

## REVIEW ARTICLE

# The impact of ultraviolet radiation on skin photoaging – review of in vitro studies

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**Abstract**

**Background:** Photoaging, ultra violet (UV) induced skin aging is a gradual process that depends on the time and intensity of solar radiation.

**Aim:** The aim of this paper was to review of the literature focused on in vitro studies explaining the mechanisms of photoaging.

**Methods:** Electronic databases, including PubMed and MEDLINE, were searched for in vitro studies on the importance of UV radiation in the skin photoaging process of peer-reviewed scientific journals. Only articles available in English and full version publications were considered for this review.

**Results:** Three main modes of UV radiation action on skin cells which lead to photoaging, there are changes in cell metabolism, induction of oxidative stress due to the change in enzyme activity.

**Conclusion:** The information gathered in this publication will help to better understand the complex and multidirectional mechanism of skin photoaging, which will contribute to the development of research on potential cosmetic products that provide effective and safe sun protection or repair damage caused by UV radiation.

**KEYWORDS**

fibroblast, keratinocytes, mechanism of photoaging, review, UV radiation

## 1 | INTRODUCTION

Skin aging involves internal and external processes. Changes occurring as a result of genetic conditions (internal, chronological aging) overlap with aging symptoms stimulated by environmental conditions (extrinsic aging). The most harmful external factor threatening the skin is ultraviolet (UV) radiation. UV radiation consists of three components: UVA ( $\lambda = 320\text{--}400\text{ nm}$ ), UVB ( $\lambda = 280\text{--}320\text{ nm}$ ) and UVC ( $\lambda = 100\text{--}280\text{ nm}$ ). UVC radiation, unlike UVA and UVB radiation, is almost completely absorbed by the ozone layer. UVA and UVB rays reach the earth in sufficient quantities to damage skin structures.<sup>1,2</sup>

Nevertheless, the negative impact has been also observed during skin exposure to infrared radiation (IR;  $\lambda = 760\text{ nm}\text{--}1\text{ mm}$ ).<sup>3</sup> IR penetrates deeper layers of the skin than the rest of optical radiation. Even up to 17% of the incident infrared light can directly penetrate into the subcutaneous tissue. IR is absorbed by tissue chromophores (e.g., water) and converted into heat so that deep tissues can be heated. The heat is then transferred deeper by conduction, and pathological changes such as skin and corneal burns can occur.<sup>4</sup>

The human skin, an important part of the innate immune system, has various molecular mechanisms that protect this organ from UV exposure. The first of these is the layered structure of the

epidermis, which provides the first line of defense against harmful external agents. Additionally, immune cells such as Langerhans cells and T lymphocytes are located within the skin. Another line of protection for the skin is the melanocytes. Melanin, a pigment synthesized by these cells, impedes the penetration of UV radiation into the living layers of the epidermis by absorbing it. Furthermore, to maintain homeostasis, UV-induced DNA damage can be repaired at the molecular level by nucleotide repair and base excision mechanisms or apoptotic mechanisms as well as cell cycle checkpoints are activated.<sup>5,6</sup>

UV radiation increases the risk of long-term damages such as photoaging, photoimmunosuppression, and photocarcinogenesis.<sup>1,2</sup> UVA radiation has its negative effect on the epidermal keratinocytes and dermal fibroblast and induces long-term changes. Changes arising as a result of UVB radiation are visible mainly within the epidermis but it also penetrates the upper part of dermis.<sup>7,8</sup> The harmful effects of ultraviolet exposure mainly include skin side effects such as sunburn, photodermatoses, hyperpigmentation, photoaging of the skin and precancerous lesions and cancers. The mechanisms discussed in this paper are involved in the formation of these clinical changes in the skin.

Common point of photoaging is less dermal fibers expression.<sup>8</sup> Overexposure to UV radiation increases the formation of reactive oxygen species (ROS), which at higher concentrations can damage the main proteins that make up the skin, collagen and elastin.<sup>9-12</sup> A characteristic feature of the skin affected by photoaging is the presence of solar elastosis in the dermis. Solar elastose is a dystrophic elastic material that is formed as a result of a cycle of processes leading to the degradation of elastic fibers, followed by the formation of the extracellular matrix (ECM) and its reconnection into a structure other than its original one.<sup>13</sup>

The first report about the modulating influence of UV radiation on the progress and formation of some dermatoses is dated on 1910.<sup>14</sup> Since then, there has been a lot of research to find out the relationship between solar radiation and skin lesions, both disease and esthetic. This review focuses on gathering information about photoaging, especially the impact of UV radiation on skin cells metabolism, formation of oxidative stress and modulation of skin enzymes. The information collected in this review about the mechanisms that are occurring in skin cells under the influence of UVA and UVB radiation may be helpful in the search for new, effective compounds that show protective activity on the skin and reduce the effects of photoaging.

## 1.1 | UV and cellular metabolism

UV radiation can penetrate into the skin and interact with skin cells, both fibroblasts and keratinocytes.<sup>15</sup> Senescent cells secrete a number of factors such as cytokines, chemokines, growth factors and matrix metalloproteinases (MMPs), that is known as senescence-associated secretory phenotype.<sup>16</sup> The formation of premutagenic photoproducts is dependent on the type and dose of UV radiation.

Cyclobutane dimers Py (CPD) are mainly induced by UVB, while 8-hydroxy-2-deoxyguanine (8-OHdG) is one of the most common markers for the estimate of DNA damage from UVA.

DNA damage is one of the most serious effect of excessive skin exposure to UV radiation and plays a major role in inducing photocarcinogenesis and is also directly involved in photoaging. The destructive mechanism of UVB and UVA action on DNA molecules differs, which is related to the amount of energy absorbed by base pairs in the DNA chain.<sup>17</sup> The direct action of UVB radiation on cellular DNA results in characteristic mutations in the structure of the nucleic chain, such as the formation of CPD and pyrimidine base transversions.<sup>18</sup> DNA damage due to UVA radiation, like UVB, includes the formation of CPD, pyrimidine (6-4) pyrimidone photoproducts, as well as damage to and transition of DNA bases.<sup>19,20</sup>

Exposure to UVA causes direct damage of skin cells through an inflammatory reaction and indirectly through the induced oxidative stress. This initiates peroxidation of polyunsaturated fatty acids (PUFA) in the skin membrane and the formation of DNA adduct, 8-hydroxy-2'-deoxyguanosine (8-OHdG), which is the most numerous and highly mutagenic factor, considered as a reliable marker for oxidative DNA damage.<sup>21,22</sup>

Under exposure to UVB radiation on the skin, an inflammatory response is triggered in keratinocytes, resulting in the activation of the protein kinase R signal transduction pathway, which blocks this signal transduction pathway. A long non-coding RNA, nc886, suppresses the signal transduction pathway with protein kinase R to protect the cell from UV radiation.<sup>23</sup>

Autophagy, which is an intracellular cleansing system, is essential for maintaining homeostasis in skin structures. In the case of skin aging, the basic level of autophagy increases during the replicable aging of human facial fibroblasts.<sup>24</sup> Furthermore, UVA induce autophagy in fibroblasts<sup>25</sup> and UVB in human keratinocytes.<sup>26</sup> However, the process of autophagy is not capable of completely cancelling out the aging reaction of these cell types and only delaying it.<sup>27,28</sup> ROS production induced by UV stimulates autophagy, which regulates the reaction to oxidative stress due to solar radiation. Exposure to UVA radiation results in an increase in the quantity of oxidized phospholipids, oxysterols and cholesterol in epidermal cells, which is a signal to induce autophagy in keratinocytes. Autophagy plays a multiple role in response to oxidative stress caused by UVA radiation by removing oxidized molecules while minimizing the antioxidative reaction in various cell types. It has been shown that UVA regulates the transcription of a certain of genes which take part in autophagy, for example adaptive protein p62, as well as autophagic activators p53 and Sestrin2 (SESN2) that can induce autophagy through 5' adenosine monophosphate-activated protein kinase (AMPK) signalling.<sup>29</sup> The results of an experiment conducted by Endo et al. (2020) showed that repeated UVA radiation negatively affects the autophagy process in fibroblasts due to modifications in lysosomal functioning.<sup>30</sup> The impairment of intracellular degradation in UVA-treated fibroblasts occurs through molecular mechanisms underlying impaired autophagy such as decreased lysosomal acidity and reduced expression of cathepsins B, L and D.<sup>31</sup> That suggests that

anomalies in the process of autophagy are the leading agent in the process of photoaging of the skin. However, the basic dysfunctional mechanism of lysosomes in repeated UVA radiation fibroblasts is still not clear.<sup>30</sup>

Multiple exposition to UVB radiation causes a fail-safe process in the epidermis, which results in the forming of sunburn cells (SBC), that is, keratinocytes which undergo apoptosis.<sup>32</sup> Damages of keratinocytes DNA caused by UVB leads to the release of signals which initiate the release of inflammatory response mediators, for example, cytokines IL-1 $\alpha$ , IL-6, and TNF- $\alpha$ .<sup>33</sup> UVB directly induces the AMPK autophagy activator, a gene associated with UV resistance (UVRAG) and p53. Stabilized by UVB p53, initiates transcription of AMPK, SESN2, tuberous sclerosis complex 2 (TSC2), and UVRAG for activation of autophagy.<sup>29</sup>

## 1.2 | UV and oxidative stress

One of the main effects of UV radiation on skin molecules (e.g., uronic acid, nicotinamide-adenine dinucleotide (NADH) or melanin) is sensitization to ROS formation from absorbed energy. ROS (e.g., singlet oxygen, hydrogen peroxide, peroxide) are able to react and damage most of the molecules in their pathways, such as lipid membranes of cells, proteins or DNA. Moreover, ROS stimulate cell surface receptors, especially those for the epidermal growth factor (EGF), keratinocyte growth factor (KGF), interleukin (IL)-1, and tumor necrosis factor (TNF)- $\alpha$ . In addition, ROS causes damage to the membrane lipids, which leads to the release of ceramides and then the activation of AP-1.<sup>34</sup>

UVA radiation causes the release of prostaglandin-F2 $\alpha$  (PGF2 $\alpha$ ) and 12-HETE from arachidonic acid (AA) by causing an inflammatory response in skin and upregulating cyclooxygenase and lipoxygenase enzymes. The formation of these metabolites has been found to be associated with immunological reactions, inflammatory disorders, skin pigmentation and the wounds healing.<sup>35-37</sup> Short-term exposure of keratinocytes to sunlight may modify the composition of PUFA and its metabolism in skin cells. An *in vitro* study on epidermal cells carried out by Leung et al. (2017) has shown that keratinocytes may have defensive mechanisms at exposure to UVA, for example raised docosahexaenoic acid (DHA) levels, which prove to be helpful in regeneration after potential lesions.<sup>22</sup>

The effects of UVB radiation on the generation and release of ROS in human keratinocytes have been studied by Beak et al. (2004). The results showed an increase in intrinsic cellular production and release of nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase and cyclooxygenase (COX), that might play an essential role in UVB-induced ROS production and nuclear factor B (NF- $\kappa$ B) activation in keratinocytes in a dose-dependent mode.<sup>38</sup> Cavinato et al. (2017) have studied the role of protein quality control systems and their functional interaction in mediating the cellular aging of UVB-treated fibroblasts *in vitro*. The results suggest that early events in the process of senescence of fibroblast after UVB exposure include increased production of ROS and an inhibition of proteasome, followed by initiation of autophagy. The obtained results

suggest that increased ROS generation and autophagy and reduced proteasome activity contribute to the aging of fibroblasts treated with UVB. Autophagy is necessary to establish the phenotype of aging of UVB-induced fibroblasts, and suppression of autophagy is needed to modify the path of cells from aging to apoptosis death.<sup>39</sup> Deactivation of proteasomal system in fibroblast cells under the influence of UV radiation is associated with the generation of singlet oxygen, oxidation of proteins and activation of transcription agents known from the regulation of MMP-1 expression.<sup>40</sup>

## 1.3 | UV- enzymes and fibers

One of the main effects of UV radiation on the skin is an increase in expression of MMPs, which are responsible for the degradation of ECM proteins such as collagen, fibronectin, elastin, and proteoglycans.<sup>41</sup> Excessive degradation of these proteins caused by excessive production of MMP-1, MMP-3, and MMP-9 contributes to the photoaging of the skin and thus to the formation of thick wrinkles and sagging of the skin through photodestruction, phototransformation and photooxidation of collagen and elastin.<sup>33,42</sup>

MMPs play an important role in the development of solar radiation-related cancer, as they regulate various processes associated with the cancer process, including tumor location, growth, angiogenesis and metastasis.<sup>43</sup> The data presented by Dong et al. (2008), as the main initiator of processes leading to the induction of MMP-1 production, indicate DNA damage caused by UVB radiation. Their studies revealed a more than fourfold increase of the expression of the MMP-1 gene in keratinocytes mRNA induced by UVB treatment of cells.<sup>33</sup> Changes in protein expression play an important role in the process of skin photoaging, including the transforming growth factor- $\beta$  (TGF- $\beta$ ), Smad2, MMP-1, MMP-3, MMP-9. Moreover, UV radiation, the increase in the amount of ROS and the expression of MMPs, which are one of the major agents involved in the process of skin changes associated with photoaging, may also interact with cathepsins.<sup>44-46</sup> Citing the results of a Zheng et al. (2011) study, the modified gene expression of cathepsins by repetitive exposures to UVA radiation is a prospective clarification of the alteration of cathepsin activity and content in photoaging skin. Their results suggest that the level and activity of cathepsins B, D, K and G may be considered as potential biomarkers in photoaging of human skin.<sup>44</sup> Cathepsin K is one of the factors involved in the degradation of elastin, which leads to the formation of solar elastosis. It plays a dominant role in this process due to its elastolytic activity. Cathepsin D is a factor that induces cellular mitosis, which leads to weakening of the immune response and inhibition of dendritic cell function. It is assumed that down-regulation of cathepsin D, as a growth regulator of keratinocytes, may contribute to photoaging-related disorders of epidermal cell proliferation, such as disorders of the keratinization process. Also cathepsin B is responsible for matrix degradation and cell invasion.<sup>44,45</sup> Another factor responsible for regulating MMP-1, MMP-2, MMP-3, and MMP-9 in human UVA-treated fibroblasts is opsin 3 (OPN3), as first demonstrated by Lan et al. (2020). Through

a calcium-dependent signalling pathway coupled with G-proteins, OPN3 initiates the process of transduction in UVA-exposed fibroblast cells. OPN3 influences the phosphorylation of activator 1 protein and regulates the action of MMPs by activating protein kinase II. The process of activation of protein kinase II is dependent on many factors, including  $\text{Ca}^{2+}$ /calmodulin, cyclic adenosine monophosphate protein binding response elements, extracellular signal kinase, N-terminal c-JUN and p38.<sup>47</sup>

The ROS produced as a result of UV radiation stimulates the mitogen-activated protein kinase family (MAPK), which is responsible for the formation of activator-1 protein (AP-1). AP-1 plays an instrumental role in regulating the transcription of MMP-1, MMP-3, and MMP-9, which results in progressive degradation of collagen.<sup>48,49</sup> In addition, AP-1 inhibits the signalling of TGF- $\beta$ , which is responsible for regulating the synthesis of pro-collagen type I in human skin, resulting in a reduction in the synthesis of this collagen precursor.<sup>50</sup> One other important transcription factor that is activated in response to UV radiation is NF- $\kappa$ B. The main role of NF- $\kappa$ B is to regulate gene expression of growth factors, chemokines, cytokines and cell adhesion molecules, both in physiological state and in many diseases. NF- $\kappa$ B activity is responsible for regulating the expression of MMPs such as MMP-1 and MMP-3 in human skin fibroblasts. Therefore, both transcription factors, both AP-1 and NF- $\kappa$ B, are responsible for the formation of changes characteristic for photoaging.<sup>51</sup>

## 2 | CONCLUSIONS

Sun exposure leads to the thickness of the epidermis, dermal elastase, decrease in the amount ECM proteins, increase in the activity of MMPs and fragmentation of collagen, increase in inflammatory infiltrates and telangiectasia. Despite a significant number of studies conducted so far, this mechanism is not clarified. It can be stated that DNA damage in the skin is one of the key events in photoaging processes. A deep explanation of the mechanisms of photoaging will help in the search for potential cosmetic ingredients which provide sun protection or repair damage caused by UV radiation.

### CONFLICT OF INTEREST

The authors of this manuscript do not declare conflicts of interest.

### ETHICAL STATEMENT

The conducted literature review did not require the agreement of the bioethics committee.

### DATA AVAILABILITY STATEMENT

Data sharing not applicable – no new data generated.

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## REFERENCES

1. Sanches Silveira JE, Myaki Pedroso DM. UV light and skin aging. *Rev Environ Health*. 2014;29(3):243-254.
2. Bosch R, Philips N, Suárez-Pérez JA, et al. Mechanisms of photoaging and cutaneous photocarcinogenesis, and photoprotective strategies with phytochemicals. *Antioxidants (Basel)*. 2015;4(2):248-268.
3. Calles C, Schneider M, Macaluso F, Benesova T, Krutmann J, Schroeder P. Infrared A radiation influences the skin fibroblast transcriptome: mechanisms and consequences. *J Invest Dermatol*. 2010;130(6):1524-1536.
4. Grandi C, D'Ovidio MC. Balance between health risks and benefits for outdoor workers exposed to solar radiation: an overview on the role of near infrared radiation alone and in combination with other solar spectral bands. *Int J Environ Res Public Health*. 2020;17(4):1357.
5. Mohania D, Chandel S, Kumar P, et al. Ultraviolet radiations: skin defense-damage mechanism. *Adv Exp Med Biol*. 2017;996:71-87.
6. Natarajan VT, Ganju P, Ramkumar A, Grover R, Gokhale RS. Multifaceted pathways protect human skin from UV radiation. *Nat Chem Biol*. 2014;10(7):542-551.
7. Debacq-Chainiaux F, Leduc C, Verbeke A, Toussaint O. UV, stress and aging. *Dermatoendocrinol*. 2012;4(3):236-240.
8. Zhang JA, Yin Z, Ma LW, et al. The protective effect of Baicalin against UVB irradiation induced photoaging: an *in vitro* and *in vivo* study. *PLoS One*. 2014;9(6):e99703.
9. Ryu J, Park SJ, Kim IH, Choi YH, Nam TJ. Protective effect of porphyra-334 on UVA-induced photoaging in human skin fibroblasts. *Int J Mol Med*. 2014;34(3):796-803.
10. Pérez-Sánchez A, Barrajón-Catalán E, Caturla N, et al. Protective effects of citrus and rosemary extracts on UV-induced damage in skin cell model and human volunteers. *J Photochem Photobiol B*. 2014;136:12-18.
11. Rinnerthaler M, Bischof J, Streubel MK, Trost A, Richter K. Oxidative stress in aging human skin. *Biomolecules*. 2015;5(2):545-589.
12. Ngan CL, Basri M, Tripathy M, Abedi Karjiban R, Abdul-Malek E. Skin intervention of fullerene-integrated nanoemulsion in structural and collagen regeneration against skin aging. *Eur J Pharm Sci*. 2015;70:22-28.
13. Rijken F, Bruijnzeel PL. The pathogenesis of photoaging: the role of neutrophils and neutrophil-derived enzymes. *J Investig Dermatol Symp Proc*. 2009;14(1):67-72.
14. Alderson HE. Brief notes on skin diseases in the hawaiian territory-the sun as a modifying factor. *Cal State J Med*. 1910;8(8):267.
15. Gilchrist BA. Photoaging. *J Invest Dermatol*. 2013;133(E1):E2-E6.
16. Waldera Lupa DM, Kalfalah F, Safferling K, et al. Characterization of skin aging-associated secreted proteins (SAASP) produced by dermal fibroblasts isolated from intrinsically aged human skin. *J Invest Dermatol*. 2015;135(8):1954-1968.
17. Almeida IF, Pinto AS, Monteiro C, et al. Protective effect of *C. sativa* leaf extract against UV mediated-DNA damage in a human keratinocyte cell line. *J Photochem Photobiol B*. 2015;144:28-34.
18. Griffiths HR, Mistry P, Herbert KE, Lunec J. Molecular and cellular effects of ultraviolet light-induced genotoxicity. *Crit Rev Clin Lab Sci*. 1998;35(3):189-237.
19. Drobetsky EA, Turcotte J, Châteauneuf A. A role for ultraviolet A in solar mutagenesis. *Proc Natl Acad Sci USA*. 1995;92(6):2350-2354.
20. Schuch AP, Moreno NC, Schuch NJ, Menck CFM, Garcia CCM. Sunlight damage to cellular DNA: focus on oxidatively generated lesions. *Free Radic Biol Med*. 2017;107:110-124.

21. Agar NS, Halliday GM, Barnetson RS, Ananthaswamy HN, Wheeler M, Jones AM. The basal layer in human squamous tumors harbors more UVA than UVB fingerprint mutations: a role for UVA in human skin carcinogenesis. *Proc Natl Acad Sci U S A*. 2004;101(14):4954-4959.
22. Leung KS, Chan HF, Leung HH, et al. Short-time UVA exposure to human keratinocytes instigated polyunsaturated fatty acid without inducing lipid peroxidation. *Free Radic Res*. 2017;51(3):269-280.
23. Lee KS, Shin S, Cho E, et al. nc886, a non-coding RNA, inhibits UVB-induced MMP-9 and COX-2 expression via the PKR pathway in human keratinocytes. *Biochem Biophys Res Commun*. 2019;512(4):647-652.
24. Wen X, Wu J, Wang F, Liu B, Huang C, Wei Y. Deconvoluting the role of reactive oxygen species and autophagy in human diseases. *Free Radic Biol Med*. 2013;65:402-410.
25. Jain A, Lamark T, Sjøttem E, et al. p62/SQSTM1 is a target gene for transcription factor NRF2 and creates a positive feedback loop by inducing antioxidant response element-driven gene transcription. *J Biol Chem*. 2010;285(29):22576-22591.
26. Chen X, Li L, Xu S, et al. Ultraviolet B radiation down-regulates ULK1 and ATG7 expression and impairs the autophagy response in human keratinocytes. *J Photochem Photobiol B*. 2018;178:152-164.
27. Taguchi K, Fujikawa N, Komatsu M, et al. Keap1 degradation by autophagy for the maintenance of redox homeostasis. *Proc Natl Acad Sci USA*. 2012;109(34):13561-13566.
28. Settembre C, Zoncu R, Medina DL, et al. A lysosome-to-nucleus signalling mechanism senses and regulates the lysosome via mTOR and TFEB. *Embo J*. 2012;31(5):1095-1108.
29. Sample A, He YY. Autophagy in UV damage response. *Photochem Photobiol*. 2017;93(4):943-955.
30. Endo K, Katsuyama Y, Taira N, Yoshioka M, Okano Y, Masaki H. Impairment of the autophagy system in repetitively UVA-irradiated fibroblasts. *Photodermatol Photoimmunol Photomed*. 2020;36(2):111-117.
31. Huang Y, Li Y, Qu Y, et al. UVA-induced photoaging inhibits autophagic degradation by impairing lysosomal function in dermal fibroblasts. *Biochem Biophys Res Commun*. 2019;518(4):611-618.
32. Cavinato M, Jansen-Dürr P. Molecular mechanisms of UVB-induced senescence of dermal fibroblasts and its relevance for photoaging of the human skin. *Exp Gerontol*. 2017;94:78-82.
33. Dong KK, Damaghi N, Picart SD, et al. UV-induced DNA damage initiates release of MMP-1 in human skin. *Exp Dermatol*. 2008;17(12):1037-1044.
34. Yaar M, Gilchrist BA. Photoaging: mechanism, prevention and therapy. *Br J Dermatol*. 2007;157(5):874-887.
35. Ichihashi M, Ueda M, Budiyo A, et al. UV-induced skin damage. *Toxicology*. 2003;189(1-2):21-39.
36. Sugimoto M, Arai I, Futaki N, Hashimoto Y, Honma Y, Nakaike S. Role of COX-1 and COX-2 on skin PGs biosynthesis by mechanical scratching in mice. *Prostaglandins Leukot Essent Fatty Acids*. 2006;75(1):1-8.
37. Rhodes LE, Gledhill K, Masoodi M, et al. The sunburn response in human skin is characterized by sequential eicosanoid profiles that may mediate its early and late phases. *Faseb J*. 2009;23(11):3947-3956.
38. Beak SM, Lee YS, Kim JA. NADPH oxidase and cyclooxygenase mediate the ultraviolet B-induced generation of reactive oxygen species and activation of nuclear factor-kappaB in HaCaT human keratinocytes. *Biochimie*. 2004;86(7):425-429.
39. Cavinato M, Koziel R, Romani N, et al. UVB-induced senescence of human dermal fibroblasts involves impairment of proteasome and enhanced autophagic Activity. *J Gerontol A Biol Sci Med Sci*. 2017;72(5):632-639.
40. Catalgol B, Ziaja I, Breusing N, et al. The proteasome is an integral part of solar ultraviolet a radiation-induced gene expression. *J Biol Chem*. 2009;284(44):30076-30086.
41. Quan T, Qin Z, Xia W, Shao Y, Voorhees JJ, Fisher GJ. Matrix-degrading metalloproteinases in photoaging. *J Invest Dermatol Symp Proc*. 2009;14(1):20-24.
42. Chiang HM, Lin TJ, Chiu CY, et al. Coffea arabica extract and its constituents prevent photoaging by suppressing MMPs expression and MAP kinase pathway. *Food Chem Toxicol*. 2011;49(1):309-318.
43. O'Grady A, Dunne C, O'Kelly P, Murphy GM, Leader M, Kay E. Differential expression of matrix metalloproteinase (MMP)-2, MMP-9 and tissue inhibitor of metalloproteinase (TIMP)-1 and TIMP-2 in non-melanoma skin cancer: implications for tumour progression. *Histopathology*. 2007;51(6):793-804.
44. Zheng Y, Lai W, Wan M, Maibach HI. Expression of cathepsins in human skin photoaging. *Skin Pharmacol Physiol*. 2011;24(1):10-21.
45. Zheng Y, Chen H, Lai W, et al. Cathepsin D repairing role in photodamaged skin barrier. *Skin Pharmacol Physiol*. 2015;28(2):97-102.
46. Ciążyńska M, Bednarski IA, Wódcz K, et al. Impact of ultraviolet radiation on expression of transforming growth factor  $\beta$ , Smad2, metalloproteinases-1, -3, -8, -9, cathepsin K and progerin. *Photochem Photobiol*. 2018;94(2):362-369.
47. Lan Y, Wang Y, Lu H. Opsin 3 is a key regulator of ultraviolet A-induced photoaging in human dermal fibroblast cells. *Br J Dermatol*. 2020;182(5):1228-1244.
48. Kim J, Lee CW, Kim EK, et al. Inhibition effect of Gynura procumbens extract on UV-B-induced matrix-metalloproteinase expression in human dermal fibroblasts. *J Ethnopharmacol*. 2011;137(1):427-433.
49. Chiang HM, Chen HC, Chiu HH, Chen CW, Wang SM, Wen KC. Neonauclea reticulata (Havil.) merr stimulates skin regeneration after UVB exposure via ROS scavenging and modulation of the MAPK/MMPs/collagen pathway. *Evid Based Complement Alternat Med*. 2013;2013:324864.
50. Chen B, Li R, Yan N, et al. Astragaloside IV controls collagen reduction in photoaging skin by improving transforming growth factor- $\beta$ /Smad signaling suppression and inhibiting matrix metalloproteinase-1. *Mol Med Rep*. 2015;11(5):3344-3348.
51. Lee YR, Noh EM, Han JH, et al. Brazilin inhibits UVB-induced MMP-1/3 expressions and secretions by suppressing the NF- $\kappa$ B pathway in human dermal fibroblasts. *Eur J Pharmacol*. 2012;674(2-3):80-86.

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