB radiations reach the earth after filtration through ozone layer. UVB band width is 40 nm which is half when compared to UVA. This shorter wavelength property of UVB radiations reveals that they possess high energy with more skin damaging effects (thousand times more damaging power than UVA). These rays cause sunburn, skin ageing and most severely skin cancer with only two to three hours exposure [5]. Additionally, there are various previous reports regarding UVB's role in initiating DNA damage, inflammations and development of tumors [17-21].

1.3. UVC

UVC are the radiations which possess more dangerous power than the other two types (UVA and UVB) because of low wavelength and high energy radiation

beam. Many studies have accredited that the stratospheric ozone layer completely filter these radiations before they reach surface of earth but still these rays have very high carcinogenicity level [5, 22-24].

2. Effect of Ozone depletion on UV radiations

Climatic change is a matter of serious concern for scientists. World's population is continuously expanding which is one of the major reasons behind climatic change. According to William J. Manning et al, (1995) urbanization, developmental constructions and industrialization are the major factors contributing to population explosion. Deforestation and habitat are severely affected by developmental constructions. Sadly, human activates in developmental procedures are contributing towards the production of dangerous and hazardous gases like; CO_2, N_2O and chlorofluorocarbons (CFCs). These toxic gases are gradually accumulated in atmosphere. Industrial processes, combustion of fossil fuels and agricultural processes are major players in this regard. When the level of these hazardous gases is raised, they lead towards somewhat permanent changes in chemical composition of atmosphere, together with increase in temperature. This raised temperature is technically termed as global warming. Scientifically, the UV rays which are able to penetrate ozone layer and reach earth, cannot be reflected out of atmosphere. Thus, this results in gradual continuous increase in the temperature. Moreover, the toxic gases like CO_2 and CFCs deplete the O_3. As a result, the porous O_3 layer filters more and more UV radiations into the earth surface effecting biological beings such as plants, animals and microbes [25].

3. UV radiations and human skin cancer

3.1. Structure of skin

Skin is basically composed of two basic layers. First is the stratified epithelium, composed of keratinocytes and have thickness of 50 to 100 um. Secondly, a cellular dermis below epidermis with 1000 um thickness. Dermis contains some extracellular regions or matrix that have extracellular fluid to nourish the dermal cells and it is secreted by fibroblast. Some other tissue structures are considered as supporting structures such as nerve cells, inflammatory cells, blood vessels and ground substances etc. These components are also present in the dermal layer region. It reveals that nerve crest derived melanocytes and langerhans cells also occupied a space of about 10% in the dermal region [26] (**Figure 1**).

3.2. Human skin color variation

According to recent reports, the color variations of skin are probably due to blood supply in the superficial plexuses and melanin. Skin color varies due to the difference in the amount and types of melanin. Moreover, erythema sensitivity to UVR has a significant effect on color variations of skin with in the same localized body sites or different body sites of a person. According to a study, keratin producers called keratinocytes are also very important in contributing to skin color [27]. Melanocytes when mature produce melanin in basal layer, which is a major contributor in protecting skin against UV radiations. Melanin is further divided into classes named eumelanin (black and brown) and pheomelanin (red and yellow). The existing ratio of both of these determine the intensity of skin pigmentation [28]. Moreover, melanin has the capacity to filter out UV radiations and scavenge the free oxygen radicals to protect skin from harmful effects because of inflammation [29]. Genetic study of the human skin pigmentation suggested that there are many genes that are directly involved in pigmentation i.e. melanin deposition. Harrison et al., identified four genes involved in the skin color variations. One of the most important and significant gene involved in human skin color variation is Melanocortin 1 Receptor (MC1R) located at locus mc1r [28]. Human MC1R gene is responsible for coding a 317- amino acid which is a member of melanocortin G-coupled receptor. Alpha melanocyte-stimulating hormone (alpha-MSH) is a metabolic product of the ligand pro-opiomelanocortin (POMC) which is present on the MC1R gene. Alpha-MSH activation leads to the production of cAMP. cAMP elevation activate the protein-kinase A, which leads to the increase transcription of microphthalmia transcription factor (MITF), which control the melanogenesis concerning with eumelanin and pheomelanin production [30].

3.3. Skin sensitivity

An access exposure of UVR to the skin results in many cellular inflammatory responses of the skin. Considerably, a high dose of UVR may result in erythema; redness of the skin, edema; rupture of the skin and blistering; sunburn. Excessive exposure of UV rays, results in redness of skin because of

vasodilation, which may retain for 8-24 hours after exposure [31]. On the other hand, edema is rupturing of the tissue and is a wastage of the fluid from the capillaries, with pain and sensation. It is also reported that 48-72 hours after the UV exposure leads to the inhibition of the S-phase of the keratinocyte's cell division, which may in future result in the thickness of the epidermal stratum coreneum [32]. However, previous studies suggested that the melanin deposited keratinocytes show the properties of the protective responses against the UV exposure. It is also reported that the keratinocytes without melanin also have the protective properties for skin as proved by thickening of the stratum coreneum [33]. Transmission of the UV radiations through the various layers (dermis and epidermis) of the skin is dependent upon the factors like melanin pigmentation, amino acids present in the tissues and light scattering properties of the melanin and amino acids [34].

3.4. Relationship between vitamin D, UV and skin cancer

In 1981, Suda and his colleagues determined vitamin D-cancer relationship for the first time [35]. Most of the *in-vivo, in-vitro* and several epidemiological studies suggested that vitamin D (called a sunshine vitamin) has an anticancer affect and also have protective role in inhabiting the development of the cancer [36-38]. Some of the recent studies also demonstrated that the elevated rate of the vitamin D reduce the death cases associated with cancer [36, 39-41]. Association between UV radiations and vitamin D (especially D_3) is prominent because UV rays are very much directly involved in the synthesis of vitamin D. Studies have also demonstrated that during the long day of summer, more vitamin D production is observed as compare to the short day of the winter [42-44]. 7-dehydrocholesterol present in the skin absorbs ultraviolet B radiations. During sunlight exposures it is converted to previtamin D_3. Previtamin D3 is thermodynamically very unstable molecule, it isomerizes to form vitamin D_3 with in few hours of exposure. Additionally, every human has got the potential to synthesize vitamin D_3 in the presence of a sensible sunlight exposure. This process could be effective in maintaining blood levels of 25-hydroxyvitamin D [45].

3.5. UV induced skin cancers

Throughout the world, one of the most common cancer in wide range of populations having varying skin color from fair to dark is "skin cancer" [46]. UV radiations among the other existing radiations play a very prominent role in development of skin cancer. Studies revealed that there is a consistent relationship between the UV radiation exposure, DNA damage and genetic mutations followed by immunosuppression, which altogether results in skin cancer. Key players for enhancing UV exposure are ozone depletion, elevated UV light, latitude, altitude and different weather conditions [47]. Skin cancer is commonly divided into two main types as Melanoma and non-melanoma skin cancers (NMSCs). Non-melanoma (NMSCs) is further divided into basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Melanoma is known for its lethalness malignancy and mortality, while non-melanoma skin cancer is related to benign cancer, which is not so much as dangerous as compared to the melanoma. But still nevertheless it is considered as a common type of cancer [48].

3.5.1. Non-melanoma skin cancer

Yearly estimation of the reported cases of NMSCs around the world are about 2-3 million [49]. There is variation in the estimated UV-induced NMSCs cases with a high rate in the Caucasian populations. Yearly average elevation rate of NMSCs lies between the 3-8% in Europe, Canada, USA and Australia [48]. About 80-85% of BCC of all the NMSCs is translocated to the other organs [47]. Incidence of increasing NMSCs is about 10% in elderly men and young women [50]. Nevertheless, NMSCs has a huge burden on the world health care system. The problem is elevated because of undiagnosed and under-estimation of the cases due to benign nature of NMSCs [47]. The easily affected areas by the BCC and SCC of the body is most commonly head and neck region. Because these areas face high exposure to sun's UV radiations. NMSCs occurrence also has a comparative high consistency rate in female's legs than males as they are more exposed to sunlight [51]. Skin pigmentation also have influence upon the NMSCs occurrence because high pigmentation or melanin deposition lowers the chances of NMSC [52].

3.5.2. Melanoma

Yearly, the estimated new melanoma cases around the world are about 1,32,000 [49]. Caucasian is considered to be most affected population around the world, possessing incidence rate of 16 times greater than the African Americans and 10 times greater than Hispanics [53]. The yearly survey of WHO shows that the cases of melanoma are more than 48,000 form total of 65,161 reported cases [49]. Incidence

occurrence of melanoma cancer is only 3% and the death rate is estimated to be 75% [54]. Melanoma is lethal because its diagnoses is limited in early stages. Thus, it may lead towards patient's death. Pigmentation is considered as key factor in the development of the melanoma. Studies suggested that greater the pigmentation darker the skin, which is the inverse of the melanoma [53]. UV radiations are major contributors of skin cancer leading the world's cancer rate to an alarming situation [51] (**Figure 1**).

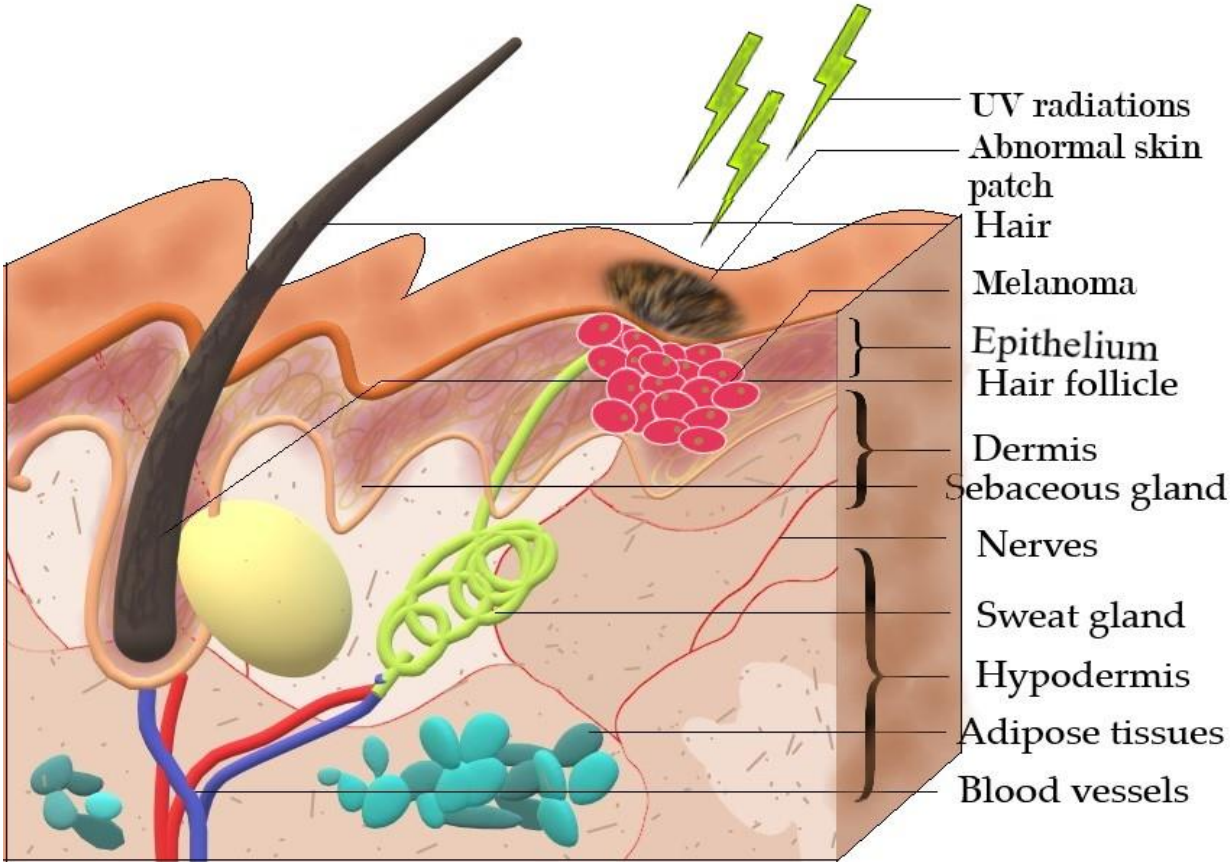

Fig. 1: Structural representation of skin layer and expansion of skin melanoma.

4. Potential contributors of skin cancers

In the world's population, skin cancer is consistently associated with UV radiation exposures because of increased outdoor activities [54]. Moreover, the major constituent of carcinogenic radiations i.e. UVA and UVB have a significant role in skin germ cell cancer and DNA damage, respectively [17]. Sunburns in childhood are a major contributor of elevated rate of melanoma cases. Higher UV radiation exposure physically damage the skin part exposed to the sunlight, it includes skin aging, wrinkles, uneven skin, pigmentation, damaged skin elasticity and abnormality in skin barrier functions. All these symptoms are termed as 'photo-aging' [55]. Genetically, UV radiations also induces mutations in the cancer suppression gene. DNA damages induced by UV radiations are an important contributing factor for causing skin cancer [56].

4.1. Photo-immunology

Immunosuppression is caused by the excessive continuous direct exposure of the ultra-violet radiations. UV radiation are like two sides of same coin with both beneficial and harmful effects. Cell response associated with antigen, suppressing the immunosuppressive cytokinine synthesis and minimizing the hyper sensitivity, are the adverse effects of the excessive UV radiation [57]. Latest study indicated that the renal transplant patients are treated with UV radiations immune-suppressive therapies to suppress the immune system function to not to recognize the transplanted organ as foreign part

but such individuals have considerable high risk of cancer [5]. Moreover, as per latest reports the excessive UV radiation or solarium exposure induced adverse effects in the keratinocytes to produce cytokinine product, such as interlukin-10 (IL-10) interlukin-12 (IL-12) and interferon gamma (IFN-Gamma). The inhabited antigen-presenting ability and hyper-sensitivity response is due to the immune-suppression effects of IL-10 [58]. IL-12 and interferon-gamma are considered to inductive agents for amplifying the effects of T helper cell 1. The IL-10 production and blockage effects resulting in microphage activity are also controlled by IL-12 and interferon gamma [59]. A stunned statement about the UVA radiations is that it has a controversial reverse effect depending on the exposure dose. At low dose-exposure (3 days) UVA has immunosuppressive effects while a high dose-exposure (5 days) it has immune-protective effects [60]. Fourtanier et al., 2000 demonstrated that solar radiation effects which are responsible for the immune-suppression can be reduced by applying the sunscreen UVA protection [61]. Ultimately, long-lasting exposure to UV irradiation results in photo-aging, immunosuppression, and photocarcinogenesis.

4.2. DNA Damage and mutations

Radiations exposed from the sun or solar stimulated radiations have some damaging effects particularly on DNA of the skin cells [8]. Experiments by Burren et al. year show that when solar stimulated radiations are exposed to the skin, it induces the DNA damages because of pyrimidine dimers formation and the increased level of the P53 protein product [62] (**Figure 2**). According to the international agency of the research on cancer, UVA is a human carcinogen [63]. Absorption of UVB and UVC induces the formation of cyclo-butan pyrimidine dimers. In addition to this, bipyrimidine photoproducts are not formed by UVA because the DNA does not absorb UV radiations in this region. Narrow band UVA (365nm) have a high cyclobutane pyrimidine dimer (CPD) induction effects as compare to UVC (254nm) [64]. Basically, UVA interact with water molecule to split it into free radicals as singlet oxygen (type-2 photosensitization), electron abstraction (type-1 photosensitization) or hydroxyl radical. These radicals cause the induction of the single-strand break (SSB) and DNA proteins-crosslinking as previously reported in bacteria, phages and mammalian cell [65]. UVA radiation mediated oxidative DNA damage results in single strand break and oxidized nitrogen bases (purine and pyrimidine). Singlet oxygen radical have a major contribution in promoting 8-oxoguanine, which is considered as most abundant oxidative DNA damaging agent. By fenton reaction, OH^- radical promote single stand DNA break and oxidized pyrimidine. Additionally, 6-4 photoproduct is a special product induced only by UVB which are usually repaired by nucleotide excision repair (NER) [66]. 6-4 photoproduct photo-isomerize in the presence of water into dewar photoproduct by UVA as revealed by the recent studies [67]. However, evident reports show that cyclobutane pyrimidine dimer (CDP) and 6-4 photoproduct formation does not involve the photo-sensitization but they involve the direct absorption of the UVA in both plasmid DNA and isolated DNA [68].

5. Remedial measures to reduce exposure of UV radiations

After having a complete knowledge about the damaging effect of the UVR to the human skin, we hereby summarize some protective or remedial measures that should be adopted to reduce the harmful effects the UVR.

These measures may include:

Behavioral activities like diminishing the body exposure to the sunlight during the peak hours (10am - 4pm).

Wearing of the protective clothes in reflecting-sunlight colors can reduce risk of malignant lesions and moles [69].

UV radiation blocking sunscreen usage can minimize the actinic keratinoses and squamous cell carcinoma (SCC) with titanium dioxide (TiO2) and zinc oxide (ZnO) in the form of inorganic UV filters [70]. Use of nanotechnology is another exponential field playing a very vibrant role in skin protection treatments. There are many indications which support the fact that nano-sized particles have more efficient effect on skin protection than larger sized particles [71]. Tanning should be avoided as the studies demonstrated that the risk and effects for the number of mole formation on skin is due to the UV radiation exposure, and pre-malignant skin damage can be reduced by protective sun wearing [69]. Use of some naturally occurring herbal botanical products like green tea in daily diet because these have some extraordinary antioxidant potentials which protect skin from UV damage. Similarly, grape seed polyphenols, honokiol, quercetin, sulforaphane, apocynin, aloe vera, turmeric, silymarin milk thisle, ginseng, algae and

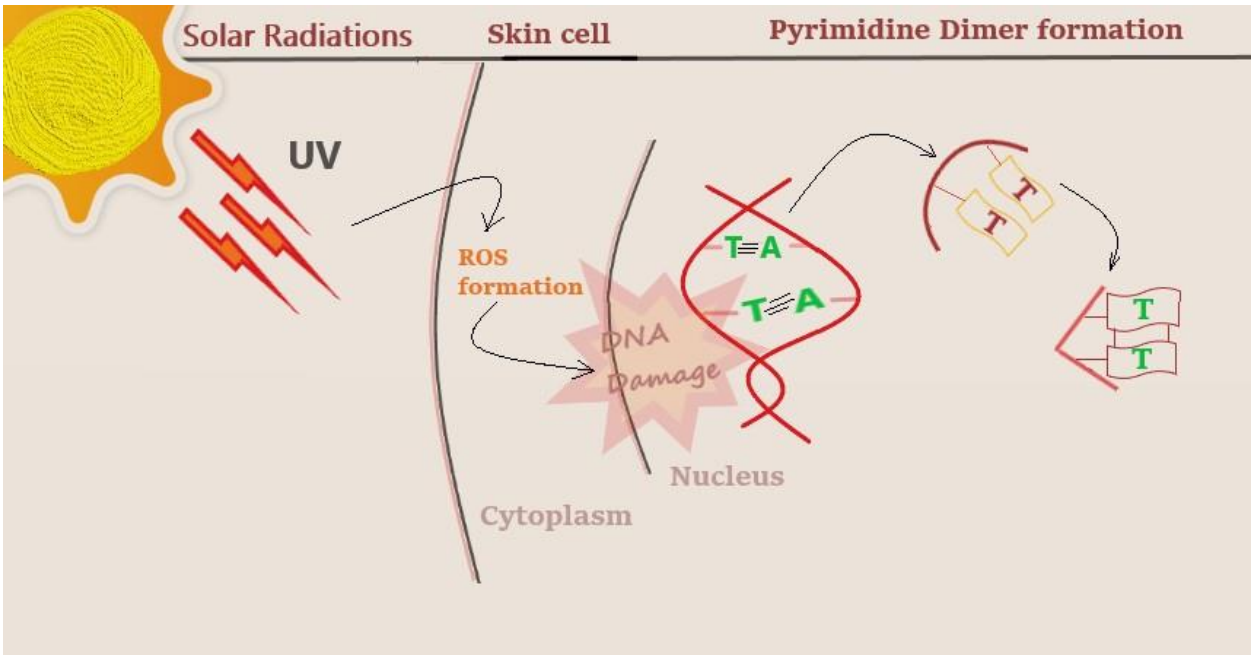

Fig. 2: DNA damage caused by UV exposure and formation of pyrimidine dimers.

and propolis have reported to have potentials in treating UV exposed skin [72].

Conclusion

Conclusively, UV radiations are the main reason of skin cancer. DNA damage buildup in cells due to solar radiations cause nearly all types of skin cancers. Various preventive measures are suggested to reduce risk. Among those one of the most emerging and latest methods is the use of nanotechnology.

Conflict of interest

The authors declare no conflict of interest. Afifa Zaeem has written the manuscript. Muhammad Sultan Abbasi, Ayesha Maqbool and Masroor Ellahi Babar has assisted Afifa Zaeem in write up. Tanveer Hussain conceived the idea, facilitated and reviewed the manuscript critically.

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