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Review

Agro-Industrial By-Products and Their Bioactive Compounds—An Ally against Oxidative Stress and Skin Aging

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Abstract: The increased consumer awareness towards hazards related with sun exposure has given a boost in the cosmetics industry and particularly the sun care market. Human skin is continually being threatened by the UV irradiation present in sunlight and acute UV exposure leads to skin photoaging. Cosmetic and/or dermatological applications include several bioactive compounds that contribute to the regulation of epidermal homeostasis by providing protection against solar radiation and improving the antioxidant activity of epidermis. Plant extracts are sources of active ingredients with intense therapeutic properties, and the topical application or oral intake of these compounds could ameliorate skin condition. Nowadays, there is a growing demand for the application of the bioactive agents contained in agro-industrial byproducts in sun care products, since many of them have shown promising properties as skin photoprotectants. However, well-conducted clinical studies are required to prove their safety and efficacy before they could be regularly used. Environmentally friendly extraction and sustainable techniques are therefore under examination for recovering such compounds from agro-industrial byproducts and converting them into innovative high-value natural ingredients used in cosmetic formulations.

Keywords: agro-industrial byproducts; ellagic acid; flavonoids; lycopene; oleuropein; polyphenols; resveratrol; skin aging

1. Oxidation Processes and Skin Aging

Arachidonic acid (AA, 20:4*n*-6) and docosahexaenoic acid (DHA, 22:6*n*-3) are the main polyunsaturated fatty acids (PUFAs) that are responsible for the maintenance of fluidity and permeability of cell membranes. This fraction of PUFAs located in membrane phospholipids is susceptible to oxidation processes and their extent is strongly related with the number of double bounds of the molecules. Oxidation procedure results in the production of free radicals that are further decomposed into non-radical products, such as alkanes, conjugated dienes and aldehydes. These secondary compounds adversely affect cell structure and functionality and lead to deterioration of membrane integrity, disturbation of transport processes and dysfunction of cell organelles [1].

A free radical is a molecule capable to exist in an independent state that carries one or more unpaired electrons in the valence orbit. It is characterized by high reactivity and instability and is produced by a loss or a gain of a single electron from a non-radical. The formulation of free radicals is a natural process during the metabolic activity in body tissues and can adversely influence DNA, proteins, lipids and carbohydrates [2]. Reactive oxygenated species (ROS) are involved in the pathology of several diseases [3]. When these oxidation products exceed the endogenous antioxidant defense system potential (perturbation of redox signaling), toxic effects on cells and tissues are observed, i.e.,

oncogene genes are over-expressed, mutagen compounds are generated and atherogenic activity, senile plaque occurrence or inflammation are promoted [1].

Skin is a dynamic organ of the human body and serves as a cutaneous barrier between the external and internal environments. It also possesses additional properties, such as prevention of percutaneous loss of fluid, electrolytes, and proteins, temperature maintenance, sensory perception, homeostatic regulation and immune surveillance [4]. Skin aging (SA) is a complex, progressive and inevitable biological process that is closely related with oxidation events. Inflammation and modifications in the skin barrier functionality are caused by lipids peroxidation in membranes or in stratum corneum, and the degradation of elastic fibers or collagen in dermis results in elastic fiber remodeling events and SA [5]. SA is assessed by a variable prevalence of tissue degeneration over tissue regeneration, since adult dermal fibroblasts cannot adequately replace the cutaneous elastic fibers, leading to elasticity loss and reduction of metabolic activity [6]. These consequences are associated with deep wrinkling, scaling, roughness, dryness, sagging, laxity and pigmentation abnormalities of the skin [7]. SA is induced by both internal and external factors that result in a decline of physiological functions and deterioration of structural integrity of the skin [8]. In detail, mitochondria do not function in a proper way (reduced adenosine triphosphate (ATP) production), intracellular communication is negatively affected, and cellular senescence and malfunction of the extracellular matrix (ECM) are observed as consequences of the oxidative events occurring in the skin [6]. The ECM is the structural basis of the skin, composed of glucosaminoglycans (GAGs; e.g., hyaluronic acid), structural proteins (collagen and elastin), proteoglycans and distinctive macromolecules, such as fibronectin that are produced by the fibroblasts of the dermis [9], and the oxidation products (ROS) can cause its deterioration. Moreover, skin inflammation is associated with immune cells' accumulation, ROS production and the activity of specific degrading enzymes that subsequently damage surrounding tissue [10].

Intrinsic SA is an effect of the decreased replicative ability of keratinocytes, fibroblasts and melanocytes and the increased degradation rate of ECM caused by enzymes, such as the serine protease elastase, the mucopolysaccharase hyaluronidase and the matrix metalloproteinases (MMPs; e.g., collagenase). Moreover, it is also closely related with the accumulation of ROS in the electron transport chain of the aerobic metabolism in the mitochondria of fibroblasts and keratinocytes [7,11]. The extrinsic SA is observed as a result of exposure to several external factors, such as solar radiation (ultra violet (UV) A and B radiation), cigarette smoke and air pollution [12]. UV radiation is absorbed by the chromophores in the skin and is characterized as the primary factor of extrinsic SA (skin photoaging). UV activates cell surface receptors for cytokines (interleukin-1 (IL-1) and tumour necrosis factor alpha (TNF-α) and growth factors such as epidermal growth factor (EGF) on keratinocytes and fibroblasts [13]. Photoaging stimulates signal transduction cascades that induce important cellular biochemical responses, including altered kinase-dependent signal transduction pathways that increase the expression of nuclear factor NF-κB and activated protein-1 (AP-1) transcription factors, promote expression of MMPs and impair procollagen synthesis by inhibiting the transforming growth factor-β (TGF-β). As a result, excessive connective tissue damage, DNA and RNA mutations, induction of apoptosis and significantly increased ROS production are observed [7]. Apoptotic keratinocytes are present in the skin after high-dose UVA or UVB irradiation, and the number of these cells is determined by not only the intensity, duration and frequency of solar exposure, but also the protection provided by skin pigmentation (melanin type and its density—distribution between the keratinocytes) that depends on the skin type [14].

2. Antioxidants

Cells are protected through specific mechanisms against the negative effects of free radicals. Subcellular compartments, organelles and the extracellular space contain endogenous antioxidants that fortify cells against oxidative injury (antioxidant system). Antioxidants are categorized into primary (chain breakers that act as scavengers of ROS) and secondary (UV radiation absorbers, oxidative enzyme inhibitors, peroxide decomposers, singlet oxygen quenchers or metal chelators).

Endogenous antioxidant protection is provided by enzymes (catalase, glutathione peroxidase and superoxide dismutase), metal-binding proteins (i.e., lactoferrin, ferritin, ceruloplasmin, transferrin), water soluble vitamins (i.e., ascorbic acid), fat soluble vitamins (i.e., carotenoids, vitamin E, vitamin A), bilirubin, melatonin, reduced coenzyme Q, uric acid and the thiol redox system consisting of the thioredoxin and the glutathione system (provision of electrons for antioxidant defense, deoxy ribonucleotide formation and redox regulation of signal transduction, transcription, cell growth and apoptosis) [1]. Among the endogenous agents for ROS removal, the transcription factor NF-E2-related factor 2 (Nrf2) serves as an important cytoprotector that generates the formation of non-enzymatic and enzymatic ingredients that are necessary for the function of antioxidant systems [15].

Antioxidants can participate in different phases (initiation, propagation and chain termination) of the oxidative radical process in the cell [16] as constituents of the antioxidant enzymes or by deactivating several lipophilic and hydrophilic pro-oxidants [17]. There are three levels of antioxidant defense. At first, metal-binding proteins and antioxidant enzymes remove precursors of free radicals by limiting the radicals' initiators or by inactivating catalysts due to their bond with metals, such as copper and iron. Unfortunately, the first level is not adequate and some peroxyl radicals remain active. In this case, peroxidation is inhibited by several chain breaking antioxidants (i.e., water and fat soluble vitamins) through the collection of peroxyl radical intermediates or the donation of electrons with the intention to break and terminate the oxidation cycle or to maintain the chain length of the propagation reaction as small as possible (second level). Sometimes, even the second level is not sufficient to prevent oxidation events and the integrity of the biological molecules is deteriorated. As a result, the third level of antioxidant defense that includes proteolytic, lipolytic and other enzymes is accelerated and repairs or eliminates the deteriorated molecules. The cooperative interaction between the three levels of cell antioxidant defense is essential for the maintenance of the critical balance among free radicals, repair systems and antioxidant defense [1,2].

The antioxidant system is significantly affected by external parameters of environmental (increased temperature, UV radiation, atmospheric pollution, etc.) or nutritional (deficiencies of vitamins or elements, toxicants, high levels of PUFAs, etc.) origin that cause an enhanced production of free radicals. Cells can be usually protected against mild oxidative stress by additional synthesis of antioxidants in an effort to re-establish the equilibrium between free radicals and antioxidants. Natural antioxidants (phenolics, carotenoids, vitamins, etc.) and adequate levels of several minerals (Zn, Se, Mn, Cu, etc.) that are included in the diet can contribute to the maintenance of this equilibrium in body tissues [1]. However, depending on dosage and type, natural antioxidants can negatively affect the consistency of organelles and cell membranes with further cytotoxic consequences on living cells. Although the application of bioactive compounds of agro-industrial byproducts is generally recognized as safe (GRAS) and the accumulation of their ingredients in body tissues is improbable due to their rapid exhalation (carbon dioxide) or elimination (glucuronides by the kidneys), no analytical methods suitable for their in vivo quantification (toxicity or possible residues) exist [18]. Computational methods could possibly play an important role in the elucidation of the above mechanisms, since they possess the potential to facilitate advances in environmental and toxicological risk assessment through the support of the experimental data with additional results and in silico studies [19].

The most classical approach to skin protection against oxidation events involves the topical application of synthetic sunscreens to limit ROS formation as a result of solar exposure. A new, more appealing skin care strategy is based on the "green" perspective, i.e., the use of natural bioactive agents (Table 1) that can activate the endogenous antioxidant defense systems due to consumer disposition for natural occurring ingredients and consideration about the possible adverse effects of synthetic antioxidants (phototoxic and photoallergic reactions, allergic and contact dermatitis). The majority of natural antioxidants are phenolic compounds that can minimize oxidant levels and inhibit hyaluronidase, elastase, tyrosinase and collagenase enzymes [20,21].

Table 1. Major plants and their active ingredients against skin photoaging [20–22].

Plant	Major Ingredients with Skin Protecting Effects
Aloe vera	Polysaccharides, β-carotene, alpha-tocopherol
Gooseberry	Flavonoids, ellagic acid and ascorbic acid
Green tea	(−)-Epigallocatechin-3-gallate and epicatechin-3-gallate
Rosemary	Rosmarinic acid, carnosic acid and carnosol
Coffee berry	Chlorogenic acids and alkaloids
Eucalyptus	Flavonoids, terpenoids and catechins

Under normal conditions, alpha-tocopherol triggers glutathione (GSH) synthesis in human keratinocytes through the upregulation of gamma-glutamylcysteine synthetase mRNA [23]. Alpha-tocopherol further prevents UVB-induced edema, erythema, and lipid peroxidation events by inhibiting NADPH oxidase activity, downregulating AP-1 DNA binding activity and reducing the expression of IL-8 mRNA and the secretion of IL-8 protein that are closely related with MMP-1 (collagenase) expression [24].

As a consequence of their amphiphilic properties, plant polyphenols can act as hydrophilic or lipophilic scavengers functioning in different cell compartments. Apart from antioxidant activity, polyphenols (especially isoflavones and flavonoids) display additional biochemical activities, such as enzyme inducers or inhibitors, and impact cell division and anti-inflammatory pathways [25,26]. As indicated, polyphenols inhibit UV-dependent activation of mitogen-activated protein kinases (MAPK) and AP-1 [27]. Application of a polyphenolic antioxidant-based serum on the skin improves epidermal thickness, enhances fibroblast density and increases hyalinization of the papillary dermis with newly deposited collagen fibers [28]. Moreover, phenolic compounds of *Emblica officinalis* L. have a modulatory action on UVB-induced free radicals, stimulate pro-collagen content and restrict MMP levels in skin fibroblast [29]. Polyphenols from rosemary (*Rosmarinus officinalis*) and thyme (*Thymus vulgaris*) also appear to downregulate collagenase, elastase and hyaluronidase expression and fortify the major components of the ECM against UVB irradiation-induced effects [30].

Among polyphenols, green tea polyphenols (GTPs) are extensively studied as skin protective agents against UV-induced damage [31,32]. The major phenolic compounds contained in green tea are the flavanols (−)-epicatechin gallate, (−)-epigallocatechin-3-gallate, (−)-epigallocatechin, (−)-epicatechin, (+)-gallocatechin, and (+)-catechin that alleviate the negative effects of UV exposure (lipid peroxidation, erythema and skin damage) after their oral or topical application [33]. Oral GTP administration could be useful to ameliorate solar UVB light-induced premature SA by blocking oxidative damage and MMPs (MMP-2, -3, -7 and -9) expression in SKH-1 hairless mice and in human skin fibroblast HS68 cells [34]. Moreover, green tea extracts appear to inhibit collagenase, elastase and tyrosinase activities contributing to skin physical stability [35]. GTP and their metabolites are also bioavailable in skin after their dietary administration and provide a promising link between green tea consumption and protection against UV-induced inflammation of the skin [36].

Mnich et al. [37] observed that the direct application of green tea extract on human skin results in a decrease in the number of apoptotic keratinocytes and UV-induced p53 expression. Moreover, topical use of GTPs or their major constituent (−)-epigallocatechin-3-gallate (EGCG) suppresses MMP-2, -3, -7, and -9 expression, lowers depletion of antioxidant enzymes, decreases UVB-dependent oxidation of lipids and proteins and downregulates phosphorylation of proteins of the MAPK family, such as extracellular signal-regulated kinase 1 (ERK1/2), c-Jun N-terminal kinase (JNK), and p38 in hairless mouse skin [38,39]. In human skin, topical application of EGCG at about 1 mg/cm^2 offers protection against UV-induced oxidative stress [40,41], since it ensures efficient skin penetration and retention, which can favor its skin effects [42]. EGCG acts by blocking collagenase transcriptional levels and UV-induced collagen secretion and by inhibiting the binding activities of the UV-induced nuclear transcription factors NF-κB and AP-1 (collagen breakdown) [33,43,44]. Treatment of human keratinocyte cultures with EGCG minimizes UVB-induced cytotoxicity, inhibits mRNA expression

of apoptosis-regulating genes p53 and p21, downregulates c-fos expression (AP-1) and blocks the secretion of cytokines IL-6 and TNF-α [45–47]. Apart from topical application, oral administration of EGCG for eight weeks also significantly prevents disruption of the epidermal barrier function caused as a result of UV exposure [48]. According to Bae et al. [49], EGCG markedly downregulates UVB-induced MMP-1, -8, and -13 expression in a dose-dependent manner via its interference with MAPK pathways. Epicatechin-3-gallate (ECG) is another phenolic compounds in green tea that offers protection of human keratinocytes against UVA and UVB radiation by inhibiting hydrogen peroxide production and membrane lipid peroxidation (blockade of ERK1/2, p38 and JNK), respectively [50,51].

Nutritional strategies that offer a systemic protection against UV radiation is nowadays an emerging topic of interest in preventive medicine and public health, and the modification of signaling cascades by nutrients is a rapid developing area of research [17]. The chemopreventive approach refers to skin fortification by oral supplements that provide an additional protection at sensitive dermal target sites, beyond that ensured by direct, and temporary coverage by sunscreens. However, some queries should be initially answered, i.e., the optimum levels and the ideal time frame for efficient function at the target skin area. As indicated in several studies, the efficacy of antioxidants in protection against SA depends on the duration of treatment before exposure to UV radiation and on the dose. In general, eight to ten weeks of dietary supplementation with antioxidants are necessary, while protection by topical sunscreen is virtually immediate [17]. At the same time, the activity of natural photoprotectans is affected by their ability to diffuse through the barrier and their levels in the formulation; small soluble lipophilic and hydrophilic molecules can cross the stratum corneum more easily than polymers, particles or highly lipophilic substances [52].

3. Potential Use of Agro-Industrial Byproducts in Skin Protection

In the last decades, there is an increasing concern about the bioactive compounds contained in agro-industrial byproducts as media for ameliorating some aspects of our life. Agro-industrial byproducts can be used for various purposes providing economic benefits, since the existent technologies allow their recycling and sustainable use. At the same time, their processing diminishes the environmental effects induced through their disposal (owing to their high organic load and low pH). At the moment, there is no European legislation regulating the disposal of agro-industrial wastes and this issue is controlled by national regulations of each country (levels of some chemical compounds, such as Cd, Cu, Fe, Mn, Pb and Zn, and microbial parameters) [53]. Skin care market and cosmetic industry can benefit from these remaining bioactive compounds (Table 2), since many of them have shown promising properties as skin photoprotectants [54].

Table 2. Agro-industrial byproducts and their major bioactive compounds that could be potentially used as skin photoprotectants [21,24].

Agro-Industrial Byproduct	Compounds
Tomato pomace	Lycopene
Olive cake	Tyrosol and oleuropein
Citrus pulp	Hesperidin and naringin
Apple pomace	Quercetin
Grape pomace or marc	Proanthocyanidins and resveratrol
Pomegranate pulp	Ellagic acid
Onion pomace	Anthocyanins and quercetin
Garlic extract	Alliin and allicin
Mango pulp	Quercetin, anthocyanins, gallic and ellagic acids

3.1. Tomato

Tomato (*Solanum lycopersicum*) is the second most important vegetable crop in the world and the byproducts derived during its processing (pomace) contain valuable compounds, such as fibers, proteins, sugars, pectins, fat, minerals and antioxidants (e.g., lycopene) [55]. Due to its lycopene content,

tomato paste could serve as a natural dietary source that provides protection against UV-induced erythema [56–58], matrix changes (MMP-1, procollagen I and fibrillin-1) and mitochondrial DNA (mtDNA) damage [59] in humans. Moreover, oral administration of a lycopene-rich tomato nutrient complex completely inhibits UVA1- and UVA/B-induced upregulation of intercellular adhesion molecule 1, heme-oxygenase 1 and matrix metallopeptidase 1 mRNA [60].

Lycopene protects the skin against UV damage [61] through the downregulation of epidermal ornithine decarboxylase activity, the maintenance of cell proliferation at normal levels and the prevention of DNA damage from apoptosis blockage (in particular by blocking caspase-3 of apoptotic pathway) [62]. Topical delivery of lycopene contained in a microemulsion is a convenient way to increase lycopene delivery to the skin and the antioxidant activity in the tissue [63]. Nanoparticle formulations further stabilize lycopene in the cell culture medium and enable efficient cellular uptake [64]. Lycopene can also serve as an effective inhibitor of stromal fibroblasts' migration [65] through the inhibition of platelet-derived growth factor (PDGF)-BB-induced ARPE19 cell migration by downregulating phosphoinositide-3-kinase–protein kinase B/Akt (PI3K/Akt), extracellular-signal-regulated kinase (ERK) and p38 activation [66].

3.2. Olive

Olive (*Olea europaea*) cultivation plays a fundamental economic and social role in the Mediterranean Basin. Olive oil extraction produces increased quantities of byproducts (cake) that are potential pollutants [67]. In general, approximately 800 g of olive cake are obtained per 1 kg of olives [68]. Olive and its byproducts contain functional bioactive compounds like carotenoids, phospholipids, tocopherols and phenolics (e.g., tyrosol, and oleuropein) [69] that can be used in cosmetic industry [70]. Oleuropein is a phenol that acts as a free radical scavenger and offers protection against UVB-induced skin damage by suppressing ROS intracellular levels and the amount of oxidized proteins through the induction of conformational changes in the proteasome activity [71]. At the same time, skin thickness and elasticity loss are inhibited after oleuropein application [72]. Finally, a polyphenol extract derived from olive pomace that contains tyrosol and oleuropein downregulates TNF-α and MMP-1, -2, -9 expression [73].

3.3. Citrus

Dried citrus pulp is derived after the extraction of the juice from citrus fruits and drying of the residues. It is a mixture of peel, inside portions and culled fruits that constitute rich sources of energy, fiber and calcium. The derived citrus fibers contain bioactive compounds, such as flavonoids. These phenolic compounds (hesperidin, naringin, etc.) have intense antioxidant and anti-inflammatory properties, since they contain one or more aromatic hydroxyl groups that actively scavenge free radicals [74].

A protective effect of red orange extract in human keratinocytes has been observed since it modulates cellular responses, i.e., procaspase-3 cleavage and AP-1 and NF-κB translocation as a response to UVB radiation [75]. Furthermore, monocyte chemoattractant protein-1 (MCP-1) and interleukin-8 (IL-8) secretion are inhibited and inter-cellular adhesion molecule-1 (ICAM-1) expression is downregulated [76]. Lemon balm extract (*Melissa officinalis*, L.) also protects against UVB-induced oxidative stress and DNA skin damage by suppressing intracellular ROS production and promoting melanogenesis [77]. At the same time, a combination of rosemary and citrus bioflavonoids extracts appears to inhibit UV harmful effects on human keratinocytes [78]. Apart from oral administration, direct application of hesperidin enhances epidermal permeability barrier homeostasis through the stimulation of epidermal proliferation, differentiation, as well as lamellar body secretion [79]. Naringin also protects UVB-induced skin damage by regulating the p38 MAPK signal pathway [80]. At the same time, naringenin treatment has an anti-apoptotic effect on human keratinocytes as indicated by the modulation of UVB-induced poly(ADP-ribose) polymerase PARP-1 cleavage, caspase activation, and Bax/Bcl2 ratio [81].

3.4. Apple

A great quantity of solid and liquid sludge wastes is produced during apple (*Malus domestica*) processing, as apples are one of the major fruits around the world. The solid residues (apple pomace: 20–30% of the original fruit) contain a mixture of pulp, skin and seeds, are highly biodegradable and contribute to the release of greenhouse gases [82]. At the same time, apple pomace is a valuable source of bioactive molecules, such as hydroxycinnamic acids (chlorogenic acid), benzoic acids (gallic acid), chalcones (phloridzin), flavanols (catechin) and flavonols (quercetin) [83].

Quercetin is a well-known flavonol with intense anti-inflammatory, antioxidant and immunomodulatory properties. Recent studies recognize quercetin as a promising natural agent for treating inflammatory skin diseases [84,85]. However, due to its inferior solubility, quercetin has limited skin penetration ability, and various formulation approaches have been already examined to increase its dermal penetration. An efficient and feasible approach is its incorporation into liposomal and glycerosomal nanoformulations that show a strong ability to scavenge free radicals and protect human keratinocytes against hydrogen peroxide damage [86,87]. As indicated, quercetin provides protection of cutaneous tissue-associated cell types (i.e., human skin fibroblasts, keratinocytes, and endothelial cells) against the injury caused by intracellular peroxides generated by UVB irradiation and further limits secretion/activity of MMPs and GSH depletion [88–91]. In detail, quercetin and its glycosylated form quercitrin suppress MMP-2 and -9 activities through the decrease of ROS formation [92,93], modification of TGF-β expression [94] and upregulation of protein levels of the transcription factor Nrf2 [95].

3.5. Grapes

Grapes (*Vitis vinifera*) contain valuable phenolic components and their byproducts are low-cost sources of natural ingredients that can be used in cosmetic industry [96]. Grape pomace or marc is consisted of stems, seeds and peels and accounts for about 20% of the weight of the grape processed into wine [97]. Flavonoids (epicatechin-3-*O*-gallate and epicatechin, catechins, anthocyanins and proanthocyanidins) and stilbenes (resveratrol) are also contained in grape byproducts and possess several biological properties, such as anticancer, antiviral, antimicrobial, cardioprotective, neuroprotective, hepatoprotective, anti-inflammatory and antioxidant [98,99]. Grape seed proanthocyanidins (GSPs) reduce UVB-induced hydrogen peroxide formation, oxidation procedures and DNA damage. They are potent antioxidants and free radical scavengers that protect skin against premature ageing [100] by inhibiting collagenase and elastase activities [101] and suppressing inflammatory molecules such as IL-1 and prostaglandin (PGE) metabolites [102]. GSPs further inhibit skin tumor formation in hairless mice exposed to carcinogenic UV radiation [103]. At the same time, phosphorylation of ERK1/2, JNK, p38 and MAPK proteins and activation of NF-κB/p65 pathway is suppressed after GSP application [104,105].

Resveratrol (3,5,40-trihydroxy-trans-stilbene) is found in natural products such as the skin of red grapes and displays a protective action against SA and various other cutaneous disorders by downregulating MMP-9 expression, protecting collagen from UV radiation [106], minimizing mitochondrial dysfunctions and blocking apoptotic events in keratinocytes [107–109]. Human skin has specific bonding sites for resveratrol [110] that inhibits the formation of ROS in UVB-exposed human keratinocytes, suppresses the activation of caspases-3 and -8 pathways [111], decreases phosphorylation of survivin [112] and downregulates ornithine decarboxylase (ODC), cyclooxygenase [113] and tyrosinase activities (cAMP signaling pathway) [114]. Moreover, it appears to block UVB-mediated activation of the NF-κB pathway in the normal human epidermal keratinocytes in a time- and dose-dependent manner [115,116].

On the other hand, resveratrol activates the Nrf2 pathway that regulates the expression of numerous genes encoding antioxidant enzymes and modulates cellular antioxidant status, partially by stimulating cellular GSH biosynthesis [117]. Furthermore, resveratrol causes significant decreases in UVB-mediated upregulation of MAPK [118]. At the same time, it protects human keratinocytes against

UVA-induced oxidative stress damage by downregulating Kelch-like ECH-associated protein 1 (*Keap1*) expression [119]. Resveratrol is also able to induce phosphorylation of epidermal growth factor receptor (EGFR), of which signaling pathway regulates the expression of IL-8 by human keratinocytes [120]. In addition, resveratrol upregulates the heat shock protein *Hsp70B* gene expression that plays an important role in the cytoprotection [121]. Topical application of resveratrol to the skin seems to be more efficient in mammals than dietary administration, because of its rapid metabolism into glucuronides and sulfonates by the intestine and liver that leads to a poor plasmatic bioavailability [122]. Moreover, resveratrol could be delivered through lipid nanoparticles that are viable carriers providing long-lasting antioxidant benefits to the skin [123].

3.6. Pomegranate

Pomegranate (*Punica granatum* L.) cultivation has gained interest in the last few decades due to its important properties against several diseases. The antioxidant potential of pomegranate is attributed to polyphenols, such as punicalins, punicalagins, gallagic and ellagic acid [124]. Pomegranate extracts provide a significant protection against UVB-induced damage in cultured human skin fibroblasts [125]. In detail, pomegranate fractions promote procollagen proliferation and synthesis and downregulate MMP-1 (also known as interstitial collagenase) production in dermal fibroblasts of human skin cells [125–127].

Pomegranate byproducts resulted in amelioration of UVB-mediated damage by inhibiting cyclobutane pyrimidine dimers (CPD), MMPs (MMP-1, -2, -3, -7, -9 and -12), 8-dihydro-2′-deoxyguanosine (8-OHdG), protein oxidation and proliferating cell nuclear antigen (PCNA) protein expression [128]. Furthermore, the pomegranate extract protects human skin fibroblasts against UV exposure by reducing activation of the pro-inflammatory transcription factor NF-κB and by blocking proapoptotic caspase-3 pathway [129]. At the same time, direct application of pomegranate extracts results in inhibition of MAPK phosphorylation and downregulation of NF-κB pathways in mice [130] and humans [131]. Ellagic acid is a phenolic acid found in pomegranate that blocks infiltration of inflammatory macrophages in the integuments and diminishes the production of pro-inflammatory cytokines IL-1β and IL-6, when topically applied to hairless mice chronically exposed to UVB [132].

3.7. Onion and Garlic

Onion (*Allium cepa* L.) byproducts possess antiallergic and anti-inflammatory properties due to the presence of flavonoids (anthocyanins and quercetin) [133]. The effects of these flavonoids have been described above in detail (Sections 3.4 and 3.5, respectively). Garlic (*Allium sativum*) also has a high phenolic content and its application could offer protection against UV radiation, contributing to an improvement of fibroblasts' proliferative capacity [134], skin rejuvenation [135] and reverse of certain clinical features of cutaneous aging [136,137].

3.8. Mango

Mangoes (*Mangifera indica* L.) are one of the most important fruits worldwide with enormous quantities of waste that possess anti-inflammatory and immunomodulatory properties as a result of its phenolic compounds [138], such as quercetin, anthocyanins, gallic and ellagic acids [139]. As indicated, mango extract plays a protective role against UVB-induced SA in hairless mice through the inhibition of epidermal thickness and hypertrophy and the increase in collagen bundles [140].

4. Conclusions

Several intrinsic mechanisms and compounds, such as melanin, apoptosis, increased epidermal thickness, DNA repair mechanisms, tissue inhibitors of metalloproteinase and antioxidants, protect the skin against exogenous damage. However, the efficacy of these defense mechanisms declines with age or is negatively affected by environmental insults leading to SA. As shown in this review paper, the use of agro-industrial byproducts or their bioactive compounds could serve as an alternative,

aiming to prevent environment-induced SA. However, growing advances in research in the fields of molecular biology are necessary in order to take advantage of these opportunities for future natural skin photoprotectans development. Research should be also targeted at treatment approaches of agro-industrial byproducts that will allow sustainable recovery, stability and safety of their bioactive components.

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