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A REVIEW ON IMPLICATION OF PHOTORADIATION IN DNA: ROLE OF FLAVONOIDS AS A PHOTOPROTECTION

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ABSTRACT

Long-term UV exposure can cause major side effects, including photoaging, wrinkles, and the development of skin cancers, including melanoma and non-melanoma cancer. The formation of erythema and erosions is triggered by such UV exposure, which is regulated by mutation, apoptosis, carcinogenesis, and immunosuppression. The purpose of this review was to discuss flavonoids and their role in photoprotection. In the skin epidermis and dermis, flavonoids (catechin, genistein, naringenin, and Kaempferol) may prevented UV-B induced erythema and reduced the development of cyclo-butane pyrimidine dimers in the DNA. When administered topically, flavonoids protect DNA while also preventing other UV-light-induced effects such as sunburn, immunosuppression, and skin photoaging. It also lowers the risk of skin cancer and improves the condition of the skin. We discussed the health-related issues of chemical photoprotection agents, including their side effects and stability in hormone dysfunction, as well as some major environmental issues. However, in the Present Scenario; The aim of this review to protect our skin from UV radiation as well as sunscreen also using sunscreen have a number of

drawbacks, including the development of photoallergy dermatitis, pollution, and vitamin D insufficiency. As a result, Customers should use the right items to increase and protect our skin towards radiation and avoid the negative effects of sunscreen.

Keywords: Photoprotection, Flavonoids, Immunosuppression, SPF factor, Photoaging, UV radiation, Nanotechnology

INTRODUCTION

Many harmful diseases are initiated by ultraviolet radiation, such as skin cancer, premature aging of the skin, and many signs of sun damage such as wrinkles, leathery skin, liver spots, actinic keratosis, and solar elastosis due to UV-A radiation. The concentration of active absorbing molecules is proportional to the efficacy of radiant energy. UVA and UVB radiation are linked and cause carcinogenesis, damaged cellular damage, and skin cancer **[1]**. UV-A radiation is the most dangerous and it can directly affect the DNA and generate oxygen and hydroxyl radicals, which damage a cellular protein, lipids. UV-B radiation gives energy to the skin that forms vitamin – D from cholesterol, but excessive rays harm the topmost layer of the epidermis such as burns and premature aging, and also increases the cell damage that leads to skin cancer (melanoma, non-melanoma cancer). The UV-B region is the most precarious and most of the chemical sunscreen always blocks the UV – B rays. Titanium dioxide and zinc oxide are reacting as UV-A blockers. But these chemical compounds have many side effects due to their stability and safety **[2]**. Sunscreen was initially sold in the United States in 1928, and it has since been an essential element of photoprotection strategy all over the world **[3]**. Recent sunscreens have been discovered to protect the skin not just from UV rays, but also from other hazards (e.g., IR, blue light, and pollution) **[4]**. According to FDA rules, commercial products of sunscreen must be labelled with SPF values that indicate how long they will protect the skin from UV radiation and must be illustrate the efficacy of protection **[5]**. Generally, SPF values vary from 6–10, 15–25, 30–50, and 50+, equating to low, medium, high, and very high protection, respectively **[6]**. Current scenario of world health organization of skin cancer as per their gender in 2018; the highest rate of skin cancer countries with their age-standardized rate as per 100,000; Australia had the highest rate of melanoma cancer i.e. 33.6 and also states that skin cancer in men and women i.e.40.4, 33.1 in Australia (men) and

Denmark (women) **[7]**. Sun radiation continuously reaches towards the earth such as:-50% visible light (400-800nm), 40% infrared radiation (IR) (1300-1700nm), 10% ultraviolet radiation (UV) (10-400nm). Ultraviolet radiation is generally classified into 4 different parts:-UV-A (320-400nm), UV-B (290320nm), UV-C (100-290nm), and Vacuo UV (10-100nm) **[8]**.

Most common in the United States, even one in five people in America will suffer skin cancer in their lifetime. Worldwide, 19.3 million cases excluding non-melanoma cancer **[9]**. In the United States, 1.8 crore new cancer cases are expected in 2020, with 6 lakh deaths **[10]**. In 1996, the Japan Cosmetic Industry Association (JCIA) developed an in vivo persistent pigment darkening (PPD) technique to assess UVA effectiveness in the sunscreen **[11]**.

This review specially focused on discussing the role of phytochemicals that present in the herbal plant such as flavonoids or phenolic compounds. It refers the novel properties of herbal sunscreen that can satisfy consumers demand and consumer's awareness towards chemical sunscreen and side effects. Herbal sunscreen may fulfil all the requirement of consumer's safety and stability purpose such as DNA Repairment, anti-oxidant, anti-pollutant, and shows defence mechanism towards IR and blue light.

Why do we protect our skin from radiation?

Ultraviolet Radiation; is a part of the electromagnetic spectrum. It may be classified as UVA, UVB, and UVC. Non-melanoma skin cancer is developed due to regular exposure to the sun. With longer exposure to UVB rays, it may lead to genetic mutation, i.e., development of cyclobutane pyrimidine dimer and it directly damages the DNA by phytochemicals and UVB radiation may form precancerous and cancerous lesions.

While UVA Radiation directly enters deeper into the skin, generation of free radical species at the cellular level **[12]**.

Mechanism of Action:

The Photo oxidative mechanism always provokes the reactive oxygen species that trigger skin photoallergy and some skin-related diseases.

UV-A rays directly get through the top layer and second layer of the skin, i.e., epidermis and dermis and that is mediated by photo-oxidative damage.

The immediate pigment darkening and persistent pigment darkening is major feedback of photo-oxidation into the skin

shown by the pre-existing of melanin and its precursor **[13, 14]**.

UV rays generate a high level of free radical and its reaction into the skin and further activates the enzyme i.e. (protein kinase C). The reaction between the reactive oxidative species (ROS) and protein, DNA, a lipid that develops the cyclobutane pyridine dimmer **[15]**.

Which shows many symptoms like cellular apoptosis, edema, skin sunburn, and erythema. Solar irradiation initiates the cell surface growth factor and cytokine receptor on keratinocytes and fibroblasts in a corium **[16]**.

THE INTERPLAY BETWEEN UV-RADIATION AND SKIN

UV-Radiation induced DNA damage, mutation, and photocarcinogenesis:

UV radiation produces mutagenic products or lesions that affect a CC to TT dimer, whereas CC dimer is mispaired with two adenine bases when the replication is done and formation of cyclobutane pyrimidine dimer between C-4 and C-5 carbon atom of any other two adjacent pyrimidines **[17]**. UV-induced DNA damage may inhibit the transcription factor binding, which shows the carcinogenic effect. If it may not be repaired, it leads to permanent damage in the DNA sequence and it is caused by UV induction in the DNA damage. These mutations are in the form of CT and CCTT transition, UV-"SIGNATURE" mutation. A rule explains how DNA signature mutation may be formed by DNA damage. According to the A rule, the DNA polymerase enzyme replaces A residue with a default residue where the correct base is not displayed **[18]**.

In the mutation, DNA replication changes the base pair strands. In several terms, the unexpected increment in the mutation activates transcription factor binding sites of melanoma **[17, 19]**.

Mutation can lead to loss of cell cycle control:

In the mutation, UV radiation act as a promotor; it initiates the cell insidely such as mutation arisen from the DNA polymerase, depurination, and deamination of 5-methylcytosine or oxidative damage from the free radical. UVA radiation is a promotor in the case of skin carcinogenesis, and UVA is a less efficient carcinogen.

In the mice model, UV-A and UV-B were irradiated and UV-A radiation alone was ineffective as a carcinogen, But UV-B radiation increased the carcinogenic effect, and UV-A was found to have a less effect on the cell cycle as compared to UV radiation in epidermal cells of exposed mice **[20]**.

UV- induced apoptosis:

Although UV radiation induces apoptosis in cells, it first damages the DNA, lipid peroxidation, and protein oxidation, and then it releases cytochrome c by the mitochondria, and the production of ROS (reactive oxidative species) begins, which belongs to the intrinsic pathway of apoptosis.

In the extrinsic effect, it is the final mechanism. UV radiation directly triggered the group of the death receptor, tumor necrosis factor, and further activated the caspase8 to caspase 3 at last cell death **[21]**. It followed the three mechanisms that activate the ataxia telangiectasia and rad3 (ATR) and ataxia telangiectasia mutated (ATM) and DNA-PK kinase. The p53 protein synchronizes the transcription of several cell cycle proteins such as p21 and pro-apoptotic factors such as APAF1, BAX, and BAK, and these factors arrest the cell cycle.

When DNA repair fails, the downstream effector modulates mitochondrial permeability; it may allow the release of cytochrome-c, and several enzymes are activated, forming an apoptosome; it then activates the caspase enzyme chain, resulting in cell death **[22]**.

UV-induced immunosuppression:

The major factor due to exposure to UV radiation that causes various forms of skin cancer-i.)

Cutaneous malignant melanoma, ii.) Squamous cell carcinoma iii.) Basal cell carcinoma. In UV-induced immunosuppression, finding a tumor arises when radiation is exposed to the body. Generally, UV-B radiation suppresses the immune system and directly suppresses antigens, increases the release of immunosuppressive cytokines and the result indicates apoptosis of white blood cells and histamine deamination product is majorly present in the skin **[23]**.

UV-radiation inhibits Langerhans cell activity by increasing interleukin **[6, 10]** and TNF- levels, which directly suppresses the skin immune response. UV-B exposure also elevates the expression of the cyclooxygenase (COX-2) enzyme. This enzyme initiates the immunosuppressive process by converting arachidonic acid to prostaglandin, which leads to the development of various types of tumors. Finally, it activates a final activator, urocanic acid, which when inhibited delays tumor formation in the affected skin **[24]**.

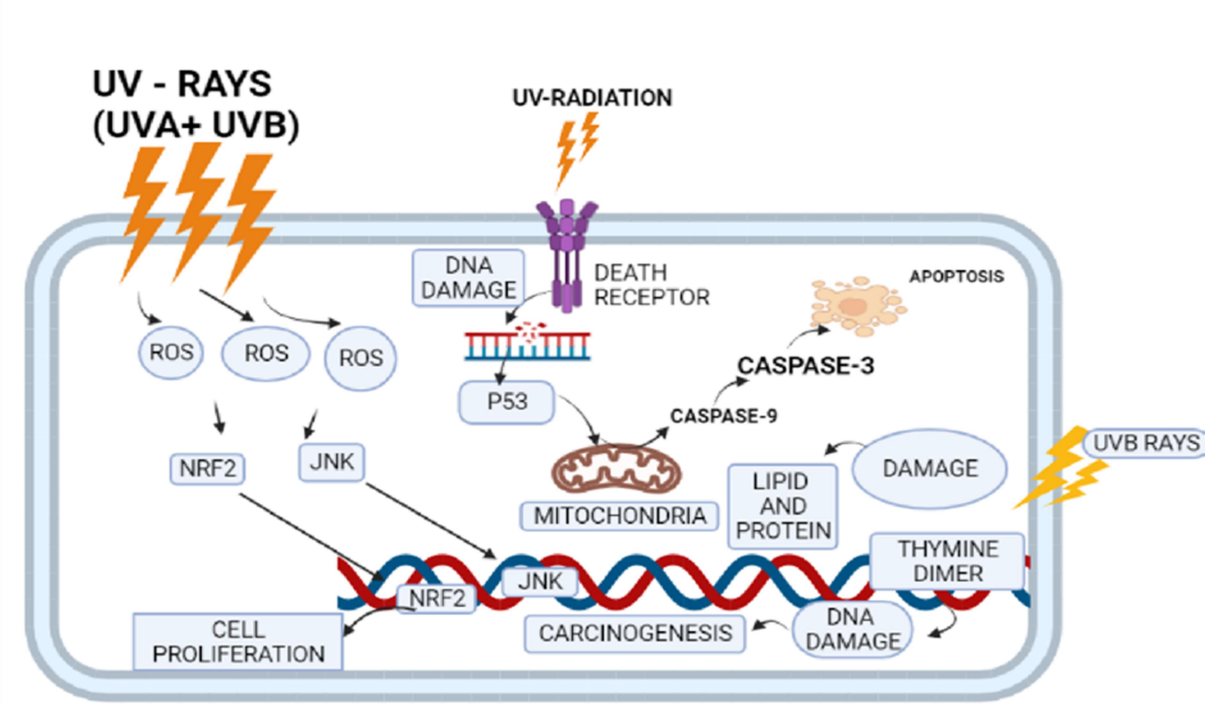

Figure 1: Mechanism of UV- induced DNA Damage, Mutation, Carcinogenesis, Apoptosis, and Immunosuppression

SPF FACTOR

Chemical sunscreen with a sun protection factor (SPF) of at least 30 is recommended by skin care specialists because it protects the skin from UV-B radiation at least 97% of the time and cures sunburns and skin darkening caused by an increase in melanin levels **[25]**. SPF 30 takes 300 seconds for the skin to burn with sunscreen and only 10 seconds without sunscreen, and no sunscreen protects 100% of the dermis or epidermis from UV-B radiation.

SPF = MINIMAL ERYTHEMA DOSE IN SUNSCREEN PROTECTED SKIN

MINIMAL ERYTHEMA DOSE IN NON-SUNSCREEN PROTECTED SKIN **[26]**.

Many flavonoids and polyphenols tend to be protected by UV radiation especially in (UV-A region). Some chemical sunscreen formulations that are on the market do not have properties, i.e. anti-aging, anti-inflammatory and wound healing.

FLAVONOIDS

Flavonoids are a type of metabolite that has anti-oxidant and cell signaling properties, resulting in health benefits. Flavonoids are polyphenol compounds present in fruits, flowers, seeds, and vegetables, as well as in small amounts in beer. The term flavonoids come from the Latin word flavus, which means "yellow." In today's world, there are over 4000 variations of flavonoids to identify. The main property of flavonoids is

that they protect the plant from direct UV exposure while also removing the Reactive Oxygen Species (ROS) produced by UV light. Flavonoids, which have direct and indirect antioxidant capabilities, UV absorbance, and modified signaling pathways, have three different sun protection effects **[27]**.

Function of flavonoids:

• Flavonoids regulate cellular activity and fight against free radicals that generate oxidative stress in our bodies.

• It protects the body from toxins and stress.

• Flavonoids are powerful antioxidant agents.

Flavonoids have biochemical properties and antioxidant effects that relate to various diseases such as Alzheimer's disease (AD), heart-related disease, and cancer. Flavonoids are linked broadly with cosmetics, pharmaceutical, nutraceutical, and medicinal applications and, in other cases, are coupled with cellular enzymes. Flavonoids are a potent inhibitor of several enzymes that are cyclo-oxygenase (COX), lipo-oxygenase, aldose reductase, and phosphoinositide3-kinase **[28]**.

Structure of flavonoids:

The general structure of flavonoids is of a 15 carbon skeleton ring having 2 benzene rings (1and 3) that are linked with a heterocyclic pyran ring (2). This structure is an aglycone derivative **[29]**.

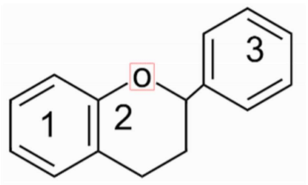

Figure 2: general structure of flavonoid

Division of flavonoids:

Flavonoids are generally divided into 3 parts:-

- **Flavones:**

Flavones are one of the most important flavonoid subclasses. Flavones are found as glucosides in a variety of plants, including leaves, flowers, and fruits. Flavones can be found in celery, parsley, red peppers, chamomile, mint, and *Ginkgo biloba*. Flavones have antiallergic, antiviral, anti-inflammatory, ant oxidation, anticancer, and antitumor properties **[30, 31]**.

- **Flavanone:**

Another major class of flavonoids is a flavanone, which is found in citrus fruits such as oranges, lemons, and grapes. This group of flavonoids includes hesperitin, naringenin, and eriodictyol. Because of their free-radical-scavenging characteristics, flavanone is linked to a variety of health advantages. These chemicals are responsible for the bitter flavour of citrus juice and peel. Citrus flavonoids have antioxidant, anti-

inflammatory, and cholesterol-lowering properties in the body **[32]**.

- **Flavonols:**

Flavonoids with a ketone group are known as flavonols. Proanthocyanins are made up of these basic units. Flavonols can be found in a wide range of fruits and vegetables. Examples: Kaempferol, quercetin, myricetin, and fisetin. Apart from fruits and vegetables, good sources include onions, lettuce, tomatoes, apples, grapes, and berries. Flavonols can also be found in beverages such as tea and red wine. Flavonol consumption has been linked to several health benefits, including antioxidant potential and a lower risk of vascular disease **[30, 33]**.

Flavonol and flavanone have the same structure but they differ by hydroxyl group at the 3 position and double bond at the carbon 2-3 and have six condensed six-membered rings with the benzene ring i.e. α-pyrone or dihydro derivative **[34]**.

- **Isoflavonoid:**

Isoflavonoids are found mostly in soybeans and other leguminous plants and have a limited distribution in the plant kingdom. Isoflavonoids have a lot of potential in terms of fighting illnesses. Because of their estrogenic activity in animal models, isoflavones like genistein and daidzein are often classified as phytoestrogens. Microbial organisms have also been shown to contain certain Isoflavonoids. During plant-microbe interactions, they are also discovered to play a significant function as precursors for the formation of phytoalexins **[30, 35, 36]**.

ROLE OF FLAVONOIDS IN SUN PROTECTION ACTIVITY

Because of the increased exposure of UV light to the skin, reactive oxygen species (ROS) are produced, which can lead to skin cancer, burns, wrinkles, and photo-aging. Flavonoids, phenolic acid, and polyphenols are phytochemical compounds that are effective against photon radiation. The majority of flavonoids have anti-radiation and anti-oxidant effects **[37]**. I). Kaempferol was found to be a powerful inhibitor of two enzymes, RSK2 and MSK1 Kinase, which reduced UV-induced mouse skin carcinogenesis in skin cells by phosphorylating CREB and histone h3 in skin cells **[38]**. II.) Catechin, which is obtained from green tea polyphenol as a beverage and has been shown in in-vitro experiments to protect skin from damaging rays and improve women's skin grades **[39]**. III.) In vitro studies of naringenin and pinocembrin revealed the highest UVC and UVB absorption peak zones. Only the UVC to UVA absorption peak was seen in

Apigenin **[40]**. IV.) Genistein is a photoprotection molecule derived from soybean isoflavones that have been shown to work as an in vitro model of photo-carcinogenesis in human skin fibroblasts **[41]**.

HEALTH RISK OF CHEMICAL PROTECTION AGENT

The usage of sunscreen has been linked to an increase in the incidence of melanoma. the chance of acquiring melanoma as a result of sunscreen use, and suggested that persons living at latitudes greater than 40 degrees may have a higher risk of acquiring melanoma. This could be because sunscreens absorb UVB almost entirely but transmit high amounts of UVA.

Retinyl palmitate, a type of vitamin A that is extensively used in cosmetics and sunscreens (as an antioxidant against the aging effects of UV radiation), has been linked to an increase in the occurrence of skin cancers and lesions **[42,43]**.

- **Effect on Hormones:** Concerning probable hormone disturbance from sunscreen chemicals, benzophenone, particularly oxybenzone, which has been widely used since the 1970s, is growing. In vitro investigations have revealed that it has ant androgenic and estrogenic properties **[44, 45]**.
- **Effect of Anti-Oxidant:** Many sunscreen manufacturers now include antioxidants in addition to the active component to reduce the negative effects of free radicals produced by UV exposure. In vivo investigations have indicated that using stabilized antioxidants reduces matrix metalloproteinase-1 activity and reduces pigment induction **[46]**.
- **Effect of Nanotechnology:** Concerns have been raised about the increasing use of nanotechnology in sunscreens (to make them more cosmetically appealing), as nanoparticles can release free radicals when exposed to UV light. Nanoparticle confinement is limited to the stratum corneum, according to several studies. Furthermore, the utilization of coated nanoparticles has rendered them safe for human consumption. However, until more data is available, treatment at sites with substantially compromised barrier function should be limited **[47, 48]**.
- **Environmental problems:** Since water sources are contaminated with sunscreens, particularly oxybenzone, the environmental consequences of organic sunscreens. They can react with chlorine in pools to produce brominated transformation products, which are difficult to filter out with standard water filters **[49]**. Furthermore, research has

suggested that oxybenzone may have a role in coral bleaching **[50]**.

CONCLUSION

Despite the ozone layer's filtering of damaging UVC radiation, the two remaining solar ultraviolet wavelengths reaching the earth's surface are proving dangerous. UVB radiation damages the DNA of exposed cells directly, whereas UVA radiation damages the DNA of exposed cells indirectly by causing reactive oxygen species to form. After a period of induced stress, cells that fail to repair the damage can go into apoptosis or endure, with their damaged DNA progressing to the UV signature CT transition. These alterations have been found in several genes linked to skin cancer, implying a relationship between UV exposure and tumorigenesis. Flavonoids are a promising bioactive agent in the pharmaceutical and medical industries, with the potential to improve human health, prevent illness, and treat skin diseases. Several combinations of these substances or extracts coupled with synthetic filters have a synergistic effect, enhancing the sun protection factor (SPF) and stabilizing some formulations.

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Author contribution statement

Ms Payal Saxena conceptualised and gathered the data with regarding this work and Mr Sudhakar Kaushik supervised the project. Mrs Bhawana Bhatt helped and give comments on the manuscript. Ms Payal Saxena wrote the manuscript and all author discussed and commented on the manuscript.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

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