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"Inflammation in Photoaging: The Body's Response to Uv Assault"

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ABSTRACT
Inflammation acts as a natural defense mechanism and as part of its defense strategy, the immune system launches an inflammatory response when it encounters threats such as pathogens, damaged tissue, toxic chemicals, or radiation exposure. Hence inflammation is a very important to health. Inflammation, a complex chain reaction, eliminates harmful agents and repairs tissue damage. Inflammation can be short-lived and intense (i.e.acute) or long-lasting and persistent (i.e. chronic), depending on the body's ability to defend itself and how long it takes to respond. UVR damages the skin and stimulates inflammation (UVA and UVB). UVB exposure elicited an early and intense inflammatory response, while UVA exhibited a delayed but sustained effect. UVA radiation is capable of inflicting DNA damage and triggering oxidative stress within skin cells. When our DNA gets damaged, it can actually dampen the body's inflammatory response. UV light hitting the skin's outermost layer (epidermis) triggers the exhibition of injurious molecules called reactive oxygen species (ROS) within skin cells.'Regulatory T cells (Tregs)' stand as the key players in immune suppression. UVR exposure triggers a much faster and distinct type of 'immunosuppression'compared to typical inflammatory processes. UVR-induced immunosuppression and its potential implications for skin health. Exposure to ultraviolet radiation (UVR) doesn't just suppress the immune system in the skin (UVR-induced immunosuppression), it can also weaken the body's overall immune system in a way that resembles the natural decline seen with aging (immunosenescence). UVR-induced photoaging lead to cellular senescence and inflammation.

Key Words: UVR (UVA and UVB), Inflammation, Skin-aging, Photo-aging, Immune system, Regulatory T cells (Treg), ROS, Immunosuppression, Inflamm-aging.

I. INTRODUCTION

Humans are exposed to ultraviolet (UV) radiation from the sun, mostly UV-A (320-400 nanometers) and UV-B (280-320nanometers)[1]. While controlled inflammation acts as a natural defense mechanism, prolonged and uncontrolled reactions caused by UV radiation (particularly UV-A and UV-B) can significantly contribute to the progress of numerous skin diseases[2] Recent research has demonstrated that abnormalities in the NF-kB and TLR pathways, which are crucial for immune signaling, contribute to the process of UVR induced skin inflammation (UISI) [3,4].Research implicates specific cytokines like TNF-a, IL-6, IL-1aas key players in amplifying the inflammation triggered by the dysfunction of NF-kB and TLR pathways[5,6]. UV exposure had varying effects on their levels of increase[7,8]. Repeated and excessive exposure to ultraviolet radiation (UVR) triggers changes in the skin that closely resemble those occurring during natural aging. This accelerated aging process, caused by sun damage, is termed photoaging[9,10,11]. Ultraviolet radiation (UVR), specifically UVB rays, has the ability to damage both DNA and protein structures within skin cells, particularly those located in the epidermis (outermost layer). This damaging effect extends to the immune system, as evidenced by the suppression of contact hypersensitivity (an allergic reaction) following UVR exposure, highlighting the immunosuppressive nature of sunlight on the skin[12]. Subsequent studies revealed that the stresses induced by exposure to ultraviolet radiation (UVR) actually trigger localized inflammation within the skin tissue[13,14]. When the sun (UVR) damages skin, it triggers inflammation, but the body fights back with special cells (regulatory T cells) to calm things down[15,16,17].Cells like regulatory T cells, activated by UVR induced skin inflammation (UISI), can extend their suppressive effects beyond the skin, dampening the overall immune system. Notably, aging mimics this sun-driven immune response,exhibitingchronic low-grade inflammation

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and counteracting immunosuppression[18,19,20]. As part of its defense strategy, the immune system launches an inflammatory response when it encounters threats such as pathogens, damaged tissue, toxic chemicals, or radiation exposure[21] and it works like a double agent, eliminating the cause of damage while paving the way for recovery[22], Hence inflammation is a very important to health[23]. During acute inflammation, cells and molecules work together seamlessly to minimize damage from injury or infection. But sometimes, this process goes away, causing the inflammation to become chronic and contribute to various chronic inflammatory diseases[24]. Inflammation shows up in tissues as redness, swelling, heat, pain, and reduced function. These are caused by local immune cells, blood vessels, and other inflammatory cells responding to infection or injury[25]. The inflammatory response involves crucial changes in tiny blood vessels (increased leakiness), the gathering of white blood cells (leukocytes) at the affected area, and the release of signaling molecules (inflammatory mediators) that orchestrate the immune response[22,23,24,25,26]. Imagine inflammation as an alarm system going off in the body. When tissue gets hurt, the alarm triggers a chain reaction of messengers (chemical signals) to call in the repair crew (healing responses) to fix the damage[27]. Inflammaging, a chronic, inferior inflammation connected with aging, is thought to contribute to various age-related issues as it disrupts the function of cells, tissues, and organs throughout the body. Notably, the skin, being our largest organ, plays a crucial role. Damage to its barrier can trigger both localized and systemic inflammation, mirroring what happens in many inflammatory skin diseases[28]. The skin, a dynamic guardian, uses an intricate structure and diverse cell types to work together seamlessly. Its outermost layer, the epidermis, acts as a shield, with subdivisions specializing in tasks like protection and renewal[29]. Thick skin adds a clear waterproofing layer (stratum lucidum) before reaching the common fortifying layer (stratum granulosum). Both types then build new cells in the spiny layer (stratum spinosum), resting on the base where everything starts (stratum basale). This deepest layer also houses immune defenders and pigment creators[30]. Inflammation, a complex chain reaction, eliminates harmful agents and repairs tissue damage. This process starts through two pathways: innate immunity, with rapid responses from white blood cells like neutrophils and macrophages, and adaptive immunity, involving B and T cells that build long-term memory against specific threats[31].Inflammation can be short-lived and intense (acute) or long-lasting and persistent (chronic), depending on the body's ability to defend itself and how long it takes to respond. “Acute inflammation” is the body's initial rush to heal within 2 weeks. It causes quick symptoms like redness, swelling, and pain, but resolves fast and usually leads to recovery.“Chronic inflammation” isn't a quick fix; it lingers for extended periods. Often, it starts after the initial cause of acute inflammation hangs around[32].

INITIATIONOF INFLAMMATION (IDENTIFICATION OF PATHOGENIC AGENTS)

Inflammation initiation hinges on the interaction between receptors on host cells and pathogenic agents such as microbes or necrotic cells. This recognition system activates intracellular signaling cascades leading to inflammatory responses. Furthermore, specific circulating proteins like complement components can also function as inflammation triggers.

1) Recognition system of receptors: Host cells display an array of distinct receptors tailored to recognize diverse entities: pathogen recognition receptors (PRRs) for microbes, cell adhesion molecules (CAMs) and others for leukocytes, and damage-associated molecular pattern (DAMP) receptors for necrotic cells.

- Innate immunity relies on diverse pattern recognition receptors(PRRs)expressed by non-lymphoid cells (macrophages, dendritic and epethilial cells) to acknowledge pathogen-associated molecular patterns (PAMPs) displayed by invading microbes. These PRRs are located on various cellular components: plasma membrane (TLRs), cytosol (NLRs), and endosomes (TLRs). Notably, Toll-like receptors (TLRs) are the most prominent PRRs for microbial recognition, but other important families includeRIG-like receptors (RLRs) and NOD-like receptors(NLRs), with the latter specifically targeting viruses.
- Many leucocyte populations express receptors for the Fc region of immunoglobulin (Ig) antibodies and complement components C3b/iC3b. These receptors enable recognition and binding of opsonized microbes (microbes coated with Ig and complement), facilitating phagocytosis and triggering pro-inflammatory responses.

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- Necrotic cell death leads to the release of cytosolic molecules and nuclear DNA. These danger signals are admitted by cytosolic receptors, such as NOD-like receptors (NLRs), triggering the formation of inflammasomes. Inflammasome activation results in the cleavage and activation of caspase-1, an interleukin-1β converting enzyme (ICE) that processes and secretes pro-inflammatory cytokines, initiating and amplifying inflammatory responses.

2) Circulating proteins microbial infection leads to the activation of the complement system, a cascade of enzymatic reactions that generate various effector molecules. Among these, mannose-binding lectins and collections exhibit direct opsonophagocytic activity against pathogens while simultaneously triggering inflammatory responses through diverse mechanisms, including activation of leukocytes and production of pro-inflammatory mediators[32].

Figure 1: "Triple response" obtained by firm touch of skin of forearm with a pencil.

PHOTOAGING: ROLE OF SUN EXPOSURE IN ACCELERATING SKIN AGING

Repeated excessive exposure to solar radiation, encompassing UV-B (280-320 nm) and UV-A (320-400 nm) wavelengths, induces alterations in the skin that exhibit similarities to, but are distinct from, chronological aging. This phenomenon highlights the unique effects of UV radiation on cellular and tissue mechanisms compared to the intrinsic aging process[11,33]. The sun's harmful rays reach different depths in your skin: UVB only touches the surface (i.e. epidermis), UVA goes deeper (i.e. dermis), and visible and infrared light reach even further (i.e. fat layer)[34].

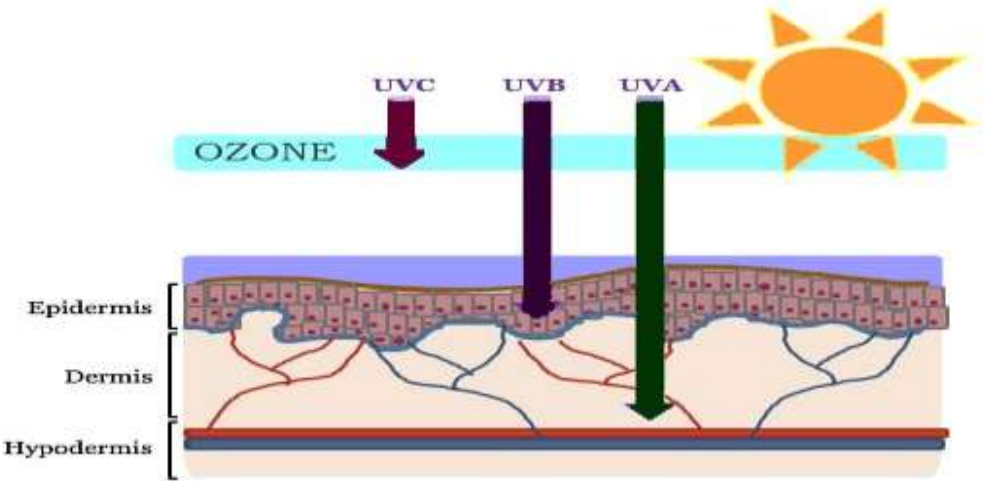

Figure 2: Diffusion of "UVR" into the layers of skin.

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When revealed to UVB radiation, the main cells of our skin (keratinocytes) can go through a specific type of cell death called ferroptosis. This process leads to the destruction of these cells and contributes to skin damage[35]. UVB exposure elicited an early and intense inflammatory response, while UVA exhibited a delayed but sustained effect. Interestingly, both types of UV radiation appear to induce 'inflammation' and subsequent 'immunosuppression' in the skin through comparable mechanisms. Additionally, UVA radiation is capable of inflicting DNA damage and triggering oxidative stress within skin cells[36,37]. When ultraviolet rays (UVR) hit our skin, they damage various molecules called chromophores. This triggers a chain reaction of stress responses inside the skin cells, alerting the immune system to take action[35,38,39]. DNA damage induced by UVR occurs through two primary mechanisms: direct formation of covalent linkages between pyrimidine bases (pyrimidine dimers) and indirect oxidation of guanine residues to 8-oxo-7,8-dihydroguanine (8-oxoG) mediated by reactive oxygen species generated during oxidative stress[40,41]. When our DNA gets damaged, it can actually dampen the body's inflammatory response[42,43,44]. UVR-induced DNA damage, a hallmark of photoaging, can paradoxically suppress inflammatory responses through mechanisms like p53 activation. However, persistent DNA damage may ultimately lead to chronic inflammation, creating a feed-forward loop that exacerbates photoaging and contributes to skin deterioration[45,46]. Both UV-A and UV-B radiation can induce apoptosis and cellular senescence in non-irradiated human dermal fibroblasts via a bystander effect mediated by the secretion of reactive oxygen species (ROS) and pro-inflammatory cytokines[47]. Pathological modifications within the extracellular matrix components have been associated with the promotion of tissue fibrosis, cellular senescence, and the initiation of inflammatory responses[48,49]. Certain elastin and collagen fragments exhibit matrikines activity, acting as signaling molecules that stimulate inflammatory responses through interaction with specific cell surface receptors[50].

INFLAMMATION CAUSED BY UV RADIATION

Exposure to UV radiation kickstarts inflammation in the skin, often showing up as redness (erythema) and swelling (edema) – classic sunburn. This happens because UV light hitting the skin's outer layer (epidermis) triggers the construction of noxious molecules called reactive oxygen species (ROS) within skin cells. These ROS create oxidative stress, damaging internal structures like mitochondria and ultimately harming the cells themselves[51]. UV rays not only burn our skin, but they also trigger chemical reactions inside our cells using enzymes called "lipoxygenase" and "cyclooxygenase." These reactions are involved in inflammation and other processes[52]. This activity triggers the production of ROS (molecules that damage cells)[53] and inflammatory lipid mediators, leading to both inflammation and additional oxidative stress, amplifying the initial damage[54]. The usual inflammatory suspects, NF-κB and p38MAPK, are well-known culprits in skin cells. But there's more to the story - compelling evidence shows that UVB radiation throws a curveball by activating inflammasomes, contributing to inflammation in yet another way[55,56,57]. Interleukins, chemokines (such as CCL2, CCL3, CXCL1, CXCL8), and GMCSF are key players in inflammation. They are secreted by cells and act as chemical signals, attracting immune cells and promoting inflammation[58]. Upon interaction with ultraviolet radiation, the skin undergoes three distinct sequential pathological phases, each characterized by different cellular and molecular events[59,60]. The very first phase, the "vasodilatory phase," lays the groundwork for inflammation. Increased blood flow leads to visible redness (erythema) and swelling (edema). Moreover, mast cells release their arsenal of inflammatory chemicals (degranulation), contributing to increased pain sensitivity. Following the initial vasodilation, the "inflammatory phase" unfolds. This stage witnesses a significant attack of neutrophils, T cells and monocytes into the skin. Additionally, the expression and production of pro-inflammatory cytokines and other inflammatory mediators increase dramatically, further fueling the fire of inflammation. The final phase, the "regressive" or "resolution" phase, acts as a counterbalance to the previous inflammation. This critical stage involves the engaging and extension of immunosuppressive cells within the affected skin, creating a calmer

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environment. Additionally, anti-inflammatory cytokines like TGF-β, IL-4 and IL-4 are secreted, further dampening the inflammatory response and initiating the healing process[61,62].

IMMUNOSUPPRESSION CAUSED BY UV RADIATION

Beyond being a physical guard, the skin doubles as an internal security system. Immune cells within this amazing organ work tirelessly to protect you from harmful invaderse.g.dendritic cells, macrophages, dendritic epidermal T cells,Langerhans cells,mast cells, Treg cells[63,64]. Regulatory T cells (Treg cells) are essential for maintaining skin homeostasis, particularly by suppressing excessive immune responses and promoting the resolution of skin inflammation[65,66,67]. Regulatory T cells (Tregs), specialized cells that suppress immune responses, are easily identifiable by the presence of two key proteins on their surface: CD25 and CD39. These proteins act as markers, signaling their immunosuppressive role[68,69]. Regulatory T cells (Tregs) stand as the key players in immune suppression. They target bothadaptive and innate immune cells, modulating their functions to prevent harmful overreactions. For example, Tregs play a critical role in inhibiting inflammatory responses, ensuring a balanced immune system[70,71,72]. Studies have observed a link between UVR exposure and immunosuppression, suggesting that sunlight weakens the immune system's ability to fight off skin cancer (carcinogenesis)[12,73]. Exposure to UVR initiates a cascade of signals in the skin, leading to the activation of local and systemic immunosuppressive pathways.

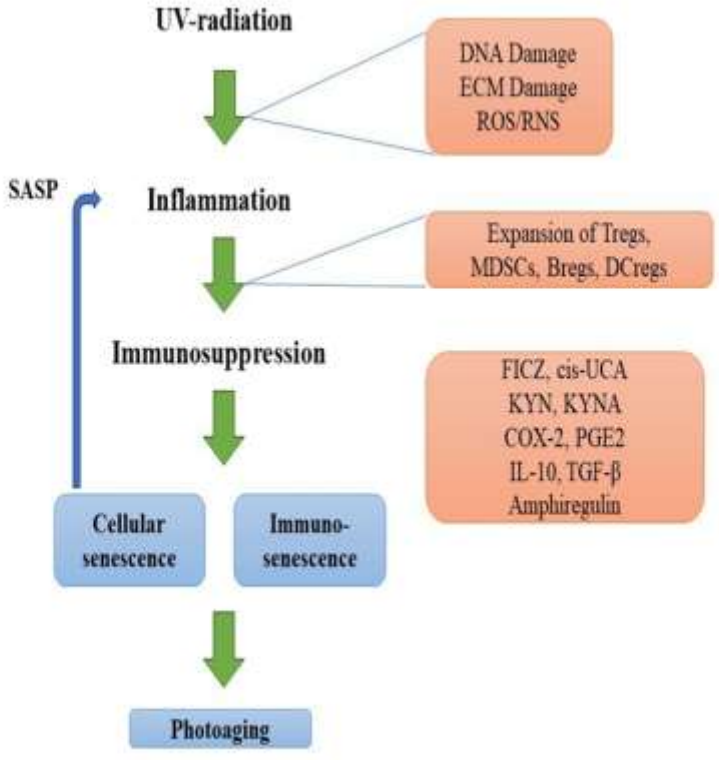

Figure 3: UVR damages the skin and stimulates the inflammation and induces photoaging in the skin.

This dampens the immune response, both at the site of UV exposure and throughout the body, potentially impacting susceptibility to various illnesses[12,15,16,17]. Chronic inflammatory states are well-established inducers of immunosuppression. However, recent research suggests that UVR exposure triggers a much faster and distinct type of immunosuppression compared to typical inflammatory processes. This finding presents an intriguing paradox, as inflammation itself is known to play a crucial role in the photoaging process. Further study is needed to

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explain the specific mechanisms behind UVR-induced immunosuppression and its potential implications for skin health[74,75]. In the outer layer of our skin (epidermis), a naturally occurring molecule called urocanic acid (UCA) readily absorbs ultraviolet (UV) radiation. This exposure triggers a specific change in its structure, converting it from the "trans" form to the "cis" form. Interestingly, this conversion plays a role in promoting the evolution of immunosuppression, meaning it weakens our body's ability to fight off infections[76,77].Applying cis-UCA to human corneal epithelial cells (HCE-2) significantly decreased the production of inflammatory molecules like IL-1β, IL-6, and IL-8. This finding suggests that cis-UCA possesses anti-inflammatory properties, probably preventing inflammation-induced immunosuppression, where the body's ability to fight infection weakens[78,79].Sun exposure causes two things: it increases immune-calming cells (Tregs) and weakens the overall immune system. While this initially prevents severe inflammation, a chronic weakening can lead to an aging immune system (immunosenescence) and disrupt the skin's balance, accelerating photoaging[80].

INFLAMM – AGING (INFLAMMATION AND PHOTOAGING)

The aging process is characterized by both immune system decline (immunosenescence) and a chronic, low-grade inflammatory state (inflamm-aging), distinguished by elevated levels of pro-inflammatory mediators circulating in the blood[81].A study compared the amounts of different inflammation-related molecules (cytokines) in the blood of younger and older people to understand how our body's immune system changes as we age[82].Despite increased inflammation markers like C-reactive protein and altered immune molecules in older people, a possible explanation is that their skin itself is a major source of inflammatory mediators, potentially driving chronic low-grade inflammation (inflamm-aging)[83].Experiments using mice provided key evidence for the skin's potential role in inflamm-aging. Disrupting the skin barrier in these animals triggered the manufacture of inflammatory molecules (cytokines) both locally in the skin and throughout their bodies, as measured by increased cytokine levels in circulation[84]. Mice studies provide two key pieces of evidence for the skin's potential role in "inflamm-aging": 1) When their skin barrier was disrupted, inflammatory markers (TNF-α and amyloid A) specifically increased in the skin, not the liver, suggesting local production. 2) These markers also significantly rose in their blood, regardless of their immune system strength, hinting that the skin might be directly releasing inflammatory signals into the bloodstream[85].Other researchers explored the connection between aging and skin-linked inflammation by studying human skin cells in the lab. They triggered inflammation in these cells by exposing them to a virus and a bacterial molecule, aiming to unravel the potential role of skin inflammation in overall body inflammation during aging[86].Considering the extensive surface area of the skin, these observations broadly submit that constant dysregulation of epidermal functions in chronologically aged individuals might play a role in the phenomenon of inflamm-aging[83].The exact reason why older adults seem more susceptible to various health issues remains somewhat of a mystery. However, the theory of "inflamm-aging", which suggests chronic low-grade inflammation plays a crucial role, is attracting increasing attention[87].One of the earliest theories on aging suggests that it's caused by damage from free radicals, molecules our bodies produce over time and from sun exposure. This same type of damage is also seen in skin aging caused by sunlight (photoaging)[88].Interestingly, exposure to ultraviolet radiation (UVR) doesn't just suppress the immune system in the skin (UVR-induced immunosuppression), it can also weaken the body's overall immune system in a way that resembles the natural decline seen with aging (immunosenescence)[89].Evidence suggests that inflammation triggers the activation of cells that suppress our immune system. This happens both as we age naturally and when our skin ages from sun exposure[90,91].Although both chronological aging and UVR-induced photoaging lead to cellular senescence and inflammation, the specific molecules responsible for these changes are probably distinct[92]. As we know inflammation is mediated by arachidonic acid metabolites (eicosanoids) via cyclo-oxygenase and lipo-oxygenase pathway. In which cyclo-oxygenase, a fatty acid enzyme present as COX-1 and COX-2 carry out activated arachidonic acid to form prostaglandin endoperoxide (PGG_2). PGG_2 is enzymatically converted into PGH_2 with generation of free radical of oxygen. The enzyme, lipo-oxygenase, a principal enzyme in neutrophils, acts on arachidonic acid to form hydroperoxyl eicosatetraenoic acid (HPETE) which on further

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peroxidation forms 1. “5- HETE (Hydroxy compound)” an intermediate product, which is a strong chemoattractant for neutrophils. 2. “Leukotrienes (LT)”, are lipid mediators and plays a crucial role in inflammation and allergic reactions. 3. “Lipoxins (LX)” act to control and counteract actions of leukotrienes[32]. UV radiation directly contributes to the development of reactive oxygen species (ROS) in the skin by causing an inflammatory response and increasing the activity of the enzymes cyclooxygenase and lipoxygenase. UV radiation generates reactive oxygen species (ROS) which, in turn, indirectly influence the release of ceramides and arachidonic acid. This happens through increased cell membrane permeability. ROS damage the cell membrane structure, leading to a loss of its barrier function and allowing these molecules to pass through more readily. The released arachidonic acid then undergoes conversion into prostaglandins by the enzyme cyclooxygenase. These prostaglandins act as signaling molecules, tempting lymphocytes to the site of injured cell membranes.UV exposure triggers a heightened inflammatory response in the skin. This quickly demonstrate as acute photodamage, characterized by symptoms like redness (erythema), blister formation (vesicle formation), and swelling[93].

II. CONCLUSION

Inflammation, a critical component of the body's defense system, acts as a natural response to external threats like pathogens, toxins, and radiation exposure. However, when this response becomes prolonged or excessive, particularly due to disclosure to ultraviolet (UV) radiation, it can have harmful consequences for the skin. This chronic inflammation can trigger various skin diseases and contribute to accelerated skin aging, a process known as photoaging. UV radiation, specifically UVA and UVB rays, damages skin cells, leading to oxidative damage and DNA damage. These cellular disruptions further exacerbate inflammation and contribute to weakened immunity, creating a vicious cycle that ultimately accelerates the visible signs of skin aging.Specifically, UVA and UVB rays within the UV radiation spectrum inflict a multi-pronged attack on skin cells. Additionally, these rays trigger an imbalance of free radicals known as oxidative stress, further harming cellular components. This combined assault by UV radiation ultimately leads to inflammation and photoaging.

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