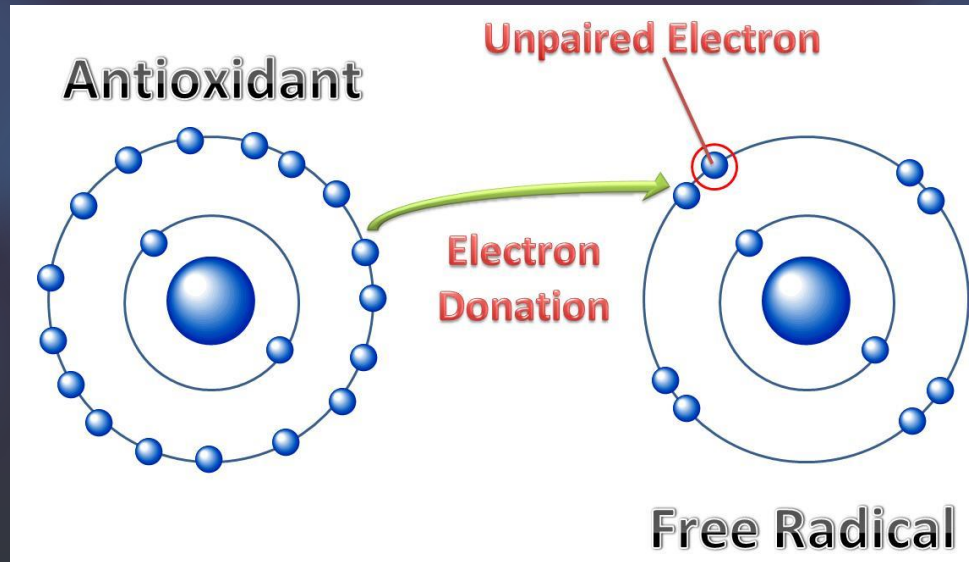




ANTIOXIDANTS IN DERMATOLOGY

INTRODUCTION



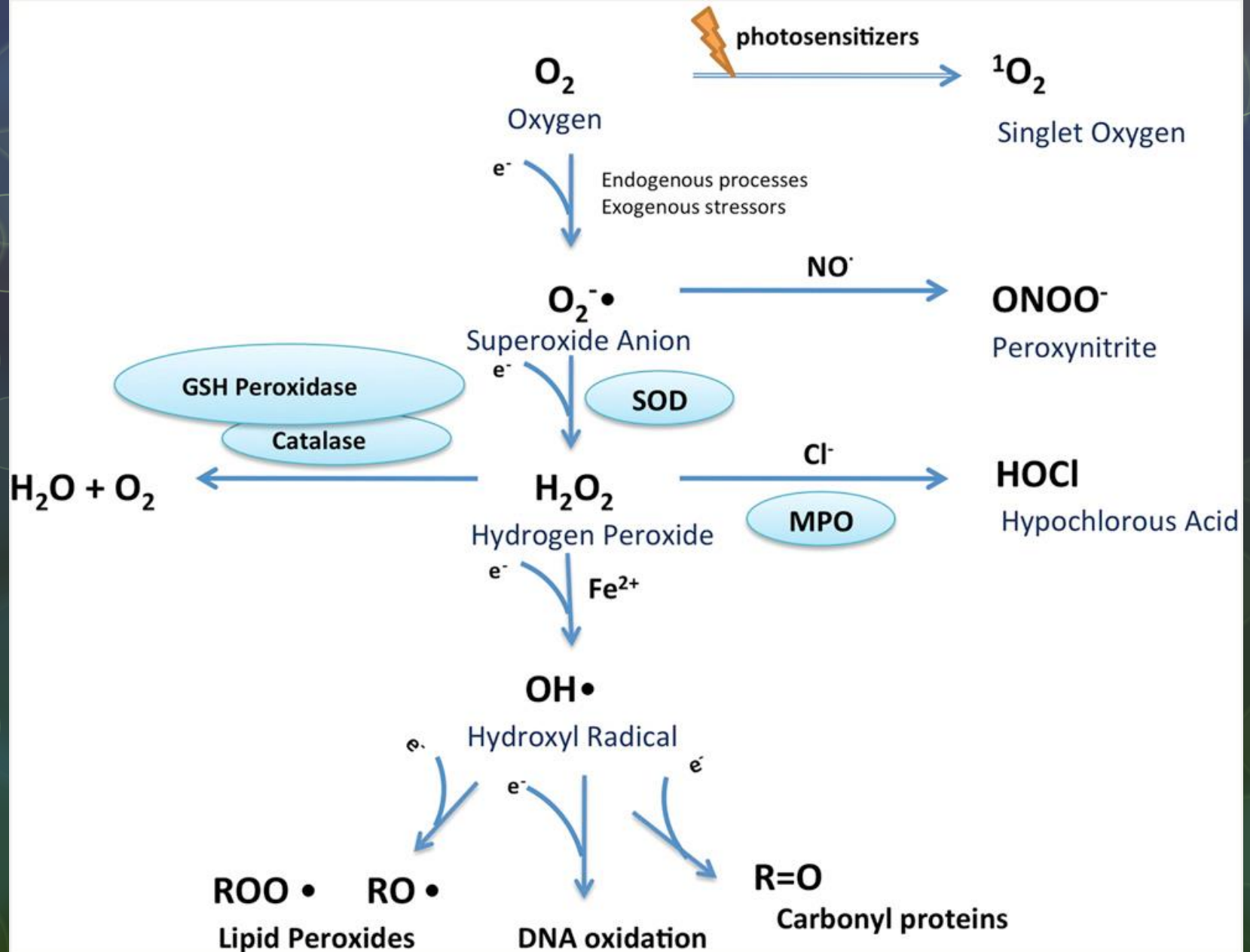
Antioxidants are natural Compounds that helps protect the body from harmful free radicals.

FREE RADICALS



- A free radical is defined as a species that can exist independently with one or more unpaired electrons.
- The most common oxygen-based ROS are
 - Superoxide anion O_2^- •
 - Peroxide
 - Hydroxyl radical $OH\bullet$
 - Hydroxyl ion
 - Singlet oxygen 1O_2
- In biological systems, ROS add electrons (oxidize) to other nearby molecules to release the extra energy and return to stable states. When not quenched by antioxidants, the oxidation reactions can continue, unravel into cascades with damaging consequences.

GENERATION OF REACTIVE OXYGEN SPECIES



ENDOGENOUS ROS

- Byproduct of oxidative metabolism in the mitochondria where adenosine triphosphate (ATP) is generated from glucose. As a side reaction, molecular oxygen is converted to O_2^- , a volatile and potent ROS.
- Xanthine oxidase for the degradation of purine nucleotides.
- Nitric oxide synthase for the production of nitric oxide.

EXOGENOUS ROS

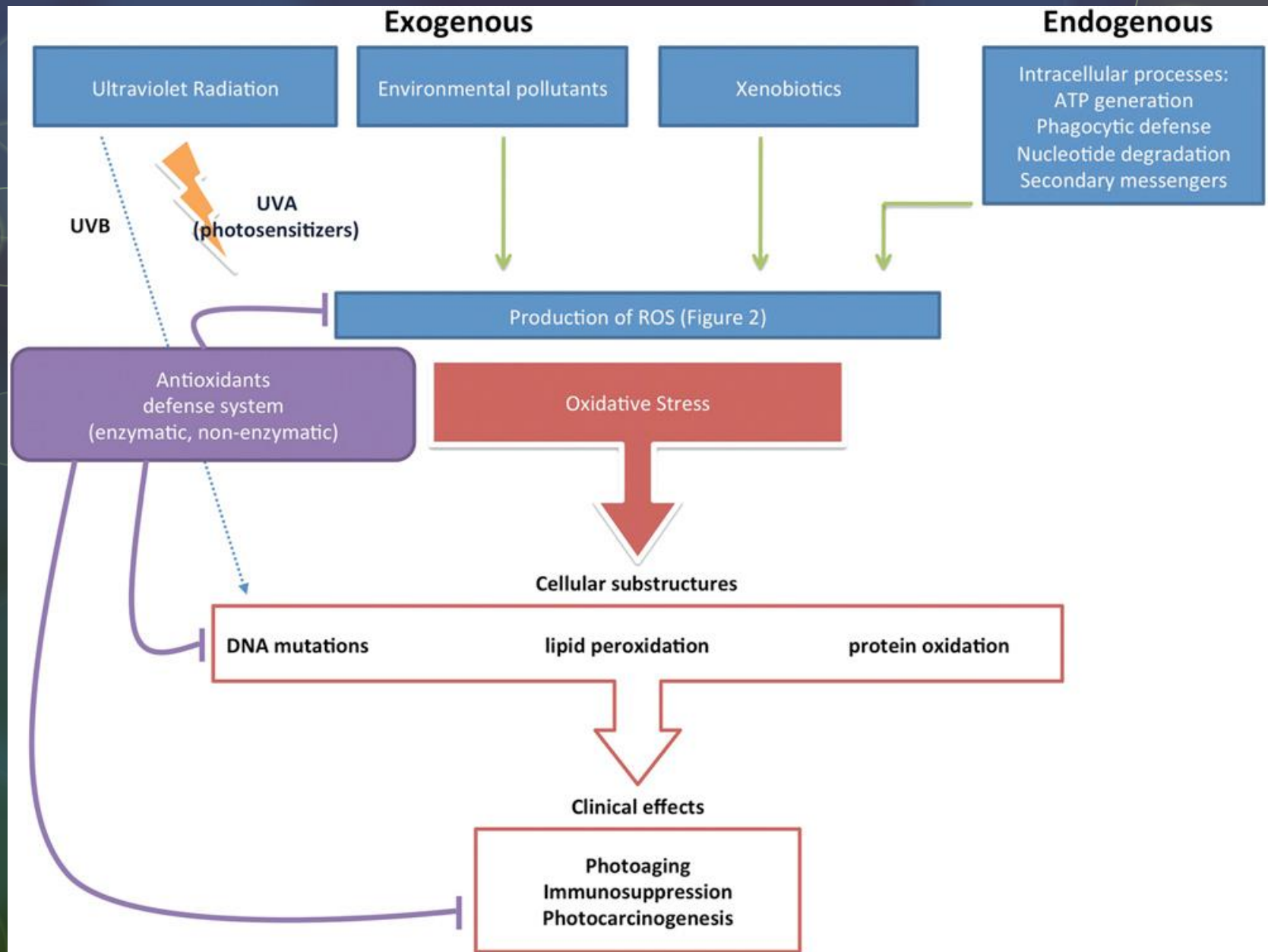
- Environmental sources - UVR, pollutants, and xenobiotics.
- Measurable levels of H_2O_2 and $\text{OH}^\bullet$ occur within 15 minutes after UV exposure and continue for up to 60 minutes.
- The action spectrum for ROS generation is predominately in the UVA range (320-400 nm).
- UVA reacts with photosensitizers or chromophores in the skin, such as cytochromes, riboflavin, heme, and porphyrin. These chromophores absorb the energy from the UVA wavelength and transition into an excited, unstable state. The energy expelled upon return to the stable state is transferred to nearby oxygen molecules to generate $^1\text{O}_2$ and other ROS
- Collectively, these ROS can cause nonspecific cellular damage to DNA, protein, and lipid structures
- UVC radiation (100 to 290 nm) is almost completely absorbed by the ozone layer and does not affect the skin. UVB (290 to 320 nm) affects the superficial layer of the skin (epidermis) and causes sunburns.

CELLULAR DAMAGE FROM FREE RADICALS

- UVA acts by ROS intermediates.
- ROS-induced DNA damages can lead to the formation of a modified guanine nucleotide (8-hydroxyguanine), single-stranded breaks, and oxidized pyrimidine bases.
- Incorporation of 8-hydroxyguanine into DNA strands has been implicated in tumor promotion, suggesting that permanent DNA damage leads to mutagenesis and carcinogenesis.
- In addition to nuclear DNA, the common deletion (4977-base pair mitochondrial DNA deletion), is prevalent in human skin irradiated with UVA. The mechanism has been attributed to the generation of $^1\text{O}_2$.

- Cellular phospholipid membranes and proteins are also targeted.
- Lipid peroxidation is initiated by an unstable $\text{OH}^\bullet$ that abstracts a hydrogen atom from nearby unsaturated fatty acid. This forms lipid molecules with extra electrons, which form peroxy radicals in the presence of molecular oxygen.
- If not quickly terminated, a chain reaction can occur, wreaking havoc on neighbouring lipids and disintegrating the cell membrane.
- Oxidative damage at the protein level is reflected in modification of the polypeptide chain to form carbonyl derivatives.
- Protein oxidation products appear to accumulate and persist preferentially in the dermis.
- As DNA, lipid, and protein damages accrue in a cell undergoing oxidative stress, events can potentially spiral toward apoptosis.
- The role of $^1\text{O}_2$ and $\text{O}_2^{\cdot -}$ in apoptosis has been demonstrated in cell culture studies

CELLULAR AND CLINICAL EFFECTS OF REACTIVE OXYGEN SPECIES



CUTANEOUS DAMAGE FROM FREE RADICALS



PHOTOAGEING

- The exposure of human skin to environmental and artificial UVR has increased significantly in the last 50 years.
 - increased solar UVR as a consequence of the stratospheric ozone depletion
 - use of sunscreens, false believe of being well protected while exposed to sun for longer time,
 - outdoor leisure activities
 - and prolonged life expectancy in industrialized countries
- After UV exposure, ROS trigger the release of proinflammatory cytokines and growth factors. Specifically, factors activation protein- 1 (AP-1) and nuclear factor-B (NF-kB) up-regulate key matrix metalloproteinases (MMP) such as MMP- 1 (collagenase), MMP-3 (stromelysin 1), MMP-8 (neutrophil collagenase), and MMP-9 (gelatinase) which degrade collagen and elastin fibres of the extracellular matrix are degraded.
- Interestingly, MMP-1 expression is associated with the presence of mitochondrial DNA common deletion, reinforcing the possibility that ROS affects many points along this pathway.

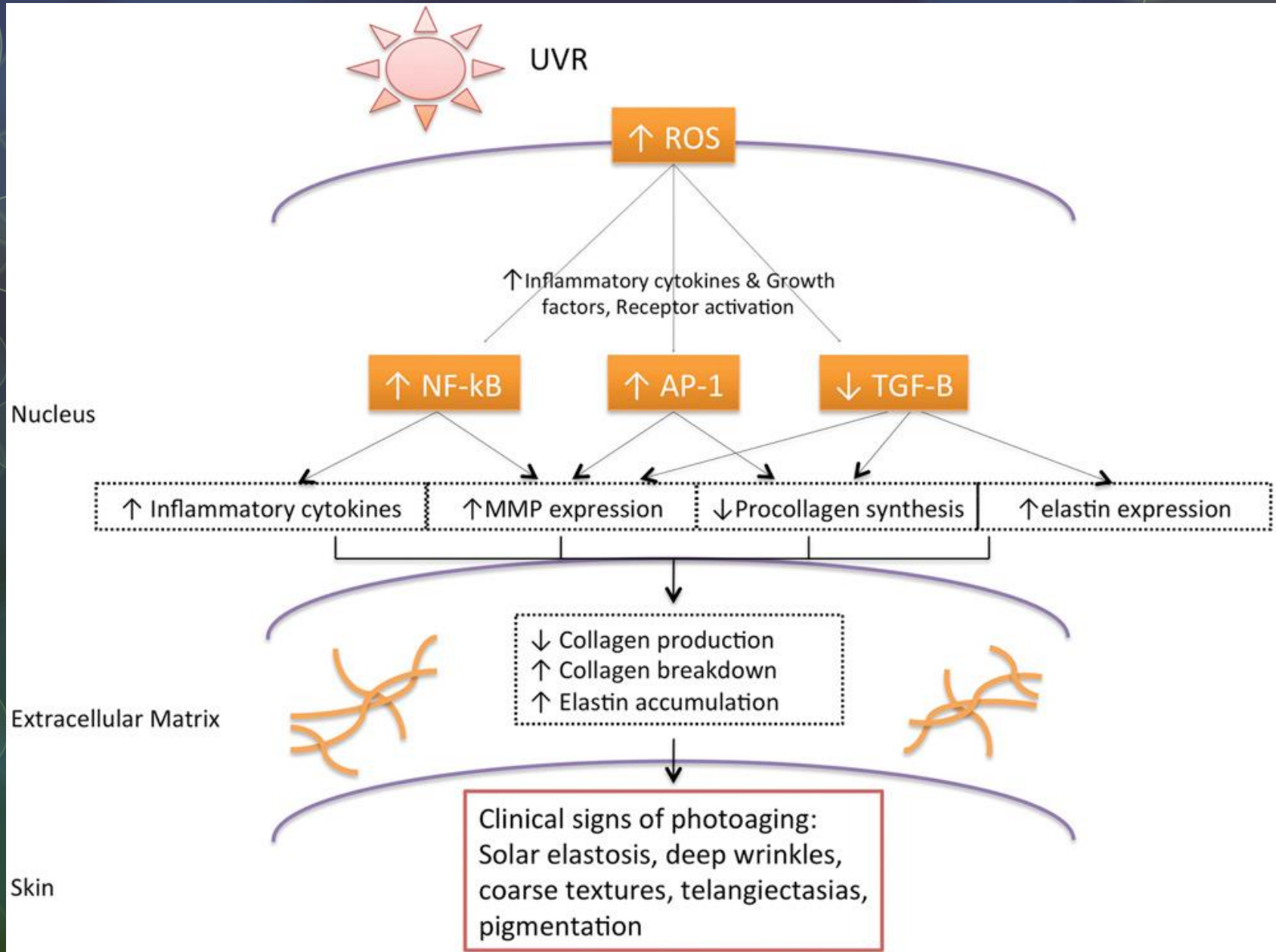
- Furthermore, UVR-induced ROS have been shown to decrease transforming growth factor B expression, which decreases collagen production and enhances elastin production. Hence, the structural integrity of skin is degraded.
- Until recently, it has become evident that also infrared radiation (IR) could induce skin damage and contribute to the skin photoaging
- Molecular mechanisms of damaging effect of IR-A on the skin are attributed to induction of matrix metalloproteinase-1, as well as to generation of reactive oxygen species (ROS)



Anti-Oxidants

ARE they a SKIN CARE MIRACLE?
SHOULD they ACTUALLY HELP FIGHT AGING?

ROLE OF REACTIVE OXYGEN SPECIES IN PHOTOAGEING



PHOTOAGED SKIN

- Deep wrinkles, rough skin, loss of the skin tone, dryness, severe atrophy, telangiectasias, leathery appearance, solar elastosis, actinic purpura, precancerous lesions, skin cancer, and melanoma
- Mottled pigmentation (hypo/hyper)
- Vascular damage present

CHRONICALLY AGED SKIN

- Fine wrinkles, benign growths like seborrheic keratoses and angiomas
- No pigmentary changes
- No vascular damage

IMMUNOSUPPRESSION

UVA-induced ROS can lead to lipid peroxidation, disturb redox potential, initiate AP-1 and NF- κ B transcription, and eventually activate downstream cytokines (interleukin-4 and -10), which are responsible for systemic immunosuppression.

PHOTOCARCINOGENESIS

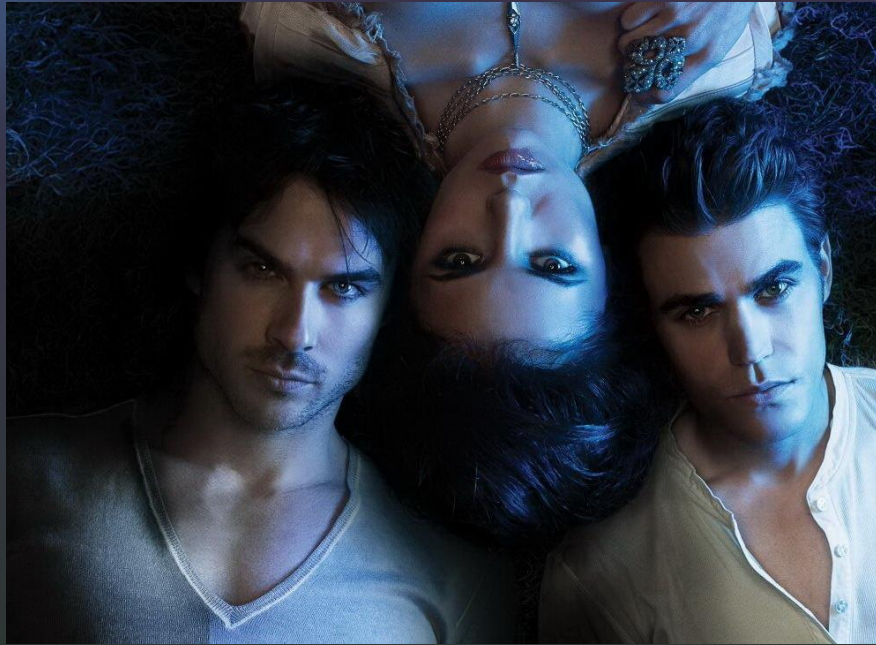
At the molecular level, it has been demonstrated that, ROS interfere with normal cell signaling by affecting expression of signal transduction genes. Aberrant AP-1 and NF- κ B pathways have been implicated in cell proliferation and apoptosis leading to carcinogenesis.

INFLAMMATORY SKIN CONDITIONS



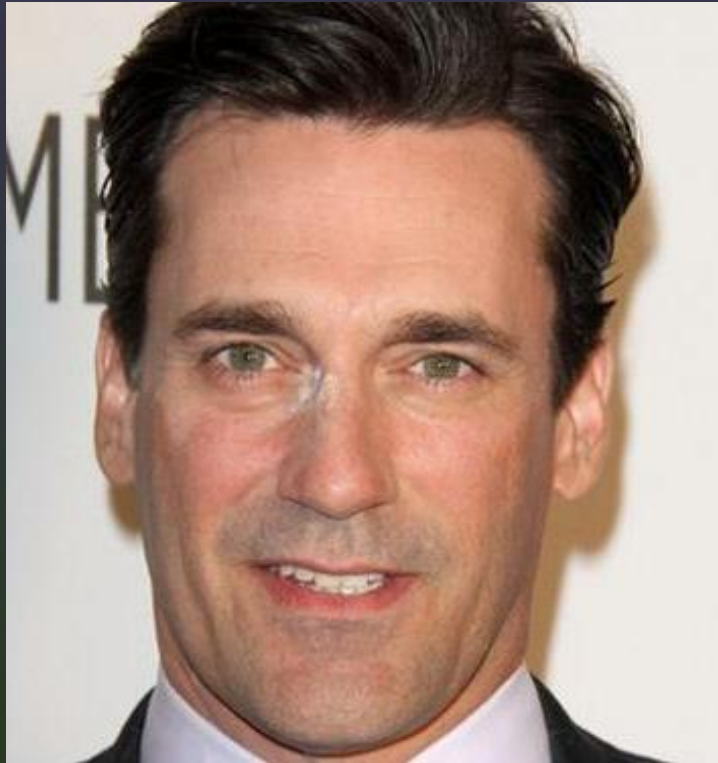
- Acne Vulgaris – ROS is responsible for follicular disruption and subsequent inflammatory changes
- Psoriasis and Behcet disease – predominant neutrophilic infiltrate responsible for generation of oxidative induced inflammatory cascade

PHOTODERMATOSES



- Melanin is the main chromophore in the epidermis absorbing photons with wavelengths from 350 to 1200 nm, however, the unabsorbed photons access other atoms and molecules and electromagnetic energy is transformed into chemical energy via oxygen atom dependant pathway producing reactive oxygen intermediates.
- Porphyrins have chemical similarities with chlorophyll.
EPP and PCT therefore, benefit from antioxidant therapies.

VITILIGO



ATOPIC DERMATITIS



WHAT ARE ANTIOXIDANTS AND WHAT DO THEY DO?



INNATE DEFENSE SYSTEM AGAINST FREE RADICALS

Non enzymatic antioxidants

- α -Tocopherol (vitamin E)
- Ascorbic acid (vitamin C)
- Glutathione
- Carotenoids
- Ubiquinone
- Flavonoids
- Uric acid

Enzymatic antioxidants

- Superoxide dismutase (SOD)
- Glutathione peroxidase
- Glutathione reductase
- Catalase

Ascorbic acid

- Water soluble antioxidant. Neutralizes free radicals in aqueous compartments of the skin.
- Stimulates the collagen-producing activity of the dermis
- In hairless mice studies, delayed skin tumor formation and hyperplasia induced by chronic exposure to UV radiation is seen. Also acts as a photo protectant when applied before exposure to ultraviolet (UV) radiation
- Reduces pigment darkening by inhibiting tyrosinase and maintains hydration by protecting the epidermal barrier of the skin
- Regeneration vitamin E
- Citrus fruits, black currants, leafy green vegetables, and red peppers
- Clinical benefits – photodermatoses, post laser erythema, melasma, stretch marks, anti inflammatory

Vitamin E

- RDA – 0.8 mg / g of EFA
- Therapeutic dose – 100-400 mg
- Lipid-soluble
- Exists as 8 major compounds (4 tocopherols and 4 tocotrienols)
 a-tocopherol is most abundant (s. corneum, sebum)
- Main function is to protect the cell membranes from oxidative stress.
- Reduction in lipid peroxidation
- Complements the photo protective effects of other antioxidants in the skin
- Skin barrier-stabilizing properties
- Fresh vegetables, vegetable oils, cereals, nuts, meats
- Cannot be synthesized by humans
- Clinical benefits – photoaging, anti inflammatory, anti carcinogenic, wound healing

Vitamin A

- RDA 5000 IU
- Prophylactic dose – 2,00,000 IU every 6months
- Therapeutic dose – 30,000 IU / day neonates
50,000 IU / day children and adults

The carotenoids (Lycopene, carotene, β -carotene, and carotenoid mix) - scavenge $^1\text{O}_2$ and quench lipid peroxidation. Upon UV irradiation, the concentrations of human skin carotenoids, β -carotene and lycopene, are markedly reduced. Supplements or a carotenoid-rich diet decreases wrinkles, sensitivity against UV-induced erythema

- Retinol and its forms (tretinoin, isotretinoin, and tazarotene) - antiaging properties.

The mechanism of action of these molecules is to bind to the nuclear receptors, retinoic acid receptors, and retinoid X, which will inhibit AP-1 and MMP-1 expression. The benefits are increased collagen production and increasing epidermal thickness.

- Red fruits and vegetables – carrot, sweet potato, tomato, pink grape fruit

Coenzyme Q10 (CoQ10)

- Fat soluble, present as a part of ETC
- Protects against oxidative stress-induced cell death
- Reduces UVA-induced **MMPs**
- Prevents **photoaging, photocarcinogenesis**
- Fish, shell fish

Glutathione

- Photoprotective agent

Zinc

- Prevents UV induced damage to fibroblasts



Resveratrol

- Prevents UVB-induced increase in skin thickness and the development of the skin edema (lab)
- Inhibits UV-B induced activation of NF-kB pathway
- Grape skins, peanuts, and red wine

Green tea (*Camellia sinensis*)

- Polyphenols (flavanols or catechins) reduce UV light-induced oxidative stress and immunosuppression
- Inhibits chemical carcinogen- or UV radiation-induced skin carcinogenesis (lab)
- Inhibits UV-B induced erythema, edema, depletion of antioxidant enzyme system, expression of MMPs

Sylimarin

- Prevents both photocarcinogenesis and skin tumor promotion (lab)
- Milk thistle plant, *Silybum marianum*

Cocoa

- Dietary flavanols from cocoa contribute to endogenous photoprotection and improve dermal blood circulation
- Photoprotection against UV-induced erythema

Soybeans

(isoflavone – genistein, diadzein)

- Scavange ROS
- Anti inflammatory, Anti carcinogenic



"Yes, it looks like a candy bar, however it's actually estate chocolate of the highest quality, and it's loaded with antioxidants."

ADVERSE EFFECTS

- Rare
- Allergic contact dermatitis, contact urticaria, and erythema multiforme like reaction.
- Slight risk of bleeding because of the inhibitory effect that oral vitamin E has on platelet aggregation and adhesion. The data are somewhat conflicting, but one should at least avoid the combined use of anticoagulants and vitamin E.

THE PARADOX

- Antioxidants as pro- oxidants
- Antioxidants itself may be oxidised and oxidative intermediate is formed.
- Vit C, freulic acid, trolox





KEEP
CALM
AND
EAT
CHOCOLATE

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