New Option in Photoprotection

Ines Sjerobabski Masnec, Lena Kotrulja, Mirna Štim and Sanja Poduje
Clinical Department of Dermatovenerology, University Hospital «Sestre milosrdnice», Zagreb, Croatia

ABSTRACT

All the people are exposed to solar ultraviolet radiation. Exposure to sun with living in an oxygen-rich atmosphere causes unwanted photodamage. Sunburned skin is a leading risk factor for melanoma and non-melanoma cancers. UV exposure causes immunosuppression via multiple mechanisms in the skin. In this review the main topic is to mention new or alternative ways of photoprotection. Sunscreens are commonly used as protection against sun damage. They reduce the penetration of damaging solar UV wavelengths in skin by reflecting or absorbing them. Sunscreens are very valuable, but they have limitations. They have to be used properly to gain the full effect (application a little while before UV exposure, at frequent time points and in adequate amounts). Also, they have the problem of photoinactivation, which is the degeneration of the UV-filter due to exposure to UV rays resulting in the loss of absorbing capacity. Products with immune protection factor contain DNA-repair enzymes and antioxidants that may reduce mutations and enable the immune system to combat photodamage. The use of antioxidants and polyphenols may exert an anti-aging effect by preventing and even reversing sun damage. Adequate photoprotection is essential to control photocarcinogenesis and photoaging.

Key words: photoprotection, UV radiation, DNA repair enzymes, polyphenols

The sun emits visible light, infrared radiation, which is not considered harmful to humans, and UV rays. Less than 5% of the sunlight that reaches the earth’s surface is ultraviolet radiation. All the people are exposed to solar ultraviolet radiation. Exposure to sun with living in an oxygen-rich atmosphere causes unwanted photodamage. Exposure of the skin to ultraviolet radiation, mainly its UVB and UVA components, results in erythema, edema, hyperpigmentation, sunburn cells, immunosuppression, photoaging and skin cancer. Having a suntan has long been synonymous with beauty, good health and dynamism in our culture. Also, an increasing number of people are exposed to artificial source of ultraviolet radiation used in industries, commercial settings and leisure activities. Sunburned skin is a leading risk factor for melanoma and non-melanoma cancers.

Four processes control the penetration of UV rays into the skin.

Reflection is diffuse and occurs at the level of cornified layer.

Diffusion is important for the cornified layer and for melanin that mainly diffuses short wavelengths.

Absorption occurs in the cornified layer where 70% of UVB is absorbed through the polar amino acid of keratin and urocanic acid, while melanin and carotenoids absorb UV rays and visible light.

The fraction of the beam escaped the three latter processes corresponds to transmission and penetrate the skin1.

When skin is exposed to sunlight, UV rays are absorbed by skin molecules that then can generate harmful compounds, called reactive oxygen species or ROS, which are highly reactive molecules that can cause oxidative damage. ROS can react with cellular components like cell walls, lipid membranes, mitochondria and DNA, leading to skin damage and increasing visible signs of aging2.

Mechanisms of UV rays exposure induced skin damage

Sun-exposed skin areas are characterized clinically by fine and coarse wrinkling, roughness, dryness, laxity, telangiectasia, loss of tensile strength and pigmentedary changes. There is also an increase in development of benign and malignant neoplasms on photoaged skin. It is a
cumulative process and depends primarily on the degree of sun exposure and skin pigment. The epidermis and dermis are both affected by UVB, but the dermis is also affected to a significant extent by UVA. It has long been thought that the majority of human photolesions due to UVB rays, now it is believed that UVA play a substantial role in photoaging. Because UVB is essentially completely absorbed in the epidermis, it has been important to understand that photoaging changes can be produced by UVA alone. Indeed, these changes have been produced in photoprotected skin by a small number of low-dose exposures of UVA radiation.

When the skin is chronic exposure to UV rays, the epidermis responds with hypertrophy. The stratum corneum thickenes, epidermis becomes acanthotic, and there is progressive dysplasia with cellular atypia, and anaplasia. Keratinocytes are irregular with a loss of polarity. Melanocytes are irregular with pockets of increased and decreased numbers. The Langerhans cell population in the epidermis is reduced and that contributed to an impaired immune response to antigen and skin cancer cells. The roughness of photoaged skin is result of combination of changes in stratum corneum and changes in the glycosaminoglycan content of the dermis. With age there is a decrease in glycosaminoglycans in the dermis. In photoaged skin there is paradoxical increase in glycosaminoglycans when compared with intrinsically aged skin. But, there are deposited on the abnormal elastic material rather than in the papillary dermis and that location may make them unavailable as a source of hydration. Chronic sun-exposed skin display thickened basement membrane. Dermal changes are reduction in collagen and precursors of types I and III collagen, a decrease in basement membrane. Dermal changes are reduction in degranulated mast cells, macrophages, and lymphocytes. Blood vessels are dilated and tortuous. In photoprotected skin by a small number of low-dose exposures of UVA radiation.

For a photochemical reaction to occur in the skin, ultraviolet radiation from the sun must be absorbed by chromophore, beginning a series of photochemical reactions. These chromophores are DNA, aromatic amino acids, 7-dehydrocholesterol, cytochromes, melanin and bilirubin. These reactions can result in changes DNA, including oxidation of nucleic acids and modify proteins and lipids, resulting in changes in function. Their accumulation may result in skin cancer or photoaging changes. DNA may absorb UVB, directly inducing changes between adjacent pyrimidine bases on one strand of DNA, although UVA can also generate thymine dimers. DNA changes are constantly being repaired by nucleotide excision repair. Whenever repair is incomplete and damage to the genome is great, photodamage may result.

Reactive oxygen species are an inherent part of the anabolism and catabolism of skin. When oxidative stress is increased, including high metabolic demands and out-side forces such as sunlight, smoking, and pollution, protective controls may not be adequate and oxidative damage may occur. The most damage occurs from free radicals which are molecules or atoms with an unpaired electron. These molecules are extremely chemically reactive and short-lived. They react at the place where they are created and called reactive oxygen species – ROS. Reactive oxygen species include superoxide anion, peroxide, and singlet oxygen. They can modify proteins in tissue to form carbonyl derivatives, which are, accumulate in the papillary dermis of photodamaged skin.

Small amount of UV radiation result in the induction of series of matrix metalloproteinase (MMP) including MMP-1, MMP-2, MMP-3, and MMP-9. These proteases are capable of degrading the collagen framework of skin. At the same time procollagen synthesis is inhibited, perhaps by a mechanism related to degraded collagen. Series of mitogen-activated protein kinases activated induction of transcription factor activation protein (AP-1). Levels of procollagen I protein are decreased, whereas MMP-1 and MMP-2 activity are increased. In addition, the transcription factor, nuclear factor-xB (NF-xB), is activated by UV radiation, which stimulates neutrophil attraction bringing neutrophil collagenase (MMP-8) into the irradiation site to future aggravate matrix degradation. Both AP-1 and NF-xB are activated by ROS. Oxidative stress can also increase elastin messenger RNA levels in dermal fibroblasts providing a mechanism for the elastotic changes found in photoaged dermis. UVA can induce lipid peroxidation in membranes that can lead to altered membrane fluidity. The DNA in mitochondria can also be altered by oxidative stress.

During the evolution the human organisms create different protective adaptation mechanisms to cope with the adverse effects on solar UV irradiation.

At tissue level, the tanning-response is probably the most beloved effect of UV rays. Augmented pigmentation, due to the increased melanin release and synthesis by melanocytes following UV irradiation, eventuate in increased protection by formation of an UV absorbing cap around the nucleus of keratinocytes. UVB and UVA exposure increases mainly epidermal but also dermal mitotic activity. Increased proliferation, and also differentiation, increases the thickness of the epidermis, resulting in an extension of the light path. Consequently, there is a decreased transmission of UV radiation to the vulnerable cells of the basal and suprabasal layers.

The keratinocytes themselves have a few protection mechanisms at their disposal. UV-induced DNA-damage will specifically be removed by nucleotide excision repair. Here we can distinguish a very fast transcription coupled repair and a slower global genomic repair mechanism. Although the main protein players of these repair systems differ, the lesions will be removed via the same differential steps in both mechanisms. After recognition of the lesion, in global genomic nucleotide excision repair by the xeroderma pigmentosum group C protein and in transcription coupled nucleotide excision repair by blockage of RNA polymerase, nucleotide excision repair pro-
teins are unraveled yet. Switch to apoptosis, from a certain level of damage, is not
lates survival (via growth arrest and repair) and the
IL-12 may clarify its immunostimulatory effect21,22.
DNA-damage is an important trigger for UV-induced
immunosuppression, the removal of DNA-damage via
DNA-damage via IL-12 may clarify its immunostimulatory effect21,22.

The precise molecular mechanisms of a cell that regu-
lates survival (via growth arrest and repair) and the
switch to apoptosis, from a certain level of damage, is not
unraveled yet.

**Photoprotection**

Sun avoidance is obviously the most efficient way of
photoprotection, however not always practical and some-
times not possible.

**Sunscreens**

Sunscreens are commonly used as protection against
sun damage, in the form of topical preparations that re-
duce the penetration of damaging solar UV wavelengths
in skin by reflecting or absorbing them. When sunscreen
is applied on the skin, special molecules called UV filters,
cut down the amount of UV radiation that can penetrate
the skin. These filters penetrate into the skin below the
surface of the epidermis, the outermost layer of skin,
leaving the body vulnerable to UV radiation.

Sunscreens are generally qualified with a sun protec-
tion factor (SPF), defined as the minimal erythema dose
(MED) of protected skin divided by the MED of unpro-
tected skin25. Sunscreens reduced acute effects of UV
rays like erythema solare or sunburn. Recent studies
show that regular use of sunscreens can also protect
against the chronic UV effects, as it reduces the carci-
genic risk24, provides protection against immune suppres-
sion25 and prevents photoaging26.

Sunscreens are very valuable and should be part of
the first line defense against UV, although they have
their limitations. They have to be used properly to gain
the full effect (application a little while before UV expo-
sure, at frequent time points and in adequate amounts).

Sunscreens have to cope with the problem of photo-
inactivation, which is the degeneration of the UV-filter
due to exposure to UV rays resulting in the loss of ab-
sorbing capacity27–29. Reactive intermediates of photoun-
stable filter substances may come into direct contact
with the skin, where they may behave as photooxidants
or may also promote phototoxic or photoallergic contact
dermatitis29. Photostability of a sunscreen depends on
the filter used, but also on the presence of other UV-fil-
ters or the solvent.

**DNA repair enzymes**

Importance of adequate DNA repair of especially cy-
clobutane pyrimidine dimers (CPD) lesions considering
the cancer prone nature of cells with disrupted DNA30.

T4 endonuclease V is a bacterial DNA repair enzyme
which specifically recognizes CPD lesions in DNA and
initiates excision repair by cleaving CPD. Subsequently,
host cell enzymes remove the hanging lesion by exonu-
clease activity and refill the remaining gap using the op-
posite strand as a template. T4 endonuclease V, use as
topical treatment in a liposome crème, increases the rate
of repair of sunlight induced DNA-damage and reduced the inci-
dence of pre-malignant actinic keratosis and basal cell carci-
noma Treatment of patients with xeroderma pigmentosum with
T4 endonuclease V lowered the rate of development of skin
cancer31,32.

T4 endonuclease V is a bacterial DNA excision repair
enzyme that repairs cyclobutane pyrimidine dimers in
DNA. As a topical treatment, it removes cyclobutane py-
rimidine dimers in DNA in the epidermis of animals and
human beings33. Topical application of T4 endonuclease
V for 1 year decreased the rate of development of actinic
keratoses and basal cell carcinomas15,33.

Photolyase, a DNA repair enzyme, decreased UVB-in-
duced DNA damage cyclobutane pyrimidine dimers for-
formation by 40% to 45% in human skin when applied im-
idately after UVB exposure35, resulting in prevention
of immunosuppression, erythema and sunburn for-
formation15.

DNA repair performed by photolyases occurs via a
mechanism known as ‘photoreactivation’ pointing to acti-
vation of the enzyme after capture of blue light (300–500
nm) photons. Photoreactivation results in partial repair
of cyclobutane pyrimidine dimers and an increased resis-
tance to UV irradiation. Photoreactivation might be ex-
pected to prevent sunburn and the appearance of skin
cancer. Topical application of photolyase encapsulated
into liposomes decreased the number of UV-induced thy-
midine dimers15.

**Antioxidants**

Antioxidants are molecules that reduce ROS in the
skin, which are generated by UV damage and lead to
breakdown of collagen. The predominant antioxidants in
skin are vitamin C and E. They neutralize reactive oxy-
gen species before these can produce oxidative stress. Al-
though the amount of vitamins, originating from nutri-
tion, delivered to skin is limited, it appears to be possible
to achieve a higher level of photoprotection by using topi-
cal vitamins36. Antioxidants have been administered or-
ally and topically for photoprotection in combination with
sunscreens to enhance efficacy. Tocopherol (vitamin E)
and ascorbate (vitamin C) reduce erythema, and sun-

259
burn cell formation. Vitamin E also reduces chronic UVB-induced photodamage and photocarcinogenesis. Their no correlation was found between epidermal content of vitamin E and MED, repeated ingestion of a combination of tocopherol and ascorbate increased the threshold for erythema induction significantly. Topical vitamin C has shown to protect the skin from UV damage caused by prolonged sun exposure by reducing the amount of free radical formation and/or sunburn cells. Exposure to UV light has also shown to decrease the naturally occurring vitamin C levels in the skin, thus topical application of vitamin C restores these photoprotectant levels. Other studies also suggest that vitamin C may play a part in the collagen biosynthetic pathway by active collagen metabolism and dermal synthesis of elastic fibres. Topical vitamin C 5% cream applied for six months led to clinical improvement in the appearance of photoaged skin with regard to firmness, smoothness, and dryness compared to vehicle. Topical vitamin C stimulates the collagen-producing activity of the dermis.

Polyphenols

Polyphenols, such as flavonoids, are efficient antioxidants due to the presence of hydroxyl groups. However, those hydroxyl groups bring about a pronounced first pass effect with a low bioavailability of free flavonoids as a consequence. According to recent data, the absorption of flavonoids might be better then originally believed. Green tea polyphenols exhibit anti-inflammatory activity, causing inhibition of UV-induced skin erythema, edema, and a decrease in the number of sunburn cells. Epigallocatechin-3-gallate (EGCG) is the main polyphenol in green tea and was found to induce differential effects between tumor cells and normal cells. EGCG was reported to induce differentiation and proliferation in epidermal keratinocytes. Topical application and oral administration resulted in a strong inhibition of the sunburn response and a reduction in sunburn cell formation. EGCG inhibits UVB induced erythema, edema, depletion of the antioxidant enzyme system, IL-10 and IL-12 production and skin carcinogenesis. Effects on photocarcinogenesis include a decrease in tumor burden, inhibition on the formation and size of malignant and non-malignant tumors and tumor regression in mice with established tumors. Effects of green tea polyphenols in photoaging include the inhibition of UVB induced expression of matrix metalloproteinases and reduction of UVB-induced collagen cross-linking.

Genistein is a soybean isoflavone with a wide range of antioxidant and anticarcinogenic effects in skin. It is a potent antioxidant and phytoestrogen presented also in ginko biloba extract, oregano, and sage. Clinical studies indicate that genistein has antiphotocarcinogenic and antiphotoaging effects for both UVA and UVB. Genistein blocks UVB-induced sunburns in humans as well as psoralen-UV (PUVA) induced molecular damage in mice. In addition, when applied after UVB exposure, genistein provides significant comfort and slightly reduces erythema or sunburn. Genistein also had a powerful potential to reduce the inflammatory edema reaction and suppressed contact hypersensitivity induced by moderate doses of solar stimulated UV radiation. Recent study has demonstrated that genistein potently minimizes the detrimental effects of UVB irradiation in human skin by preserving cutaneous proliferation and repair mechanisms, inhibition of oxidative and photodynamic damage to DNA.

Results indicate that flavonoids are promising candidates for cancer prevention, and in that matter they might be successful photoprotectants.

The plant extract Polypodium leucotomos (PLE) is fairly complex. PLE acts as a scavenger to mop up free radicals and reactive oxygen species (ROS), particularly superoxide anions. PLE inhibits the depletion of Langerhans cells and reduces the number of sunburn cells. PLE protects DNA by inhibiting the formation of cyclobutane pyrimidine dimers induced by UVB radiation. PLE preserves skin tissue structure by inhibiting the infiltration of mast cells into skin which leads to inhibition redness, inflammation and itching.

It should be considered as another layer of protection and used in conjunction with a good sunscreen and protective clothing.

PLE can also be used as a chemoprotector against PUVA-induced skin phototoxicity. Extensive PUVA treatment results in premature aging changes in the skin and can increase the chance of skin cancer. Fair skinned individuals or those with previous sun or radiation damage are most at risk. In clinical trials, PLE has proven to be the first oral agent effective in reducing the harmful side effects of PUVA treatment.

Polypodium leucotomos blocked the deleterious effect of UV irradiation both in vivo and in vitro. The molecular basis of photoprotection relies on its ability to inhibit free radical generation, prevent photodecomposition of both endogenous photoprotective molecules and DNA, and prevent UV-induced cell death. Its complete loss of toxicity combined with its multifactor protection makes it a valuable tool not only for direct photoprotection, but also as an efficacious adjuvant to phototherapy of various skin diseases.

Conclusion

In the past, carcinogenesis of the skin was mainly attributed to UVB radiation and the most sun-protection measures were geared toward blocking UVB rays. The
recently research has revealed the importance of UVA exposure in skin cancer and premature photoaging\(^7\). UVA is just as dangerous as UVB, and new developments are focused on UVA protection, immune protection, and public awareness\(^8\). The main topic of this review is to mention new or alternative ways of photoprotection.

UV exposure causes immunosuppression via multiple mechanisms in the skin including via urocanic acid. Any exposure to the sun disables the immune system’s ability to fight skin cancer. The DNA mutations formed during childhood tanning or burning may cause skin cancers in adulthood, especially with more and more sun exposure. Products with immune protection factor contain DNA-repair enzymes and antioxidants that may reduce mutations and enable the immune system to combat photodamage. Topical treatment with repair enzymes may be a promising avenue for after sun protection of UV-irradiated skin. If topical immune protection factors prove to be safe but only moderately effective, systemic medications targeted at immunomodulation of the skin and immunity-driven technology will be a future direction in skin cancer prevention and treatment.

The use of antioxidants both orally and topically, as preliminary studies demonstrate may exert an anti-aging effect by preventing and even reversing sun damage.

Adequate photoprotection is essential to control photocarcinogenesis and photoaging.

**REFERENCES**


I. Sjerobabski Masnec

Department of Dermatovenerology, University Hospital «Sestre milosrdnice», Vinogradska 29, Zagreb, Croatia
e-mail: ines@kbsm.hr
NOVE MOGUĆNOSTI FOTOPROTEKCIJE

SAŽETAK