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Chapter

Skin Aging: Implications of UV Radiation, Reactive Oxygen Species and Natural Antioxidants

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Abstract

Skin aging is an inescapable phenomenon that leads to a functional decline of the skin along with emergence of characteristics features such as coarse skin, wrinkles, loss of elasticity and an overall aged appearance. While chronological aging is inevitable occurring with time, photoaging is contributed by Ultraviolet radiation and reactive oxygen species principally which can boost the skin aging process. These processes can however be ameliorated with the help of treatment strategies, one of them being supplementation with antioxidants. This chapter summarizes diverse mechanisms underlying skin aging with regards to Ultraviolet radiation and reactive oxygen species along with role of antioxidants in impeding these processes. Further, it provides a glimpse towards possible future explorations and challenges dominating the field of skin aging.

Keywords: Skin aging, Chronological aging, Photoaging, Ultraviolet Radiation, Reactive Oxygen Species, Antioxidants

1. Introduction

It is common for an individual to aspire a young-looking healthy skin. Nowadays, skin care routines have become an integral part of people's lives belonging to different age groups. People have come to realize it as an essential investment for maintaining a flourishing skin free of aging cues and skin related ailments. But since aging does occur over time, the signs can be coped with by regular care and practicing a conscious approach towards acknowledging skin aging [1].

People grow old with advancing age. As a result of this, the skin also shows aging indications. This phenomenon, where skin aging occurs over time refers to chronological aging. However, these very people are also exposed to external factors that they encounter in the environment. Aging prompted due to these external factors is known as extrinsic aging. If the external factor is Ultraviolet radiation (UVR), then resulting aging process is called photoaging. Thin parched skin and fine wrinkles generally occur during chronological aging. In contrast, photoaged skin is characterized by thickened epidermis and coarse wrinkles [2]. These skins have uneven pigmentation and often show presence of lentigines and freckles [3]. Although underlying routes

for both the aging processes differ, but many overlaps can exist. The fundamental reason behind this is that while people experience certain stage of chronological aging, they also undergo photoaging due to exposure to some amount of UVR on daily basis [4].

The focus of this book chapter is to discuss the importance of studies related to aging especially photoaging, their various underlying mechanism, role of antioxidants in ameliorating the aging signs along with recent advances and challenges associated with skin aging.

2. Significance of photoaging studies

The concept of aging has piqued the curiosity of many people from generation to generation and as a result, huge advances have been made. Among the various scopes of the particular field, recently, the phenomenon of photoaging has grabbed the limelight not only because of limited knowledge about underlying mechanism but also because of connection with associated pathways in other skin related diseases. Possession of a healthy skin has now become of utmost value not only for esthetic reasons but also due to its functional relevance. Simply put, it is like a mirror reflecting our overall health. But for this, the general public needs to have adequate awareness about photoaging, skin cancer and other related skin diseases especially those which are influenced by UVR. In the past, immense amount of research has been performed which have established skin type and UVR exposure as prominent risk factors associated with photoaging and skin cancer development. However, despite such crucial advances, a suitable and effective treatment has been lacking.

3. Role of ultraviolet radiation

The demonization of UVR has occurred due to several investigations conforming its deadly role in eliciting different skin cancers. Consequently, it has been declared as a 'Type I carcinogen' by International Agency for Research on Cancer (IARC). Particularly of concern include UV-A and UV-B radiations. Major contribution of these radiations results in formation of photolesions such as cyclo-butane pyrimidine dimers (CPDs), (6–4) photoproducts (6–4 PPs) together with Dewar isomers through direct or indirect mechanisms [5]. CPDs generally stop advancement of cell cycle by activating the repair machinery whilst 6–4 PPs can prevent apoptosis from occurring [6]. UV-B halts maximum cells in S phase of cell cycle and triggers both p95 and p53. This does not seem to take place for UV-A which halts the cell cycle at S phase only for a limited time. Thus, lesions arising considering UV-A have a higher potential of causing mutation due to lack of active p53 which is vital for stimulating XPC, GADD45 and p48 that are required in turn to induce the Nucleotide excision repair pathway [7, 8].

Moreover, UVR act to dissociate Helicase and DNA polymerase during replication in the S-phase of cell cycle. Consequently, although Helicase keeps on generating ssDNA regions, DNA polymerase stops on encountering a lesion. If a 6–4 PP formation occurs in these ssDNA regions it can both slow repair process while stimulating ATR-Chk-1 pathway. Given the benefits of activating this pathway, one problem still resides which is the elevation of mutation level. Thus, unchecked 6–4 PPs can promote existence of cells portraying higher mutation [9].

Formation of these UV induced photoproducts is not equally distributed throughout the genome, but depends on several factors. Formation of CPDs and 6–4 PPs rely upon nucleosome structure, nucleosomal DNA rotational setting, binding of proteins to transcription factor binding site, chromatin states and particularly certain hypersensitive sites [10]. Telomeres can function as an excellent example of hypersensitive sites prone to UVR. They portray several repeats of TTAGGG sequences and end in the single stranded form at the 3′ end. This end folds and forms a T-loop in assistance with proteins at the ending of a chromosomes thus inhibiting fusion with other chromosomes [11]. Formation and further accumulation of CPDs in such distinct sequences can be high due to near about absence of damage repair [12].

Another factor involves the differential penetration of UVR through the skin layers. As skin embodies numerous cells, so CPD formation could alter with cellular functions. This analysis can be proved as occurrence of 8-oxo dGua and CPD were observed more in fibroblast as compared to keratinocytes under UV-A irradiation. Explanation for this could be as of disparity in endogenous antioxidant activity and distribution of molecules that act as photosensitizers [13, 14]. UVRs particularly UV-B are also held accountable for strand breaks and inception of modified bases such as cytosine photohydrate, thymine glycol 5,6 dihydro thymine and 8-oxoguanine among others [15].

4. Role of reactive oxygen species

An eminent feature of UVR is rise of ROS and reactive nitrogen species. They can either constitute of free radicals or other molecules that are highly toxic or mutagenic to the cell. A free radical is an atom or molecule which contains unpaired electrons in its outer orbit. Due to this property some free radicals are highly unstable and react with other surrounding molecules. They snatch an electron via reacting with another molecule and convert them into a free radical. This free radical generated performs the same process thus initiating a string of events. Among the ROS present, the 'red alert' species include hydroxyl radical, hydrogen peroxide, singlet oxygen, nitric oxide radical and superoxide radical [16].

Main pit for ROS production is the mitochondria. Till now, ten sites have been claimed in mitochondria to form ROS. Multiple sites are either linked to Electron Transport Chain or the Kreb cycle. Complex I has two sites for superoxide formation 1) the Flavin in NADPH oxidizing site 2) the ubiquinone reducing site. Complex III has one site for superoxide production, the quinol oxidizing site. Certain enzymes also take part in ROS generation such as glycerol-3 phosphate dehydrogenase, 2-oxoglutarate dehydrogenase and xanthine oxidase [17]. ROS production inside the cell also results during endoplasmic reticulum (ER) stress. ER is of high priority as it controls protein folding, attachment of additional groups after translation and regulating protein trafficking, to name a few. ROS mediated protein-alterations converts them into displaying an unusual protein structure which can get deposited in the lumen of the organelle. Consequently, this could inhibit translation of mRNA into proteins to limit the damage [18].

ROS concentration is also modulated by pH. Conventionally, the pH in stratum corneum approximates around 4.5 [19]. This value increases and at subsequently deeper layers a pH of about 7.0 is established [20]. Maintenance of this pH gradient is crucial as for its participation in specific skin functions such as defense against

microbes, recovery from injuries and activities of various proteases. This balance is however impaired with aging especially in people eighty years old or above [21]. Imbalance in pH gradient has a detrimental effect on skin from both chronological and photoaging perspective as it influences the photosensitizers contributing to ROS levels. For example, many photosensitizers such as riboflavin, porphyrins, quinones among others comprising of a carbonyl group employ type II mechanism of photosensitization for ROS production wherein energy absorbed by them is transferred directly to a O2 molecule. From this reaction, rise singlet oxygen and superoxide anion [22]. Other sources for ROS generation include 3-hydroxypyridine, N-alkyl 3 hydroxy pyridine and their respective derivatives such as pyridoxine, pyridoxal, pyridoxamine including others. They catalyze reactions by following type I mechanism of photosensitization [23].

Significant contribution towards ROS generation is lent by NADPH oxidase. Irradiation with UV increases the Ca2+ ions concentration in the cell. This increase in the Ca2+ ions level triggers NADPH oxidase to generate ROS species apart from activating Protein kinase C which can phosphorylate Rho GPIα thus permitting Rac to migrate towards the plasma membrane where it could bind to Nox1, NoxO1 and NoxA1 complex. This binding results in stimulating Nox1. Interestingly, UV-A irradiation can produce ceramides in keratinocytes. The underlying mechanisms have not been figured out yet but it is hypothesized that ceramide could activate PI3K which stimulates Rac1 by guanine nucleotide exchange factor β-Pix [24, 25]. Furthermore, leukotriene B4 (LTB4) is also associated with lysophosphatidic acid stimulated ROS level elevation in keratinocytes. LTB4 is synthesized from arachidonic acid by action of several enzymes including 5-lipoxygenase (5-LO). It behaves as a ligand and binds to receptor BLT2 which is expressed ubiquitously in all cells. Moreover, elevation of expression of LTB4 and BLT-2 takes place in keratinocytes under UV-B. BLT-2 triggers ROS levels by activating Nox-1. This event is ensued by stimulation of p38/JNK pathway in keratinocytes [26].

Lipid peroxidation involves lipid molecules reacting with free radicals to produce lipid peroxyl radicals along with hydroperoxides. Other significant outcomes include hexanal, 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA). 4HNE exhibit electrophilic properties and thus react with nucleophiles such as lysine's amino group, imidazole group of histidine and sulfhydryl group of cysteine. Certain metal ions like iron are of significance as lipid hydroperoxides on interacting with transition metals can form lipid peroxyl radicals or lipid alkoxyl radicals [27]. Un-chelated iron produce hydroxyl radical from hydrogen peroxide which can help initiate the lipid peroxidation process [28]. Further irradiation with UV-A has pointed towards elevation of intracellular peroxide levels. Fatty acids, specifically arachidonic acid serve as prime target of these radicals [29, 30]. The iron driven fenton reaction generates hydroxyl radicals along with many lipid peroxides which through the JNK-2 pathway elevate various matrix metalloproteinases (MMPs) [31]. 4 HNE is responsible for elastin modification which could potentially lead to actinic elastosis. 4HNE and acrolein are deposited on elastin fibers which decreases elastin fiber digestion by the elastase released by leukocytes [32].

5. Matrix metalloproteinases: the ECM scissors

Cells are required to maintain a specific collagen turnover. This delicate balance is crucial for remodeling activities while preventing surplus collagen deposition [33].

However, this balance is threatened by numerous agents. Pathways exist for intra as well as extracellular collagen degradation. One of the means of extracellular degradation involve MMP activity.

MMPs come under the Matrixin subfamily which belongs to Zinc metalloprotease family. They play a vital role in tissue reconstruction, cell migration, carcinogenesis, damage recovery and photoaging [34]. Since MMPs function to degrade ECM, their activities are heavily scrutinized by a cell [35]. MMP functioning can be inhibited by α-microglobulin as well as Tissue inhibitor of metalloproteinases (TIMPs). Further, many MMPs are produced as inactivated proenzymes [36]. UV triggered AP-1 expression tends to elevate MMP-1, MMP-3 and MMP-9 levels. Production of activated MMP-9 from human keratinocyte along with MMP-2 can digest type IV collagen found in the basement membrane. Further, they can also digest type V and VII collagen together with elastin [37]. MMP-1 can digest type I collagen which results in cell migration and damage recovery. MMP 14 (membrane bound MMP) can interact with TIMP-2 and pro-MMP-2 resulting in its activation [38]. Certain amount of collagen digestion also occurs due to MMP-8 released from neutrophiles [39]. Human macrophage elastase or MMP-12 acts on elastin fibers after which the degraded products accumulate in the epidermal layer resulting in solar elastosis and keratosis, the distinguishing features of photoaging [40].

6. Signaling routes: manipulation by UVR and ROS

UV induced cell signaling is ligand independent. Therefore, how the cell perceives UVR is still not well defined. A particular study has revealed that Opsin-3 expressed by dermal fibroblast might help sense UVRs. Opsin comes under the GPCR family of receptors. Upon activation they lead to increase in intracellular calcium ion levels which further activate CAMKII. Activated CAMKII can in turn phosphorylate ERK, JNK, p38 and CREB. This event is ensued by rise of MMP-1, 2, 3 and 9 actions [41].

Initially studies conducted concentrated on activation via cytokine or growth factor receptor [42]. Epidermal growth factor receptor belongs to receptor tyrosine kinase (RTK). It is managed by protein tyrosine phosphatase (PTP). PTP bears a cysteine moiety in its active site which is originally employed for catalyzing a phosphohydrolase activity and ceasing the cell signaling cascade. This cysteine moiety can be targeted by ROS which would activate RTK for a prolonged period till ROS are dealt by cellular antioxidants [43]. Activation of receptors leads to recruitment of adaptor proteins for example Src homology-2 [SH2] domains and Src homology 3 domain [SH3]. SH2 interacts with phosphorylated tyrosine residue of the active RTK. SH3 in turn interacts with a phosphorylated proline residue on other targeted proteins. Through this they lead to stimulation of other downstream molecules [44]. Ras near the cell membrane is a guanine nucleotide binding protein that shuttles between GTP/GDP bound form. The GTP bound form interacts with and activates Raf [45]. Raf sequentially activates MAP kinase kinase/MEK via phosphorylation. This is ensued by origination of active ERK [46]. These MAPKs can interact with several proteins and activate them. Interactions are mostly formed with conserved landing sites on the substrate. Jun D has two domains, a D domain and DEF domain. D domain is bound and phosphorylated by JNK under stress while DEF domain is phosphorylated by ERK which is activated by growth factors binding to EGFR receptor [47]. In presence of UVR and/or hydrogen peroxide, overexpression of c-Fos/Jun D or Jun D alone could prevent apoptosis by lowering Caspase-3 levels. Expression of c-Fos plus Jun D

also activates AP-1. Transcription factor AP-1 is a dimer of basic region leucine zipper protein which may constitute of Jun [c-Jun, Jun B and Jun D] and Fos [c-Fos, Fos B, Fra-1 and Fra-2] subfamilies in the cell. This complex is further joined by proteins from ATF and JDP subfamilies [48, 49]. AP-1 and TGFβ/Smad signaling cascade control procollagen synthesis. TGFβ are cytokines that allow pro-collagen formation by binding to their receptors, TβRI and TβRII. Upon meeting of TGFβ with their receptors, Smad 2 and 3 are activated which complex with Smad 4 to form a heteromeric molecule. This complex enters nucleus and helps in transcription of TGFβ regulated genes. In contrast, AP-1 inhibits procollagen formation coupled by destruction of existing collagen fibers by upregulating MMPs [50]. Interestingly, effects of AP-1 are subject to participating dimer proteins. Theoretically, AP-1 can appear as 18 different homo and hetero dimer and this can influence its activity. It is hypothesized that this could be as of differential DNA binding along with different transcriptional activity. Furthermore, the differentiation status of cell also influences the properties of different AP-1 transcription factor forming proteins [51].

Besides this pathway, other cascades such as JNK and p38 MAPK Pathway are also stimulated. c-Jun NH2 terminal kinases [JNK] are activated upon receiving stress signals such as cytokines, ROS, and UVR. A specific stimulus activates the MAP3Ks. The MAP3K catalyze phosphorylation of MAP2K. MAP2K has two isoforms, MKK4 and MKK7. Active MKK4 and MKK7 interact and generate active JNK. Some of its targets comprise of nuclear proteins like AP-1, Elk-1 and c-Jun. p38 MAPK is stimulated under stress [52, 53]. p38 MAPK is switched on by upstream lying MKK3 and MKK6 kinases. If JNK pathway is initially active then MKK4 of the JNK pathway can activate p38 MAPK. Apart from this, p38 can also undergo auto-phosphorylation. p38 MAPK is noteworthy as of its high interactivity with multiple nuclear proteins along with protein kinases [54]. Although many investigations involving UVR and cell fate have taken place, there are still certain gaps. A molecular switch exits between p38 and p53 proteins. If damage due to UV radiation is less, the cell opts to repair and survive. Under this situation p38 and p53 are activated separately. p53 stimulates p21waf1/CIP which stops cell cycle from advancing ahead by regulating Cdc25A/B. This leads to arrest in G1/S and G2/M phase. But if cellular damage is too high then p38 phosphorylates p53 resulting in active p53 that initiates apoptosis [55].

Recently it was shown that p38 MAPK can stimulate HIF when keratinocytes are irradiated with UVR. p38 activates HIF-1 which in turn activates Noxa. Active Noxa catalyzes degradation of Mcl-1. Mcl-1 controls differentiation and survival of keratinocytes. Therefore, its degradation leads to apoptosis. This cascade might be affected by ROS as ROS can stimulate Ask/p38 MAPK pathway. Again, HIF-1 is also responsive towards redox status in the cell [56]. Secretion of cytokines like IL-8 can stimulate the three MAPK pathways. Its activation can turn on ATF-2 nuclear protein which induces elevated secretion of MMP-3 in fibroblast [57].

Since UVR amplifies ROS generation, a prime pathway activated under such conditions is the NFκB pathway. NFκB pathway activation leads to transcription of numerous genes coupled with immunological and inflammatory responses. NFκB family constitutes of 5 proteins that is p65 (Rel A), Rel B, c-Rel, p50 (NFκB 1) and p52 (NFκB 2). Stimulation of suitable receptors upon ligand binding activates IKK (IκB kinase). IKK constitutes of IKKα, IKKβ and IKKγ. The IKK molecule phosphorylates IκBα. After phosphorylation, IκBα is poly-ubiquitinylated at lysine moieties which marks it for degradation by proteasome. The resulting active NFκB is then transported to nucleus for transcription of specific genes. Some of the prime signaling events are illustrated in **Figure 1** [58, 59].

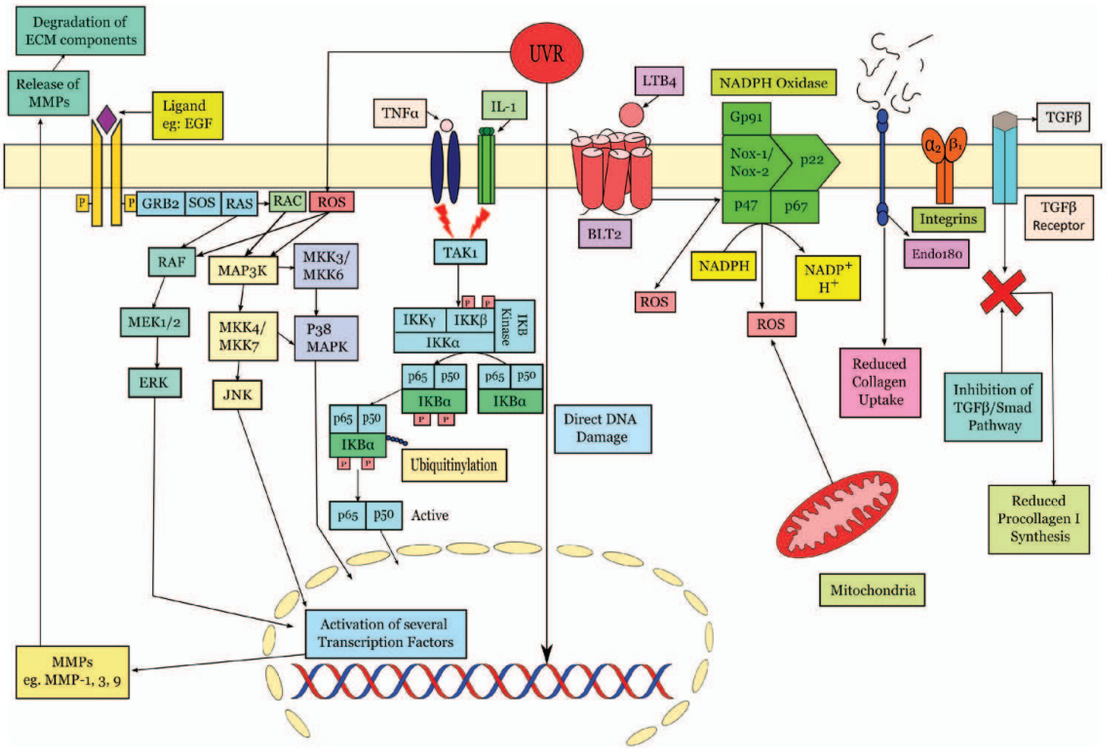

Figure 1.
Schematic diagram showing the important signaling pathways involved in Photoaging.

7. Effects of aging on extracellular matrix

ECM comprises of a network of numerous molecules and primarily functions to provide support to cells. It presents the cells with growth factors which in turn bind their respective receptors to influence response of the cells to various stimulus. Moreover, the matrix present around a cell also protects it from any possible mechanical injury [60, 61].

Depending upon specific function and anatomical position, ECM organization may differ. Exposure to UVR can adversely affect this particular organization. One instance involves the fragmentation of long collagen fibrils into short chains along with accumulation of unstructured elastin containing material which terminates in decreased skin durability [62]. Deposition of fragmented collagen fibrils can further result in decreased formation of type I procollagen [63]. Another effect UVR have is the production of MMPs that function as ECM scissors. Continued exposure to UVR results in elastin fiber injury which can terminate in wrinkle formation. In skin, elastin fibers are classified as oxytalan fibers, elaumin fibers and dermal elastin fibers depending upon their structure and position [64]. They form a network that is prone to elastase secreted from UV exposed fibroblasts and neutrophils. Fibroblast elastase can digest elaumin and oxytalan fibers while neutrophil elastase is able to digest all three elastin fibers which is crucial especially during inflammation and damage recovery. But since the numbers of neutrophils is low in dermis, major damage is contributed by fibroblast elastase which culminate in wrinkles [65, 66].

Another hallmark of photoaging involves decreased proteoglycan content [67]. Hyaluronan degradation in UV irradiated skin occurs due to increased HYBID protein activity. Large hyaluronan molecules bought inside the cell in clathrin coated vesicles

are broken down into smaller components and released into the external surrounding. These hyaluronan components act as inflammatory signals and can additionally lead to wrinkle formation [68].

ECM remodeling generally involves uptake of degraded collagen fibers inside fibroblasts via receptors like integrin α2β1 and Endo180 receptor. Endo180 receptor belongs to type I membrane protein occurring in the plasma membrane. It binds to type I, IV and V collagen to internalize them inside the cell. Few studies regarding endo180 receptor and photoaging have shown that cells exposed to UVR have low endo180 receptor expression which ultimately results in decreased internalization of collagen fragments. Additionally, IL-1α secretion from keratinocytes under UV exposure blocks endo180 receptor expression. Further investigations regarding endo180 receptor expression in photoaged skin are worth undertaking in the future [69, 70].

8. Natural antioxidants: role against aging

Role of antioxidants in quenching ROS has been appreciated for a long time. Recently, a 15 yearlong study showed that ROS formation could be lessened by 10% in people aged 45 or above by simply having an antioxidant rich diet [71].

Antioxidants are compounds that quench the free radicals by providing an electron and generating stable compounds that are less harmful to a cell. In this manner they inhibit the train of events that occur when free radicals oxidize other biomolecules. Antioxidants can be classified into different categories based on enzymatic/non-enzymatic activity, occurrence, solubility although other miscellaneous molecules displaying antioxidant properties have also been reported. Examples of certain regular antioxidants found in a cell involve Superoxide dismutase (SOD), Glutathione peroxidase (GPx) and Catalase (CAT). Non-enzymatic antioxidants include Vitamin E, C, thioredoxin, glutathione and melatonin. Further antioxidants such as minerals (Cu, Zn, Mn, Se), other vitamins, polyphenols and carotenoids are also derived from regular diet [72].

Usually, cells maintain a fine balance between ROS formation and their quenching by resident antioxidants. But, UVR shift the balance towards ROS formation resulting in a phenomenon called 'Oxidative stress', where resident antioxidants become incapable of quenching the high amount of ROS formed [73]. This state can however be circumvented by additional antioxidant supplementation. Drawbacks of synthetic antioxidants such as toxicity, low solubility, cost and a presumed negative outlook towards chemical products have increased the demand for natural antioxidants [74]. These antioxidants are naturally available in numerous sources like vegetables, fruits, spices, herbs, edible mushrooms among others [75]. Furthermore, beverages derived from these sources are also rich in antioxidants and have gained increased populace especially among younger generation.

Till date, several pure phytochemicals and plant-based compounds have been reported for their antioxidant and anti-photoaging activity. We have tried to summarize some important phytochemicals as potential antioxidant and anti-photoaging agents in **Tables 1** and **2**.

8.1 Beverages as source of antioxidants

Various beverages, specifically mixed juices have abundant antioxidants as they are made using various fruits and vegetables [86]. Other beverages like coffee and

Name of antioxidant molecule	Source of radiation	Main observations		Ref.
		Upregulation of	Downregulation of	
Neferine	UV-A UV-B	• SOD and GPx activities	• Wrinkle emergence • collagen destruction in dermis	[76]
Quercetin	Solar UV light system		• collagen breakdown • transcription factors such as AP-1 and NFκB • pERK, pJNK, pAkt and pSTAT3 levels • PKCδ and JAK2 activity	[77]
3,5-dicaffeoyl-epi-quinic acid	UV-B	• SOD-1, HO-1 antioxidant activity with pronounced Nrf-2 level manifestation	• production of ROS • TNF-α, COX-2, IL-6 and IL-1β levels	[78]
Ursolic acid	UV-B	• antioxidant activity of SOD-1, GPx, CAT and GSH • Bcl-2 levels inhibiting apoptosis	• ROS production and lipid peroxidation • Apoptosis by reducing Bax and caspase-3 levels • TNF-α activity and NFκB level • MMP-2 and MMP-9 activity	[79]
Decanal	UV-B	• cAMP and PKA Cα levels • mRNAs for *COL1A1, COL1A2, COL3A1* for collagen production • mRNA for hyaluronic acid synthase 2 required for hyaluronic acid production	• activated MAPKs such as p-ERK, p-JNK and p-P38 • AP-1 dimers that is p-c-Jun and p-c-Fos • mRNAs for MMP-1, MMP-3 and MMP-9	[80]

Table 1.
Pure phytochemicals and their anti-photoaging properties.

tea also include antioxidants and can help alleviate photoaging signs. Green tea is enriched in bioactive compounds like methyl-xanthins, flavon-3-ols and catechins such as (−)-epicatechin (EC), (−)-epicatechin-3-gallate (ECG), (−)-epigallocatechin (EGC) and (−)-epigallocatechin-3-gallate (EGCG). EGCG can inhibit erythema and neutrophil infiltration in the skin induced by UVR [87]. Drinking Green tea can ameliorate other photoaging markers like increased numbers of dermal cysts, sebaceous glands enlargement, vacuole formation and increased epidermal thickness. Green tea polyphenols are also elemental in decreasing MMP-2, 3, 7 and 9 levels along with reduced oxidation and carbonylation of proteins upregulated under UVR [88, 89]. Polyphenols and Chlorogenic acid found in coffee can help avoid free radical associated diseases. Reduction in pigmentation spots induced under UV was seen in Japanese women who consumed coffee at a higher rate [90]. *Coffee Arabica* leaf extracts are rich in caffeic acid, chlorogenic acid and phenols. These bioactive compounds help lower MMP-1, 3 and 9 expressions while elevating type I procollagen production. Further, a decrease p-ERK, p-JNK and p-p38 levels has also been shown thereby effectively blocking UV induced activation of key signaling pathways [91].

Name	Source of radiation	Main observations		Ref.
		Upregulation of	Downregulation of	
Melaleuca leucadendron L	UV-B	• antioxidant levels of SOD, CAT, GPx • number of cells present in G0/G1 phase	• ROS production • activated Caspase-3 action	[81]
Rosa multiflora Thunb	UV-B	• procollagen I production at both mRNA and protein levels	• ROS production • cytokines such as IL-6 and IL-8 • MMP-1 conc. at both mRNA and protein level • levels of p-ERK, p-JNK and p-P65 (NFκB protein)	[82]
Carica papaya	UV-B	• TGF-β cytokine levels required for collagen formation • mRNA levels for procollagen type I	• ROS production up to 60% • activated MAPKs such as p-ERK, p-JNK and p-P38 • AP-1 dimers that is p-c-Jun (44%) and p-c-Fos (89%) • MMP-1 and MMP-3 levels along with IL-6 levels	[83]
Dioscorea alata (purple sweet potato)	UV-B	• antioxidant levels of SOD, CAT and GSH-Px • Of hydroxyproline levels with diminished collagen breakdown	• ROS production and lipid peroxidation • activated MAPKs such as p-ERK, p-JNK, p-P38 levels and NFκB protein levels in nucleus • inflammation markers such as TNF-α and IL-6 • skin tissue associated changes occurring under UV	[84]
Nypa fruticans Wurmb	UV-B	• collagen content following elevated levels of COL1A mRNA levels	• ROS levels • MMP-1, MMP-8 and MMP-13 mRNA levels • p-JNK and p-P38 levels followed by diminished levels of active NFκB and AP-1 protein (p-c-Jun)	[85]

Table 2.
Plant-derived phytocompounds having antioxidant and anti-photoaging activity.

A diterpenoid, Atractyligenin found in Coffee silverskin has been shown to decrease ROS levels by 62% post UV treatment, modulate MMP-1, 2, 3 expressions, inhibit activation of MAPK pathways and increase Endo180 receptor expression [92].

8.2 Animal sources for derivation of antioxidants

Antioxidant peptides derived from *Pinctada fucata* protein have been shown to improve collagen fiber density by increasing hydroxyproline level besides inhibiting

lipid peroxidation [93]. Similar observations have also been observed with Oyster (*Crassostrea gigias*). Additionally, it could modulate AP-1 transcription factor, regulate MAPK signaling and consequently block MMP expression. It could also stimulate TGFβ/SMAD pathway enhancing collagen synthesis [94].

Usually, fish industries generate various waste products such as fish head, internal organs, scales and skin. But several investigations have shown that utilization of these resources for treatment of photoaged skin could be propitious especially in terms of waste management. One such example involves the use of gelatin polypeptides from COD fish (*Gadus microcephalus*) skin. The gelatin polypeptides contain key amino acids that are essential for collagen synthesis. They help elevate hydroxyproline level and collagen synthesis. Beside these, they are able to decrease MDA levels and improve antioxidant activities of SOD, CAT and GPx. In this way they help inhibit photoaging [95]. Similar results have also been observed for antioxidant collagen peptides obtained from Jellyfish umbrella and Silver carp (*Hypophthalmicthys molitrix*) skin [96, 97]. Tilapia (*Oreochromis niloticus*) gelatin peptides have been shown to possess hydroxyl radical scavenging property. This is crucial as hydroxyl radicals are prime ROS species that result in strong oxidative stress [98]. In a study, peptide from Tilapia gelatin hydroxylates was shown to reduce ROS levels and inhibit oxidative damage to DNA besides elevating antioxidant levels (SOD, GSH). More significantly, the peptide inhibited MMP 1 and MMP-9 expression along with regulating MAPK and NFκB pathways [99]. Similar results were also observed in another study where additionally the authors pointed out the role of C-terminus of peptide terminating with GLY-LEU in impeding MMP-1 activity [100].

8.3 Derivation of antioxidants from marine sources

Till now, different algal species have been utilized for numerous investigations aiming towards analysis of molecules effective against photoaging. *Tetraselmis suecica* microalgal extract was found to reduce MDA level while increasing SOD and GSH levels. Further, the extract could improve type I procollagen production and lower MMP-1 expression [101]. Fucoxanthin, a carotenoid found in *Undaria pinnatifida* inhibits wrinkle formation by blocking MMP-13 expression [102].

Recently, another compound known as Mycosporine like amino acid (MAA) has come into limelight. They consist of cyclic rings of aminohexenimine or aminocyclohexenone and can vary among themselves with respect to amino acids and groups attached to them [103]. They are mostly found in algal species belonging to orders Bangiales, Gracilariales, Ceramiales and Gigartinales where their prime function is to provide UV protection [104]. Production of MAA is affected by numerous factors like salt concentration, UV, amount and type of nutrient available among others [105, 106]. Recently, two MAA, Shinorine and Porphyra-334 were reported to prevent photoaging by reducing MDA levels upto ≈56% and restoring antioxidants like SOD, GSH-Px and CAT. Additionally, a reduction in NFκB, IL-1β and IL-6 was also found [107]. Porphyra-334 can further be helpful by increasing procollagen production and blocking UV induced MMP production [108]. In another study where human keratinocytes were treated with UVR, expression profiling along with functional network analysis portrayed that miRNAs regulated by porphyra-334 could modulate various genes associated with UV affected processes such as cell proliferation, apoptosis and translational elongation [109]. Another compound that has attracted the interest of many researchers is Scytonemin. It is found in polysaccharide sheath of cyanobacteria and like MAA functions as an UV protectant [105]. Like MAA, its production

is increased under photo-oxidative stress, elevated temperature osmotic stress and UVR. Recently, scytonemin from *Rivularia sp*. HKAR-4 was tested for analyzing its photoprotective function. Here, scytonemin successfully reduced intracellular ROS production along with thymine dimer formation [110]. In future it is expected that more such molecules will be revealed as research deepens in these areas with time.

9. Other compounds used for treatment of photoaged skin

Apart from use of antioxidants as the treatment strategy for photoaged skin, various other compounds are also used. Among these, Retinoids and alpha-hydroxy acids (AHA) hold a significant track record. Retinoids are Vitamin A derivatives that can be naturally occurring or synthetic. Dietary forms of Vitamin A, Retinol and retinyl esters undergo transformations by enzymes alcohol dehydrogenase and microsomal retinol dehydrogenase to yield Retinaldehyde. Retinaldehyde, in turn, is converted in to Retinoic acid by suitable retinaldehyde dehydrogenases. These retinoic acids show their effects via interacting with suitable intranuclear retinoic acid receptors (RARs) [111]. Among these, all-trans-retinoic acid (Tretinoin) serves as key retinoid for treatment of photoaged skin. However due to tendency of tretinoin to cause skin irritation, there has been a switch to more effective alternatives like Adapalene which is a synthetic retinoid [112]. Adapalene has been shown to be effective against photoaging, solar lentigines and actinic keratosis treatment. A recent study has compared the efficacy of Adapalene and Tretinoin for treatment of cutaneous photoaging. Through various experiments, it was established that Adapalene 0.3% was equally effective as Tretinoin 0.05% and thus could be employed as a future treatment for moderate photoaging [113].

While the first line approach for treatment mostly involves application of topical creams, the second line approach consists of use of chemical peels. This is where AHA play a crucial role. AHAs are a group of naturally available organic acids such as glycolic acid, lactic acid, critic acid, malic acid among others where hydroxyl groups (1 or more) are attached to alpha carbon atom that in turn is bonded to first carbon atom after acid group. AHAs are employed in peels for treatment of melasma, age spots, hyperpigmentation among others. But use of AHAs for treatment of skin photo damage is still controversial. Moreover, it has been reported that AHA function may depend on concentration as well as properties of the compound used [114]. A very recent study tested the efficacy of TCA- Lactic acid chemical peels for treatment of photoaging. It showed that the peels were able to inhibit tyrosinase, collagenase and elastase activity in in-vitro experiments. Further, an increased expression of COL1A, COL3B, elastin and fibronectin genes were shown to occur when peel solution was used for 3D human skin model [115]. Another study compared the efficacy of AHA-ReT cream (double conjugated retinoid cream) with 1% retinol cream and 0.025% Tretinoin cream for treatment of photoaging. Here, they found that AHA-ReT cream was more effective in reducing wrinkles, erythema and increasing hydration coupled with less irritation on application. Thus, such methods are expected to open new avenues in photo-damaged skin treatment [116].

10. Future perspective and challenges

Recently, role of cathepsins with respect to photoaging has been pursued to a greater extent. Cathepsins have important functions in ECM maintenance, apoptosis,

cell proliferation and differentiation among others. Thus, cells maintain a tight regulation of cathepsins that is hampered during the photoaging process. A study reported diminished levels of cathepsins B, D and K whereas cathepsin G was upregulated in the photoaged skin. Cathepsin G in turn could increase various MMP expression [117]. Such imbalance in cathepsin regulation can have strong adverse effects on the autophagy process. Several studies have shown that autophagosomes of photoaged cells display an upregulation of p62, downregulation of cathepsin L, limited degradation of LC3II protein and an unchanged expression of Beclin-1. All these changes hint towards the reduced lysosomal ability towards degradation of unwanted products [118].

Another area that has received abundant attention involves formation of advanced glycation end products (AGE). They are produced when various proteins undergo oxidation followed by glycation and get accumulated in tissues with advancing age, although they are also found in UVR exposed skin. This occurs as a result of decreased cathepsin D levels which is essential for AGE degradation inside the cell [119, 120].

With advancement in molecular field, several investigations have also concentrated on miRNA expression in terms of chronological aging and photoaging [121]. Specifically, sharp changes in miR-34 and miR-29 family regulation have been reported. For instance, increased miR-34b-5p expression in aged dermis has been reported for decreased COL1A1 and elastin expression together with increased MMP-1 expression [122].

These investigations mentioned above, only portray a fraction of the whole story required for understanding the aging process including both intrinsic and extrinsic aging. Various questions yet await their answers regarding aging. Due to the blurred line between photoaging and chronological aging, differentiating characteristics of these two aging types is often approached with confusion. This occurs because variation with respect to skin aging in different individuals is often subject to photoaging locations, natural skin pigmentation and exposure time period among the other factors. Challenges concerning antioxidants have also been proposed by many authors. Antioxidant level in the skin is affected by oxidative stress along with diet of an individual. To alleviate the signs of photoaging, exogenous supplementation of antioxidants can be given either by extrinsic application in the form of topical creams or intrinsic/systemic application in the form of tablets or capsules. Both the forms of supplementation have their own set of drawbacks and advantages [123]. Moreover, in case of plant derived antioxidants, different parts of the plant have different expression levels of a particular bioactive compound that acts as antioxidant. This forms an important factor while extracting particular antioxidants.

Apart from these challenges, a more daunting analysis that can be made is that radiation whether UV, visible or infrared can adversely affect the skin. To combat this problem various sunscreen formulations are used. But till now, most sunscreen formulations provide protection against specific wavelength ranges of UV region only. This shows the need for formulation of sunscreens which provide a broader protection [124].

11. Conclusions

Aging is a part of life. It is a complex process, affected by both intrinsic and extrinsic factors. Further addition of photoaging process induced by UVR makes studying aging and taking protective measures against it more complex. Therefore, alleviating

aging signs is still in requirement of more innovative ideas that are expected to be developed with more knowledge about the various mechanisms involved under aging and important investigations that can further shed light onto this phenomenon.

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