

Ultraviolet A protective potential of plant extracts and phytochemicals

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Chronic exposure to solar radiation is related to an increased incidence of various skin disorders, including premature skin aging and melanoma and non-melanoma skin cancers. Ultraviolet (UV) photons in particular are responsible for skin damage. Solar UV photons mainly belong to UVA wavebands, however UVA radiation has been mostly ignored for a long time. At the cellular level, UVA photons mainly provoke indirect oxidative damage to biomolecules via the massive generation of unstable and highly reactive compounds. Human skin has several effective mechanisms that forestall, repair and eliminate damage caused by solar radiation. Regardless, some damage persists and can accumulate with chronic exposure. Therefore, conscious protection against solar radiation (UVB+UVA) is necessary. Besides traditional types of photoprotection such as sunscreen use, new strategies are being searched for and developed. One very popular protective strategy is the application of phytochemicals as active ingredients of photoprotection preparations instead of synthetic chemicals. Phytochemicals usually possess additional biological activities besides absorbing the energy of photons, and those properties (e.g. antioxidant, anti-inflammatory) magnify the protective potential of phytochemicals and extracts. Therefore, compounds of natural origin are in the interest of researchers as well as developers.

In this review, only studies on UVA protection with well-documented experimental conditions are summarized. This article includes 17 well standardized plant extracts (*Camellia sinensis* (L.) Kuntze, *Silybum marianum* L. Gaertn., *Punica granatum* L., *Polypodium aureum* L., *Vaccinium myrtillus* L., *Lonicera caerulea* L., *Thymus vulgaris* L., *Opuntia ficus-indica* (L.) Mill., *Morinda citrifolia* L., *Aloe vera* (L.) Burm.f., *Oenothera paradoxa* Hudziok, *Galinsoga parviflora* Cav., *Galinsoga quadriradiata* Ruiz et Pavón, *Hippophae rhamnoides* L., *Cola acuminata* Schott & Endl., *Theobroma cacao* L. and *Amaranthus cruentus* L.) and 26 phytochemicals.

Key words: UVA radiation, ROS, skin, photoprotection, natural compounds, extract

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INTRODUCTION

Solar radiation is electromagnetic radiation produced by the Sun, ranging from about 0.25 to 4.5 μm in wavelength including infrared, visible, and ultraviolet (UV) light. Sunlight is an inseparable part of human life. It is a key factor in plant photosynthesis as well as in vitamin D₃ synthesis in human skin. However, it also has several negative effects on human health. The harmful effects are mainly associated with the UV waveband. The amount of UV radiation reaching the earth's surface has been increasing over the last few decades. Human lifestyle has changed as well, especially time spent in outdoor activities (sports, sunbathing, or sunbed tanning). As a result, our body, particularly our skin, receives higher doses of UV radiation than before, which is linked with a more frequent incidence of various acute and chronic detrimental cutaneous effects, including skin cancer. Originally, it was thought that only the high energetic photons of the UVB waveband (280–315 nm) are responsible for the adverse effects of solar light. As a result, the photoprotection of human skin was focused on protection against

UVB rays for many years. More recently, an increasing number of independent studies indicated that UVA radiation (315–400 nm) also induces damage to skin cells. It is therefore essential to have effective protection against UVA radiation as well¹. This review summarises studies on pure compounds or extracts derived from natural sources that have demonstrated protective potential against UVA radiation in skin cells and/or tissue.

UVA RADIATION

The sun is primarily a UVA source, as UVA amounts to over 90% of the UV radiation reaching the earth's surface. UVA radiation is further subdivided into UVA1 (340–400 nm) and UVA2 (315–340 nm). UVA photons penetrate deep into the epidermis and dermis of the skin. About 80% of UVA radiation reaches the dermo-epidermal junction and penetrates into the papillary dermis. In this way UVA may affect most of the skin cells, especially keratinocytes, melanocytes, fibroblasts and endothelial cells in blood vessels. UVA-induced responses in cells occur

predominantly via the activation of oxidative processes initiated by endogenous photosensitization. UVA photons primarily initialize the production of reactive oxygen and nitrogen species (ROS, RNS) through interacting with endogenous chromophores (photosensitizers). In particular superoxide and singlet oxygen is produced. The latter can be dismutated to hydrogen peroxide, which in turn can produce hydroxyl radicals after reacting with metal ions. RNS include nitric oxide and peroxynitrite. The cellular photosensitizers have not been fully characterized, but candidates include bases of nucleic acids, aromatic amino acids, NAD(P)H, heme, quinones, flavins, porphyrins, 7-dehydrocholesterol, eumelanin, urocanic acid etc. ROS/RNS can oxidize cellular proteins, lipids, and saccharides. The oxidized products of lipids include alkoxyl radicals, aldehydes, alkanes, lipid (hydro)peroxides and epoxides. These highly reactive compounds may further provoke oxidative damage to biomolecules. As for proteins, all amino acid side chains can be oxidized to generate protein carbonyl groups. The sulphhydryl groups of methionine and cysteine are particularly susceptible to oxidation. Several DNA replication and repair proteins have been shown to be targets of reactive compounds that arise upon UVA exposure. ROS/RNS can also induce various types of oxidative DNA lesions such as single-strand breaks and DNA-protein crosslinks, but mainly altered DNA bases. Due to their lowest ionisation potential, guanine bases are the most susceptible to oxidation, and 8-hydroxydeoxyguanine (8-OH-dG) is a characteristic oxidative product. UVA

was also found to produce a significant yield of cyclobutane-pyrimidine dimers (CPD). ROS/RNS, unstable oxidised products as well as DNA lesions can affect various cellular pathways and the expression of numerous genes such as inflammatory cytokines, transcription factors, matrix metalloproteinases (MMP), mitogen-activated protein kinases (MAPK), or pro- and anti-apoptotic genes. These signalling molecules initiate the development of pathological changes in skin tissue such as altered epidermal cell proliferation and differentiation, decrease in collagen synthesis, upregulation of extracellular matrix-degrading enzymes such as collagenase (MMP-1), stromelysin (MMP-3), gelatinase (MMP-9) or elastase. On the other hand, increased levels of oxidatively modified molecules stimulate the activity, activation or synthesis of protective molecules such as nuclear factor erythroid-2 related factor 2 (Nrf2), phase 2 detoxifying enzymes (e.g., glutathione *S*-transferase (GST), NADPH quinone oxidoreductase-1 (NQO1), γ -glutamate-L-cysteine ligase (γ -GCL) or heme oxygenase-1 (HO-1)), DNA repair enzymes and others that aim to suppress the adverse biological effects of UVA radiation. However, intensive exposure to UVA light can exceed protective mechanisms, and chronic exposure to UVA radiation leads to the step-by-step accumulation of oxidatively modified molecules and loss of the vascular network, all of which may result in skin inflammation, immunosuppression, photodermatosis, premature skin aging (photoaging) and/or carcinogenesis¹⁻⁴ (Fig. 1).

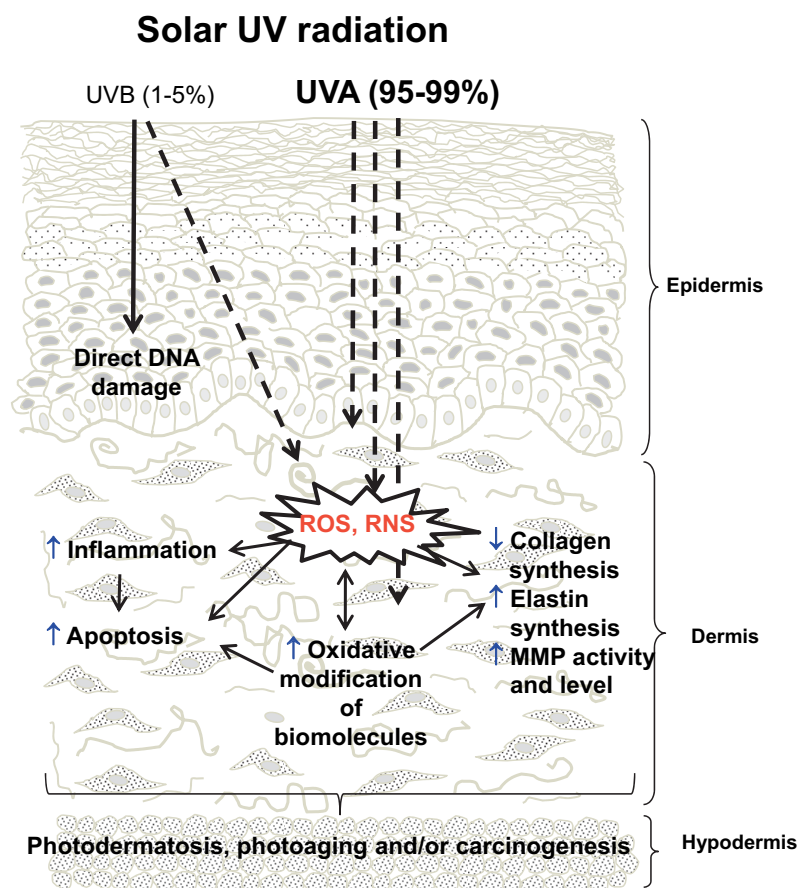


Fig. 1. Effects of solar UV radiation on skin tissue.

Table 1. Plants with UVA protective potential.

Botanical name	Local name	Family	Used parts	Method	Active phytochemicals
<i>Aloe vera</i> (L.) Burm.f.	Aloe	Liliaceae	leaves	<i>In vitro</i>	phenolic compounds, anthracene hydroxyl derivatives, enzymes
<i>Amaranthus cruentus</i> L.	Blood amaranth, red amaranth, Purple amaranth, Prince's feather, Mexican grain amaranth	Amaranthaceae	seeds	<i>In vitro</i>	flavonoids, phenolic acids, vitamins, minerals, amino acids, bioactive peptides
<i>Camellia sinensis</i> (L.) Kuntze	Tea	Theaceae	leaves	<i>In vitro, In vivo</i>	catechins
<i>Cola acuminata</i> Schott & Endl.	Cola nut	Malvaceae	seeds	<i>In vivo</i>	catechins, procyanidin, tannins, caffeine, theobromine
<i>Theobroma cacao</i> L.	Cocoa tree, Cacao tree	Malvaceae	beans	<i>In vivo</i>	flavonoids, catechins, epicatechins, procyanidins, caffeine, theobromine
<i>Galinsoga parviflora</i> Cav.	Guasca, Mielcilla galinsoga, Gallant soldier, Quickweed	Asteraceae	whole plant,	<i>In vitro</i>	flavonoids and their glycosides, phenolic acids, depsides
<i>Galinsoga quadriradiata</i> Ruiz et Pavón	Shaggy soldier, Hairy galinsoga	Asteraceae	whole plant	<i>In vitro</i>	flavonoids and their glycosides, phenolic acids, depsides
<i>Hippophae rhamnoides</i> L.	Sea buckthorn	Elaeagnaceae	soft parts, seeds	<i>In vitro</i>	polyphenols, carotenoids, sterols, minerals, amino acids, fatty acids
<i>Lonicera caerulea</i> L.	Honeyberry	Caprifoliaceae	fruits	<i>In vitro, In vivo</i>	anthocyanins, flavonoids, phenolic acids
<i>Morinda citrifolia</i> L.	Noni, Pain bush, Hog apple	Rubiaceae	leaves, fruits, roots, bark	<i>In vivo</i>	terpenoids, flavonoids and their glycosides, alkaloids
<i>Oenothera paradoxa</i> Hudziok	Evening primrose	Oenotheraceae	seeds, whole plant	<i>In vitro</i>	flavonoids, phenolic acids, hydrolysable tannins
<i>Opuntia ficus-indica</i> L. Mill.	Nopal cactus, Prickly pear	Cactaceae	cladodes	<i>In vitro</i>	flavonoids, phenolic acids
<i>Polypodium aureum</i> L.	Calaguala	Polypodiaceae	whole plant	<i>In vitro, In vivo</i>	benzoate and cinnamate derivatives
<i>Punica granatum</i> L.	Grenade, Granat	Lythraceae	fruits	<i>In vitro, In vivo</i>	phenolic acid, anthocyanins, anthocyanidins, flavanols, flavanes
<i>Silybum marianum</i> L. Gaertner	Milk thistle	Asteraceae	seeds	<i>In vitro</i>	flavonolignans
<i>Thymus vulgaris</i> L.	Thyme	Lamiaceae	leaves, flowers	<i>In vitro, Ex vivo human skin</i>	terpenes
<i>Vaccinium myrtillus</i> L.	Bilberry	Ericaceae	fruits	<i>In vitro</i>	anthocyanins

PLANT EXTRACTS AND PHYTOCHEMICALS WITH UVA PROTECTIVE POTENTIAL

In response to the environment, many living organisms produce specific secondary metabolites that help them to grow successfully and continue their lineage. Some of these secondary metabolites have been found to provide UV protective properties, even though they probably have other physiological roles. These compounds with UV protective activities are widely distributed across the microbial, plant and animal kingdoms, and share some common chemical features⁵. They act as UV absorbers (blockers) including phenolic acids, flavonoids, non-flavonoids and terpenoids. These compounds can prevent or diminish the penetration of UV photons into the skin tissue, resulting in a reduction in the interaction of UV photons with endogenous chromophores, oxidative stress, DNA damage and inflammation. Besides these abilities, some phytochemicals were also found to modulate multiple signalling pathways⁶. Therefore, these naturally occurring compounds have gained considerable attention for their potential use as effective agents for preventing or reducing the UV-induced oxidative modification of biomolecules and subsequent events involved in skin pathology such as photoaging and skin cancer. This review makes an attempt to summarize the results of research on the protective properties of various phytochemicals or extracts, with the focus on UVA radiation. Only papers with well characterized phytochemicals or extracts and experimental conditions were selected for the review.

Plant extracts

Camellia sinensis

Tea (*Camellia sinensis* (L.) Kuntze) is a plant of the Theaceae family. A hot water infusion of tea leaves is one of the most consumed beverages in the world. Tea is divided into subtypes based on its processing. White tea consists of minimally processed young leaves. Green tea originates from minimally processed mature leaves, while oolong tea is semi-fermented and black tea is fully fermented. Green tea is an abundant source of polyphenols known as catechins. They generally account for 30–42% of the dry solids in brewed green tea. The major catechins found in green tea include (-)-epicatechin (EC), (-)-epicatechin-3-gallate (ECG), (-)-epigallocatechin (EGC), and (-)-epigallocatechin-3-gallate (EGCG). EGCG is the most abundant and forms 50–80% of the total amount of catechins. The polyphenol content of black tea is different from that of green tea due to the degree of oxidation during processing. It mainly contains the following polyphenols: thearubigins, theaflavins, flavonols, and catechins. Among the tea polyphenols, EGCG has been shown to be the most effective chemoprotective agent against cutaneous inflammatory or carcinogenic responses. The potential of tea polyphenols against UVB-induced DNA damage, inflammation, oxidative stress, alterations in cell signalling pathways, and epigenetics changes that play a pivotal role in photocarcinogenesis are summarized in a recent review⁷. EGCG is also the most commonly evaluated green tea component in terms

of UVA protection. The EGCG pre-treatment of a spontaneously transformed aneuploid immortal human skin keratinocyte cell line (HaCaT) reduced UVA-induced ROS generation, DNA single-strand breaks and alkali-labile site formation, hypoxanthine-guanine phosphoribosyl transferase (HPRT) mutant frequency⁸ as well as nuclear factor kappa B (NF- κ B) nuclear translocation and interleukin-6 (IL-6) secretion⁹. EGCG protected normal human dermal fibroblasts (NHDF) against UVA damage by downregulating the transcription activity of Jun protein and the mRNA and protein level of MMP-1 (ref.¹⁰). The treatment of human infant skin fibroblasts with EGCG decreased beta-galactosidase positive cell number and the frequency of the HPRT gene mutation in UVA-irradiated cells¹¹. EGCG inhibited the UVA-induced cell death of ARPE19 adult human retinal pigment epithelial cells. In addition, EGCG suppressed intracellular hydrogen peroxide generation, extracellular signal-regulated kinases (ERK), c-Jun N-terminal kinase 1/2 (JNK) and p38 kinase activation as well as cyclooxygenase 2 (COX-2) protein expression in the irradiated cells¹². The pre-treatment of male Wistar albino rats with EGCG in a hydrophilic ointment resulted in a significant reduction in sunburn cell count and degeneration and disintegration in the dermo-epidermal junction in UVA-exposed animals¹³. Pre-treatment with EGCG reduced wrinkles in the dorsal trunk and also prevented the reduction of collagen synthesis in the skin of UVA-irradiated hairless mice¹⁴.

The UVA protection of less abundant green tea polyphenols was also evaluated in several *in vitro* studies. The pre-treatment of a FEK4 human skin fibroblast cell line with EGC caused a strong reduction in UVA-induced HO-1, but MMP-1 and COX-2 mRNA expression was stimulated. On the other hand, in a KB human oral carcinoma cell line, UVA-stimulated COX-2 mRNA was strongly reduced with EGC (ref.¹⁵). In UVA-irradiated HaCaT, EGC pre-treatment increased viability, and reduced hydrogen peroxide production and ERK activation¹⁶. The pre-treatment of FEK4 fibroblasts with EC and its metabolite 3'-O-methyl epicatechin (MeOEC) increased cell viability and reduced the number of necrotic cells. EC further prevented the suppression of HO-1 transcription¹⁷. EC and MeOEC also suppressed the UVA-mediated release of chelatable iron and the mRNA expression of MMP-1 in FEK4 fibroblasts. EC treatment also protected the lysosomal membrane against UVA-induced damage¹⁸. In both studies^{17,18}, EC was more effective than its metabolite. The application of a nano-gel formulation of catechin to the skin of male Wistar rats reduced the oxidative stress induced by UVA, most significantly improving the level of cutaneous antioxidant enzymes (superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT)), and reducing the level of thiobarbituric acid reactive substances (TBARS) (ref.¹⁹).

Silybum marianum

Silymarin (SM) is a standardized polyphenol fraction from the seeds of *Silybum marianum* L. Gaertner (syn. *Carduus marianus* L. or milk thistle) from the Asteraceae family. *S. marianum* is one of the oldest known plants, and

has been widely used in traditional European medicine since ancient times. The plant as well as SM is rich in polyphenols. SM contains approximately 70–80% flavonolignans, and 20–30% is a chemically undefined fraction, mostly comprised of polymeric and oxidised polyphenolic compounds. The main polyphenolic component of SM is the flavonolignan silybin (SB). Other less abundant components are the flavonolignans isosilybin (ISB), silychristin (SC), silydianin (SD) and the flavonoid taxifolin. A minor component but with a significant biological potential is the flavonolignan 2,3-dehydrosilybin (DHSB) (ref.²⁰). SM has been primarily used in the treatment of liver disorders including hepatitis, alcoholic liver diseases, and cirrhosis, and is also useful against toxin-induced liver toxicity. Laboratory studies suggest that there is no significant difference between SM and its major component SB in terms of biological activities. Research results showed antioxidant activity, modulation of the immune system and various signalling pathways for both SM and SB (ref.²¹). Several reports documented the ability of SM and SB to reduce chemically- and UVB-stimulated skin damage, including carcinogenesis^{21,22}.

The pre-treatment of NHDF with SM and SB resulted in a reduction in UVA-stimulated ROS and the production of DNA single-strand breaks, as well as in the prevention of glutathione (GSH) depletion, a decrease in the activation of caspase-3 and MMP-1 protein. SM also moderately increased HO-1 and reduced the level of heat shock protein 70 (HSP 70) (ref.²³). Also, less abundant flavonolignans in silymarin, ISB, SD, SC and DHSB demonstrated the ability to reduce UVA-induced damage in NHDF (ref.²⁴). The post-treatment of UVA-irradiated HaCaT with SM (ref.²⁵) and SB (ref.²⁶) resulted in the diminution of UVA-caused ROS production, caspase-3 activation, GSH and ATP depletion as well as lipid peroxidation and the formation of DNA single-strand breaks.

However, besides many reports on the photoprotection of SM and its main congener SB, there are also controversial studies demonstrating an *in vitro* phototoxic activity of SM (ref.²⁷) and SB (ref.²⁸). The phototoxic potential of the minor flavonolignan DHSB, a dihydroxy derivative of SB, was recently also described in skin cells^{24,29}. DHSB is very potent antioxidant with a moiety that is structurally similar to quercetin, which has also been shown to be a phototoxic compound. The phototoxic potential of DHSB and perhaps SM needs be confirmed *in vivo* or in clinical trials.

Punica granatum

Pomegranate also known as grenade, granats, and punica apple, is a fruit of the *Punica granatum* L. tree from the family Lythraceae. It is indigenous to the Himalayas in northern India through to Iran, parts of Southeast Asia, the East Indies, and tropical Africa, and grows in almost all parts of the Mediterranean region. Pomegranate is rich in phenolic acids, flavanols, flavones, flavonones, anthocyanidins, and anthocyanins³⁰. The fruit and its pericarp contain two main polyphenol groups, anthocyanins (cyanidin and delphinidin) and hydrolysable tannins (punicalin, pedunculagin, punicalagin, and gallagic and el-

lagic esters of glucose). Pomegranate has been recognized since antiquity for its healing properties. Pomegranate fruit extract exhibits antioxidant and anti-inflammatory properties. Many *in vitro* and *in vivo* studies demonstrated a photoprotective effect of pomegranate against UVB radiation²².

UVA-induced ROS generation and the cell death of SKU-1064 human skin fibroblasts were reduced by pomegranate extract pre-treatment in a dose-dependent fashion³¹. A concentrated pomegranate solution decreased UVA-induced MMP-1 activity in neonatal NHDF (ref.³²). The pre-treatment of normal human epidermal keratinocytes (NHEK) with pomegranate fruit extract resulted in a dose-dependent inhibition of the UVA-mediated phosphorylation of signal transducer and activator of transcription 3 at Tyr705, AKT at Ser473 and ERK1/2. The extract also inhibited the UVA-mediated phosphorylation of mTOR (a serine-threonine kinase involved in cell growth), an increase in Ki-67 (a protein associated with cellular proliferation and ribosomal RNA transcription) and proliferating cell nuclear antigen (PCNA), an essential factor in DNA replication. Pre-treatment with the extract also increased UVA-induced cell-cycle arrest in the G1 phase and the expression of pro-apoptotic proteins Bax and Bad, with downregulation of the expression of the anti-apoptotic protein Bcl-xL (ref.³³).

Polypodium leucotomos

The tropical fern *Polypodium leucotomos* (syn. *Phlebodium aureum* L. or *Polypodium aureum* L.) from the Polypodiaceae family is native to Central and South America. *P. leucotomos* is rich in phenolic compounds, especially benzoate and cinnamate derivatives. Chlorogenic, *p*-coumaric, vanillic, cinnamic, caffeic and ferulic acid are the most abundant of them, and these compounds are known for their photoprotective potential (see part *Phytochemicals with UVA protective potential*). *P. leucotomos* has been traditionally used for treating various skin disorders (e.g., psoriasis and atopic dermatitis) in its areas of origin³⁴. Clinical scientific evidence suggests that *P. leucotomos* is also beneficial for the treatment of vitiligo and the prevention of polymorphic light eruption. Photoprotective activity has been assessed in animals, healthy volunteers as well as in patients suffering from several cutaneous diseases such as vitiligo, psoriasis, idiopathic photodermatitis or melasma^{35,36}.

A hydrophilic extract of *P. leucotomos* efficiently protected NHDF and HaCaT survival and restored their proliferative capability when the cells were exposed to UVA radiation. The extract also prevented UVA-induced morphological changes in NHDF, especially the disorganisation of F-actin-based cytoskeletal structures, coalescence of the tubulin cytoskeleton and mislocalization of adhesion molecules such as cadherins and integrins³⁷. *P. leucotomos* extract inhibited the protein expression of MMP-1 and MMP-2 and stimulated the levels of the tissue inhibitors of MMP-1 and -2 (TIMP-1 and TIMP-2) in UVA-irradiated NHDF and CRL-1619 melanoma cells. The extract pre-treatment also stimulated the protein levels of collagen I and V in UVA-radiated fibroblasts³⁸.

Oral pre-treatment of male hairless rats with *P. leucotomos* extract significantly reduced GSH oxidation and the formation of oxidized GSH (GSSG) in both erythrocytes and plasma stimulated with UVB/UVA radiation (9:10). The extract also significantly increased CAT activity and the GSH/GSSG ratio, and reduced the depletion of Langerhans cells in the epidermis of irradiated animals³⁹. The oral administration of *P. leucotomos* extract to human volunteers (phototypes II to III) reduced negative clinical signs of PUVA therapy, in particular phototoxic reaction and pigmentation. In the skin of individuals treated with the extract, a significant reduction in sunburn cells, preservation of Langerhans cells, decrease in mast cells infiltration, and decrease in vasodilation were found⁴⁰.

Vaccinium myrtillus

Bilberry (*Vaccinium myrtillus* L.), is a well-known small shrub, also called blueberry, huckleberry or whortleberry that grows wild in Northern Europe, North America, and Asia. Bilberry belongs to the Ericaceae family. The fruit is a blue-coloured, fleshy berry, which contains several bioactive secondary metabolites, including flavonoids, vitamins, sugars, and pectin. In terms of flavonoids, anthocyanins are the most widely studied class of bioactive compounds of this plant. Multiple pharmacological activities (related to the anthocyanidin fraction) include antioxidant, anti-inflammatory, anti-atherosclerosis, or wound healing⁴¹. Some studies showed the beneficial effects of bilberry on skin. For example anthocyanins from bilberry have been found to alleviate pruritus in a mouse model of chronic allergic contact dermatitis⁴² or to protect HaCaT against UVB-induced damage⁴³.

The pre-treatment of HaCaT with *V. myrtillus* fruit extract resulted in the attenuation of UVA-stimulated ROS formation, lipid peroxidation and the depletion of intracellular GSH (ref.⁴⁴). In another study, *V. myrtillus* extract increased the cell viability of HaCaT and reduced UVA-provoked ROS generation, malondialdehyde (MDA) production, DNA damage and the number of apoptotic cells⁴⁵. Anthocyanins that are rich in the ethanolic extract from bilberry (BE) as well as BE-loaded ultra-deformable liposomes increased the viability of UVA-irradiated HaCaT (ref.⁴⁶).

Lonicera caerulea

Lonicera caerulea L., also called blue honeysuckle, honeyberry, edible honeysuckle or sweet berry honeysuckle, is a shrub from the Caprifoliaceae family. *L. caerulea* can be found mainly in northern Russia, China, and Japan. Its berries are oval to long in shape and dark navy blue to purple in colour. The fruits contain several groups of phenolics including anthocyanins, flavonoids and low-molecular-weight phenolic acids. These compounds have been reported to have multiple biological activities, including antioxidant, anti-inflammatory and cytoprotective⁴⁷. The potential of *L. caerulea* polyphenols and berries to reduce UVB-induced damage was demonstrated *in vitro*⁴³ and *in vivo*⁴⁸.

The pre- and post-treatment of HaCaT with the polyphenolic fraction of *L. caerulea* significantly increased cell viability and suppressed UVA-induced ROS production, lipid peroxidation and the depletion of reduced GSH (ref.⁴⁹). Consuming *L. caerulea* berries reduced MDA production and increased CAT activity and GSH level in the skin and erythrocytes of hairless mice. The protein levels of NQO-1 and γ -GCL were reduced, while HO-1 level was increased in the skin of UVA-exposed mice fed *L. caerulea* berries. The plasma level of IL-17 was increased and of IL-12 was reduced in the mice consuming the berries exposed to UVA light. Histological changes in the nuclei of basal cells induced by UVA exposure were reduced in the animals consuming *L. caerulea* berries⁵⁰.

Thymus vulgaris

A flowering, aromatic perennial herb from the Lamiaceae family, *Thymus vulgaris* L. is commonly known as thyme. *T. vulgaris* is native to southern Europe from the western Mediterranean to southern Italy. Abundant constituents of *T. vulgaris* include the terpenes thymol (2-isopropyl-5-methylphenol), carvacrol and borneol. Essential oils extracted from fresh leaves and flowers are used as aroma additives in food, pharmaceuticals and cosmetics. Thyme possesses various beneficial effects such as antioxidant, antiseptic, antimicrobial, carminative, antitussive, or spasmolytic⁵¹. *T. vulgaris* extracts were reported to be immunomodulatory, anti-inflammatory or hepatoprotective agents⁵². An ethanolic extract of *T. vulgaris* seeds reduced UVB-caused damage to NHDF and hairless mice skin⁵³. *T. vulgaris* leaf water extract was demonstrated to reduce UVB-induced damage in *ex vivo* human skin⁵⁴.

A leaf extract from *T. vulgaris* and thymol protected the low differentiated keratinocyte cell line NCTC 2544 against UVA-induced damage, and especially reduced ROS level, lipid peroxidation and DNA damage⁵⁵.

Opuntia ficus-indica

Opuntia ficus-indica L. Mill., commonly called prickly pear or nopal cactus, belongs to the dicotyledonous angiosperm Cactaceae family. *O. ficus-indica* is a tropical and subtropical plant that grows in arid and semi-arid areas in Mexico, Latin America, South Africa and Mediterranean countries. The cactus cladodes contain vitamins and various phenolic acids and flavonoids, especially quercetin 3-methyl ether, a highly efficient radical scavenger. Extracts of *O. ficus-indica* have antioxidant and anti-inflammatory activity and remarkably improve wound healing⁵⁶.

Water extract from *O. ficus-indica* cladodes was shown to protect HaCaT against UVA radiation, particularly against UVA-induced ROS production, lipid peroxidation and GSH depletion. Moreover, the cleavage of caspase-3 and caspase-7 and the phosphorylation of p38 and MAPK-activated protein kinase 2 (proteins directly involved in stress signalling pathways induced by UVA radiation) were reduced in irradiated cells pre-treated with the extract⁵⁷.

Morinda citrifolia

Morinda citrifolia L. is a tropical tree with a distinctive, ovoid, “grenade-like” yellow fruit. *M. citrifolia*, commonly known as noni (other names include Pain bush, Pain killer tree, Cheese fruit, Forbidden fruit, Headache tree, Nino, Pinuela, Hog apple or Wild pine), belongs to the Rubiaceae family. *M. citrifolia* is widely distributed in areas of Micronesia, Hawaii, Tahiti, Australia, and Southeast Asia. Various compounds were identified in its leaves, fruits and roots, such as vitamin C and A, carotene terpenoids, alkaloids, anthraquinones, flavonoids and their glycosides. The fruits, roots, bark and leaves of *M. citrifolia* have been used throughout Polynesia as a folk medicine for the treatment of many diseases including various cancers, burns, skin inflammation and wounds⁵⁸. *M. citrifolia* leaf extract was also shown to reduce UVB-induced erythema in human volunteers⁵⁹.

An ethanolic extract of *M. citrifolia* seeds exhibited an inhibitory effect on MMP-1 secretion in UVA-irradiated NHDF. A constituent of the extract, 3,3-bisdemethylpinoselinol, inhibited this MMP-1 secretion as well. The compound also reduced the phosphorylation of p38 and JNK (ref.⁶⁰).

Aloe vera

Aloe vera (L.) Burm. f. (syn. *Aloe barbadensis* Mill.) is a perennial plant with thick, succulent, and long leaves that belongs to the Liliaceae family. *A. vera* grows easily in hot and arid regions. The *A. vera* plant contains phenolic compounds, anthracene hydroxyl derivatives (namely aloin A and B (collectively known as barbaloin) emodin, anthranol), enzymes (e.g., amylase, lipase, COX, SOD and CAT) and also pro-vitamin β -carotene, vitamins (B1, B2, B6, C, α -tocopherol, and folic acid). The bioactive components in *A. vera* have been reported to have antifungal, antiseptic, antiviral, antibacterial, anti-inflammatory, antioxidant, immuno-modulatory and wound healing properties^{61,62}. Several studies also demonstrated beneficial effects of *A. vera* on UVB-induced damage⁶³⁻⁶⁵.

A whole-leaf extract of *A. vera* reduced UVA-induced photodamage to HaCaT. The extract increased cell viability, membrane integrity and lysosomal stability and reduced ROS generation and morphological changes (cell size, granularity) (ref.⁶⁶).

Oenothera paradoxa

Evening primrose (*Oenothera paradoxa* Hudziok) is a biennial herb originating from Mexico and Central America, belonging to the Oenotheraceae family. Today, it is also cultivated in Europe and parts of Asia for the production of seeds that are a great source of γ -linolenic acid. Defatted seeds represent a prominent source of polyphenolic compounds (flavonoids, phenolic acids, and hydrolyzable tannins). In traditional medicine, the whole plant or leaf juice is used for its analgesic and wound healing properties, especially as topical remedies to alleviate cutaneous inflammation. A number of studies demonstrated the antioxidant activity of *O. paradoxa* defatted seed extract^{67,68}. *O. paradoxa* defatted seed extract exhibited an

antimigratory, anti-invasive and antimetastatic potential towards prostate and breast cancer cells⁶⁹. An anticancer activity of *O. paradoxa* defatted seeds extract was also found on skin melanoma cells⁷⁰.

The pre-treatment of NHDF with an aqueous extract of *O. paradoxa* defatted seeds increased the number of viable cells, decreased the release of lactate dehydrogenase (LDH), ROS production, lipid peroxidation and the number of cells in late apoptosis after UVA exposure⁷¹.

Galinsoga parviflora and *Galinsoga quadriradiata*

Galinsoga parviflora Cav. and *G. quadriradiata* Ruiz et Pavón are annual herbs belonging to the Asteraceae family originating from the Andes region. The chemical composition of *Galinsoga* herbs is similar. They contain flavonoids and their glycosides (patuletin-7-O- β -D-glucoside), quercimeritrin (quercetin-7-O- β -D-glucoside), quercetagerin (quercetagerin-7-O- β -D-glucoside), luteolin 7- β -D-glucopyranoside, apigenin 7- β -D-glucoside, galinsoside A (5'-hydroxy-7-methoxyflavanone 2'-O- β -D-glucopyranoside), galinsoside B (3',4'-dihydroxy-7-methoxyflavanone 5-O- β -D-glucopyranoside), 7,3',4'-trihydroxyflavanone and 3,5,7,3',4'-pentahydroxyflavanone, and phenolic acids and depsides (vanillic, isovanillic, *p*-coumaric, *p*-hydroxybenzoic, *o*-hydroxyphenylacetic, caffeic, chlorogenic acid and caffeoylglucaric acids and other compounds. The topical application of *Galinsoga* species extracts is used to treat dermatological diseases, such as eczemas, lichens and poorly healing wounds, and also to treat snakebites⁷².

The aqueous extracts of both herbs decrease ROS production and apoptosis in UVA- or UVB-treated NHDF (ref.⁷²). Two isolated caffeic derivatives from *G. parviflora*, 2,3,5-(2,4,5)-tricafeoylaltaric and 2,4(3,5)-dicafeoylglucaric acid, decreased LDH release, intracellular ROS formation and the number of apoptotic cells, and increased GSH level and membrane integrity in UVA-exposed NHDF. Both compounds activated transcription factor Nrf2 and HO-1 expression in non- and/or UVA-exposed NHDF (ref.⁷³).

Hippophae rhamnoides

Sea buckthorn (*Hippophae rhamnoides* L.) is a spiny deciduous flowering shrub in the Elaeagnaceae family. It is native to the cold-temperate regions of Europe and Asia. It is used in the food and cosmetics industries. The oil prepared from soft parts and from the seeds is rich in vitamins (C, E and K), polyphenols, carotenoids, sterols, minerals, amino acids, saturated and unsaturated fatty acids. The *H. rhamnoides* seed oil protected a UVA- and UVB-treated CDD 1102 KERTr human keratinocyte cell line and CCD 1112Sk human fibroblasts. The oil pre-treatment prevents the UVA-stimulated production of ROS and depletion of non-enzymatic antioxidants (thioredoxin (Trx), GSH and vitamins A and E) and enzymatic antioxidants (SOD, glutathione reductase (GSR), GPx, Trx reductase (TrxR)) and stimulated the Nrf2 dependent enzymatic antioxidant HO-1. Sea buckthorn oil also inhibited UVA- or UVB-stimulated phospholipase A2

activity and the production of lipid peroxidation products, 4-hydroxynonenal (4-HNE) and 8-isoprostaglandin F_{2α}. The modulation of endocannabinoid receptors CB1 and CB2 was specific for the different types of UV radiation and skin cells⁷⁴.

Cola acuminata

Cola nut (*Cola acuminata* Schott & Endl. or *Sterculia acuminata*) also called “kola nut” is a popular edible plant native to West Africa. The seed of this large tree has been used in African folk medicine namely for aiding digestion and coughs. The main constituents of cola nut are caffeine, theobromine, and polyphenols, including D-catechin, L-epicatechin, procyanidin B1 and B2 and tannins⁷⁵⁻⁷⁷. The beneficial health effects of substances mentioned above are so notable as chocolate is explored as functional food⁷⁶. Topically applied cola nut extract, and pure alkaloids theobromine, theophylline and caffeine markedly reduced UVA-induced wrinkle formation and histological alterations in dorsal skin of hairless mice, including changes in extracellular matrix proteins and infiltration of leukocytes⁷⁷.

Theobroma cacao

Theobroma cacao L., also called cocoa tree and cacao tree is an evergreen tree in the family Malvaceae, native to tropical regions Central and South America. Cacao beans have been traditionally used to treat the pain of pregnancy, fever, and cough in Central America. Cacao beans contain flavonoids, catechins, epicatechins, procyanidins and xanthine derivatives (caffeine and theobromine). Cacao has been reported to have anti-inflammatory effect, modulates NF-κB and redox sensitive signalling pathways, stimulates immune response, influence insulin resistance and has positive effect on cardiovascular system^{78,79}. Topical application of cacao beans extract suppressed wrinkle formation, changes in dermal connective tissue and neutrophil infiltration caused by UVA-irradiation *in vivo*⁷⁷.

Amaranthus cruentus

Amaranthus cruentus L. is an annual plant with dark pink flowers. Its grains known as amaranth seeds are used as cereal, rich to flavonoids, phenolic acids, essential amino acids, bioactive peptides, micro- and macronutrients including minerals and vitamins. Amaranth seeds contain hydrophilic and hydrophobic antioxidants that contribute anti-inflammatory activity, in lowering risk of the oxidative stress related diseases (diabetes, obesity, cardiovascular disease) and improving gut health. Oil obtained by cold-pressing the grain is valuable due to the presence of unsaturated fatty acids, tocopherols, tocotrienols, phytosterols, and squalene^{80,81}. A recent study evaluated effect of pre- and post-treatment with amaranth oil on UVA-irradiated human skin fibroblasts. The amaranth oil activity was rather poor and its use in combination with other sunscreens is recommended⁸².

PHYTOCHEMICALS WITH UVA PROTECTIVE POTENTIAL

Ferulic acid

Ferulic acid (FA, 4-hydroxy-3-methoxycinnamic acid) is a ubiquitous phenolic acid found in *Commelinidae* plants (rice, wheat, oats, and pineapple), grasses, grains, vegetables, flowers, fruits, leaves, beans, coffee beans, artichoke, peanut and nuts, in its free or conjugated (e.g., polysaccharides, glycoproteins, polyamines) form. FA is more easily absorbed into the body and stays in the blood longer than any other phenolic acids. FA exhibits a wide range of biological effects including antioxidant, anti-inflammatory, anti-allergic, anticarcinogenic, antimicrobial, antiviral, hepatoprotective, vasodilatory or antithrombotic⁸³. Its structure (Fig. 2) is similar to tyrosine and thus FA inhibits melanin formation through competitive inhibition with tyrosine⁸⁴. FA is a strong UV absorber. FA alone⁸⁵ or in combination with vitamin C and E (ref.^{86,87}) exhibited a considerable protection against UVB-induced skin damage, including UVB-induced carcinogenesis.

Relative to UVA light, the FA pre-treatment of the B16F10 mouse melanoma cell line led to the inhibition of UVA-induced melanin synthesis as well as tyrosinase activity and its protein expression. FA also reduced UVA-induced ROS and 8-OH-dG formation and GSH depletion⁸⁸. In HaCaT, FA pre-treatment reduced the UVA-induced decrease in cell viability, ROS formation and the induction of MMP-1 activity and mRNA expression. Moreover, FA was able to upregulate GSH content, γ-GCL mRNA level as well as the activities and mRNA expression of CAT and GPx in UVA-irradiated cells⁸⁹. The pre-treatment of NHDF with FA increased cell viability after exposure to various UVA doses. UVA-stimulated G1-phase arrest in NHDF was also reduced by FA in a dose-dependent manner. Cells pre-treated with FA exhibited its effect on nucleotide excision repair with a significant increase in the expression of the genes of xeroderma pigmentosum complementation group A and C. FA reduced UVA-induced ROS formation and increased the levels of SOD-1 and CAT mRNA. FA also inhibits cellular senescence by reducing senescence-related markers, especially β-galactosidase activity and the mRNA expression of tumour suppressor protein p16, MMP-1 and MMP-3 (ref.⁹⁰). The *in vivo* application of FA in the form of a nanogel significantly increased the level of SOD, GPx and CAT and reduced the MDA level in UVA-irradiated rat skin⁹¹.

Caffeic acid

Another abundant phenolic acid, caffeic acid (CA, 3,4-dihydroxycinnamic acid, Fig. 2) occurs in free and/or various combined forms in a large number of fruits (e.g., blueberries, gooseberries, blackcurrant, orange, lemon, pears), vegetables (e.g., kale, radishes, cabbage, Brussels sprouts, carrots, celery, lettuce, potatoes, eggplant), and herbs (e.g., thyme, sage, basil, oregano) as well as in bee propolis, olive oil and beverages (e.g., apple juice, wine, tea and coffee) (ref.^{92,93}). Studies have demonstrated antioxidant, anti-inflammatory, antitumour and antimeta-

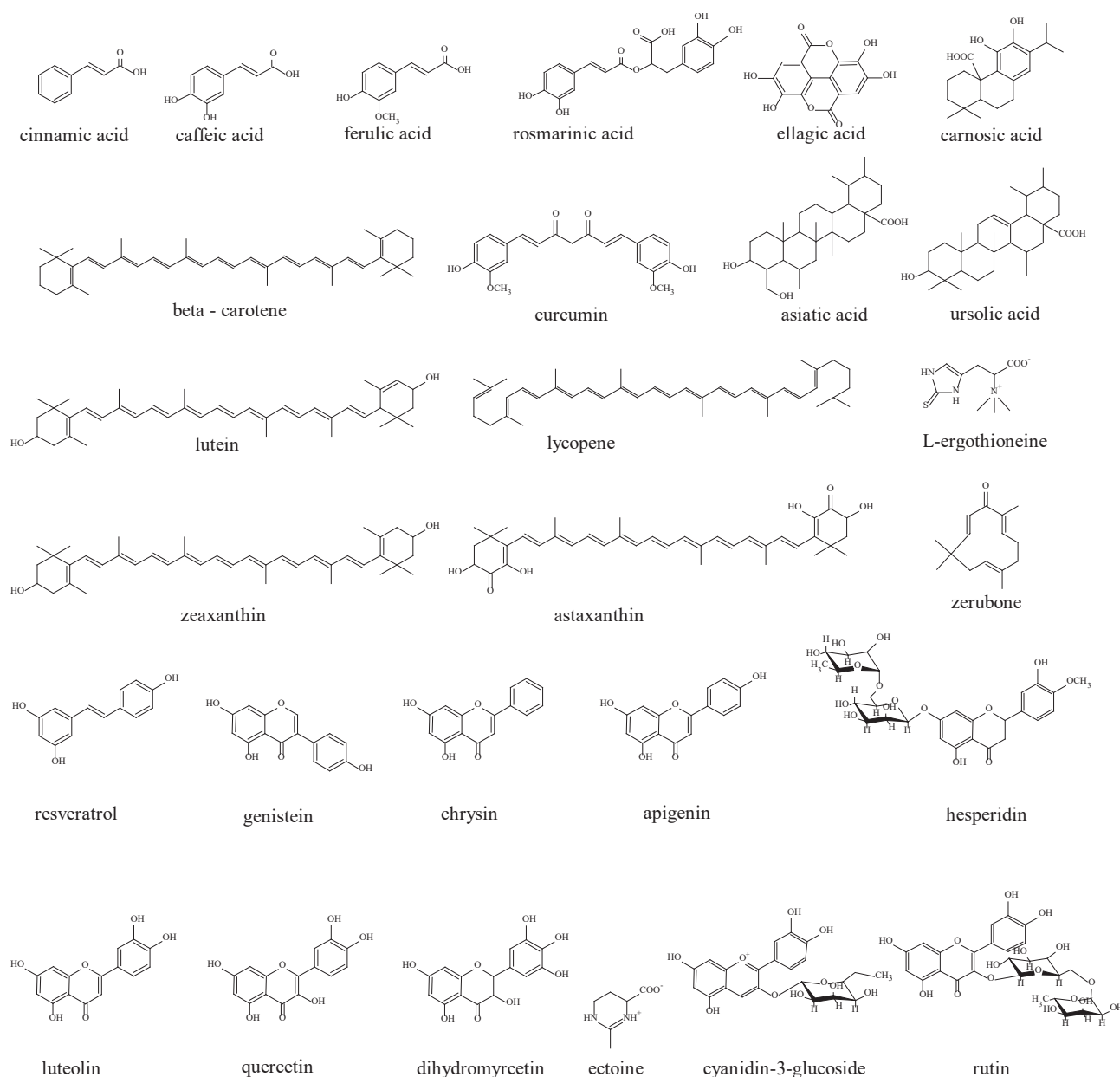


Fig. 2. Structures of phytochemicals with UVA protective potential.

static effects of CA (ref.⁹³). Several papers documented a UVB protective potential of CA (ref.⁹³⁻⁹⁶).

In a B16F10 mouse melanoma cell line, CA pretreatment reduced UVA-induced melanin synthesis and tyrosinase activity and the protein's expression. CA also reduced UVA-induced ROS and 8-OH-dG production and GSH depletion. CA further inhibited the UVA-mediated downregulation of the nuclear level of Nrf-2, the mRNA level of the γ -GCL catalytic and modifier subunit, GST and NQO1, and the protein level and activity of γ -GCL, GST and NQO1 (ref.⁸⁸). In HaCaT, CA reduced UVA-induced cytotoxicity, ROS formation and the induction of MMP-1 activity and mRNA expression. Moreover, CA upregulated GSH content, γ -GCL mRNA level as well as the activities and mRNA level of CAT and GPx in UVA-exposed cells⁸⁹. The topical and oral treatment of hairless

mice suppressed intrinsic and UVA-induced ROS generation in skin tissue⁹⁷.

Cinnamic acid

Cinnamic acid (CIN, 3-phenylacrylic acid) is a phenolic acid generally obtained from cinnamon (*Cinnamomum cassia* (L.) J. Presl). Other sources include citrus fruits, grapes (*Vitis vinifera* L.), tea (*Camellia sinensis* (L.) Kuntze), cocoa (*Theobroma cacao* L.), spinach, celery and brassica vegetables⁹⁸. CIN processes several pharmacological activities, including antioxidant, antimicrobial, anticancer and anti-inflammatory. CIN exists in *trans*- or *cis*-form. The *trans*-CIN (*t*-CIN, Fig. 2) is the predominant form in nature due to its high stability⁹⁹. CIN was demonstrated to be a potent inhibitor of tyrosinase activity, it also inhibited tyrosinase expression and

melanin production *in vitro*, and exhibited a depigmenting activity on a UVB-induced hyper-pigmentation model *in vivo*¹⁰⁰.

The pre-treatment of Hs68 human foreskin fibroblast-derived cells with *t*-CIN reduced UVA-induced cytotoxicity, ROS generation, MMP-1 and MMP-3 over-expression and procollagen type I degradation. *t*-CIN also inhibited UVA-induced photoaging via the suppression of activator protein 1 activation. *t*-CIN enhanced the nuclear translocation of Nrf2 as well as inducing HO-1 and γ -GCL protein expression. *t*-CIN-induced Nrf2 translocation was mediated through protein kinase C (PKC), AMP-activated protein kinase, casein kinase II or ROS signalling cascades. Topically applied *t*-CIN significantly suppressed MMP-1 and MMP-3 activation and maintained sufficient type I procollagen levels in the skin of repeatedly UVA-irradiated female athymic nude mice (BALB/c-nu) (ref.⁹⁹).

Rosmarinic acid

Rosmarinic acid (RA), a phenolic acid, is an ester of caffeic acid and 3,4-dihydroxyphenyllactic acid (Fig. 2). It got its name according to its initial isolation from rosemary (*Rosmarinus officinalis*). RA is commonly found in species of the Lamiaceae family. However, it is also found in species of other higher plant families and in some fern and hornwort species. RA occurs in species used commonly as culinary and/or medicinal plants such as *Ocimum basilicum* (basil), *Melissa officinalis* (lemon balm), *Origanum majorana* (marjoram), *Salvia officinalis* (sage), *Thymus vulgaris* (thyme), *Mentha piperita* (peppermint) or *Prunella vulgaris* (self-heal) (ref.^{101,102}). RA has a number of interesting biological activities, e.g., antioxidant, anti-inflammatory, antiviral or antibacterial¹⁰¹. Several studies found RA to possess the ability to reduce UVB-induced damage to HaCaT (ref.¹⁰³⁻¹⁰⁵).

Topically applied RA exhibited a concentration-dependent suppressive effect on intrinsic and UVA-induced ROS generation in the skin of hairless mice⁹⁷. The oral administration of RA to female albino Swiss mice led to a reduction in cutaneous dysplasia provoked by chronic UVA exposure¹⁰⁶. The post-treatment of UVA-irradiated HaCaT with RA increased cell viability and reduced ROS production, intracellular lipid peroxidation, ATP and GSH depletion as well as DNA damage and the activation of caspase-3 (ref.¹⁰⁷).

Curcumin

Curcumin (CUR, diferuloylmethane, Fig. 2) is a yellow-coloured compound extracted from the rhizome of *Curcuma longa* L. (turmeric). CUR has been employed as a culinary spice and for the treatment of various diseases, including skin disorders and wound healing, dating back to 4000 years ago¹⁰⁸. CUR decreased UVB-induced oxidative stress, inflammation and DNA damage *in vitro*¹⁰⁹ and *in vivo*¹¹⁰.

In UVA-exposed NHDF, CUR reduced the formation of ROS, endoplasmic reticulum stress, inflammation and apoptosis, and increased the activity of antioxidant defence enzymes (SOD and CAT). CUR also influenced collagen metabolism by decreasing MMP-1 and MMP-3

expression and promoted the reparation of cells by increasing the expression of transforming growth factor- β (TGF- β) and the protein Smad2/3, and decreased the expression of Smad7, a TGF- β inhibitor¹¹¹.

Quercetin

The flavonol quercetin (QE, 3,3',4',5,7-pentahydroxyflavone; 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-1-benzopyran-4-one, Fig. 2) is one of the most abundant naturally occurring polyphenols. It is present, primarily in the form of glycosides, in many fruits (e.g., apples, cranberries, cherries, grapes, lemon), vegetables (e.g., onion, peppers, asparagus, lettuce, tomato, broccoli, kale), herbs (e.g., *Ginkgo biloba*, *Apocynum venetum*, *Poacynum hendersonii*, *Opuntia ficus-indica*), olive oil, bee propolis or beverages such as wine and black or green tea^{112,113}. Numerous biological effects of QE have been published in a great number of *in vitro* and *in vivo* studies. Specifically, QE exhibits antioxidant, anti-inflammatory, immunoprotective, and anticarcinogenic effects¹¹². QE also possesses UVB protective activity¹¹⁴⁻¹¹⁶.

QE pre-treatment was found to reduce UVA-induced ROS and 8-OH-dG production, GSH depletion, melanin synthesis as well as tyrosinase activity and the protein's expression in B16F10 melanoma cells. QE also inhibited the UVA-mediated downregulation of nuclear Nrf2 level and Nrf2-antioxidant responsible element (ARE) transcriptional activity in cells. QE prevented the UVA-mediated mRNA downregulation of GST, NQO1 and γ -GCL catalytic and modifier subunit as well as the decrease in protein expression and activity of the Nrf2 target antioxidant enzymes (particularly GST, NQO1 and γ -GCL) (ref.⁸⁸). Further, QE pre-treatment suppressed UVA-induced ROS production, GSH depletion and apoptosis in HaCaT (ref.¹¹⁷). QE pre-treatment significantly decreased UVA-induced DNA damage to C3H10T1/2 mouse embryo fibroblasts (ref.¹¹⁸) and inhibited UVA-stimulated collagenase protein and mRNA level in NHDF (ref.¹¹⁹). In the EpiDerm™ model, QE significantly decreased UVA-induced MMP-1 and tumour necrosis factor alpha (TNF- α) secretion¹²⁰. The intraperitoneal application of QE before repeated UVA exposure resulted in a reduced MDA level and increased activities of GPx, GSR, CAT and SOD in the skin¹²¹, erythrocytes¹²² and liver tissue¹²³ of female Sprague-Dawley rats. QE was also found to enhance the photostability (UVA+UVB) of the two UV filters, butyl methoxydibenzoylmethane and octyl methoxycinnamate in oil-in-water emulsions¹²⁴.

On the other hand, QE was shown to undergo slow decomposition to a mixture of C-ring-opened products. The presence of a triplet sensitizer greatly increases UV radiation-mediated QE decomposition. Thus the presence of endogenous photosensitizers in the skin could potentially affect the UV stability of QE, suggesting that the further study of QE for both its photoprotective properties and photostability in skin is warranted¹²⁵. Besides a dose-dependent photodegradation in aqueous and organic environments, QE exhibited a phototoxic effect on fibroblasts (Balb/c 3T3 cells and NHDF) and keratinocytes (HaCaT and NHEK). QE pre-treatment and subsequent UVA ex-

posure further resulted in increased ROS production and intracellular GSH level depletion in NHDF (ref.¹²⁶).

Apigenin

Apigenin (AP, 4',5,7-trihydroxyflavone; 5,7-dihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one, Fig. 2) is a abundantly distributed plant flavone occurring in herbs (e.g., endive, clove, chamomile), fruits (e.g., apples, grapefruit, oranges, cherries, grapes), vegetables (e.g., beans, broccoli, celery, leeks, onions, barley, parsley, tomatoes) and beverages (e.g., tea, wine). In nature AP also exists as a dimer, biapigenin, mainly isolated from the buds and flowers of *Hypericum perforatum*¹²⁷. In numerous mammalian systems *in vitro* as well as *in vivo*, AP demonstrated antioxidant, anti-inflammatory, antiviral and anticancer properties¹²⁷. AP increased dermal density and elasticity and reduced fine wrinkle length as well as improving skin evenness, moisture content and transepidermal water loss (TEWL) in human volunteers¹²⁸. Several studies also documented its UVB photoprotective potential¹²⁹.

The AP pre-treatment of NHDF reduced MMP-1 protein and mRNA level in UVA-exposed cells¹¹⁹. AP further increased cell viability and inhibited ROS production in UVA-irradiated HaCaT. AP also decreased UVA-stimulated mRNA expression and activity of MMP-1 as well as the protein and mRNA expression of transcription factors c-Jun and c-Fos and the phosphorylation of MAPK, particularly ERK1/2, JNK1/2 and p38 MAPK. AP further decreased the UVA-induced influx of Ca²⁺ into HaCaT and the phosphorylation of Ca²⁺/calmodulin-dependent kinases¹³⁰. Pre-treatment with AP also protected NHDF against UVA-induced senescence. The AP post-treatment of UVA-exposed NHDF increased cell viability and decreased the expression of MMP-1 (ref.¹²⁸). A phototoxicity study found AP photostability in the UVA and VIS range and no phototoxic potential in the 3T3 neutral red uptake phototoxicity test after UVA/VIS exposure¹³¹.

Luteolin

Luteolin (LU, 3',4',5,7-tetrahydroxyflavone; 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4-chromenone, Fig. 2) is a flavone abundantly present in several plants including spices, vegetables, fruits and medicinal herbs, e.g., broccoli, pepper, thyme, peppermint, rosemary, oregano, parsley, celery, carrot, cabbage, artichoke, tea, celery, citrus fruits (especially oranges) and apples. Literary sources show that LU possesses antioxidant, anticancer, anti-inflammatory or neuroprotective effects¹³².

LU exhibited an inhibitory effect on the MMP-1 protein and mRNA level in NHDF (ref.¹¹⁹). Pre-treatment of HaCaT with LU increased cell viability and reduced ROS generation after UVA exposure. LU also inhibited UVA-induced mRNA expression and the activity of MMP-1 as well as the protein and mRNA expression of transcription factors c-Jun and c-Fos and the phosphorylation of kinases (ERK1/2, JNK1/2 and p38 MAPK). LU further decreased the UVA-induced influx of Ca²⁺ into HaCaT and the phosphorylation of Ca²⁺/calmodulin-dependent kinases¹³⁰. The application of LU to UVA-exposed NHDF

decreased ROS production and non-apoptotic programmed cell death (autophagy). In addition, the protein expression of hypoxia inducible factor-1 α and the classical autophagy-associated proteins, microtubule-associated protein light chain 3 and beclin 1 were decreased in the UVA-irradiated NHDF (ref.¹³³).

Rutin

Rutin (RU, 3,3',4',5,7-pentahydroxyflavone-3-rhamnoglucoside) also known as rutoside, quercetin 3-rutinoside, and sophorin, is a flavonol glycoside composed of quercetin and the disaccharide rutinose (Fig. 2). RU is abundantly found in plants, such as passion flower, buckwheat, tea, apples, lemons, and onions. RU exhibits several pharmacological properties including antioxidant, anticarcinogenic, cytoprotective, antiplatelet, antithrombotic, vasoprotective, cardioprotective and neuroprotective¹³⁴. As for the skin, RU was shown to increase skin elasticity and decrease signs of skin aging, especially the length, area and number of wrinkles in human volunteers. RU also increased the mRNA expression of collagen I and decreased the mRNA expression of collagenase in NHDF (ref.¹³⁵). The UVB protection of RU is also quite well documented *in vitro* and *in vivo*^{134,136-139}.

The RU pre-treatment of NHDF strongly protected against the UVA-induced increase in expression of proteins involved in antioxidant (such as SOD, TrxR, and peroxiredoxins 1/2) and inflammatory (e.g., IL-17, serine/threonine-protein kinase 2, and tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein zeta) response¹³⁶. RU also reduced the UVA-induced oxidative modification of the membrane of CCD 1112Sk human fibroblasts, specifically the negative charge on the membrane surface, sialic acid concentration and level of lipid peroxidation¹³⁷. In another study on CCD 1112Sk human fibroblasts, RU application also counteracted ROS generation and prevented UVA- and UVB-induced changes in the composition of membrane phospholipids and free fatty acids content, the oxidation of phospholipids and biomembrane destruction, depletion of the GSH/GSSG ratio, GPx activity and levels of vitamins E and C (ref.¹⁴⁰). RU further reduced UVA-induced pro-inflammatory response and ROS generation, and enhanced the activity/level of antioxidants (SOD, GPx, vitamin E, GSH, and Trx). RU also normalized UVA-induced Nrf2 expression and prevented changes in the levels of the lipid peroxidation markers MDA and 4-HNE. RU pre-treatment prevented the protein modifications (particularly tyrosine derivatives formation) and decreased the levels of the proapoptotic markers caspase-3 and cytochrome c (ref.¹³⁸). The pre-treatment of B16F10 cells with RU lead to the inhibition of UVA-induced melanin synthesis as well as the activity and protein expression of tyrosinase, a reduction in UVA-induced ROS and 8-OH-dG formation and GSH depletion⁸⁸. The pre-treatment of C3H10T1/2 fibroblasts with RU significantly decreased UVA-induced DNA damage¹¹⁸. RU also reduced UVA-stimulated damage to a CDD 1102 KERTr immortalized keratinocyte cell line and CCD 1112Sk human fibroblasts. RU especially stimu-

lated antioxidant enzyme activity (CAT, SOD, TrxR) and reduced ROS generation. The effect of RU was increased by its combination with ascorbic acid, which besides other effects stimulated the UV-induced activity of the transmembrane transporter bilirubin translocase, responsible for the transport of RU into cells¹³⁹.

Chrysin

Chrysin (CH, 5,7-dihydroxyflavone; 5,7-dihydroxy-2-phenyl-4H-chromen-4-one, Fig. 2), is a natural flavone occurring in honey, propolis, the mushroom *Pleurotus ostreatus* and many plants e.g., chamomile or blue passion flower (*Passiflora caerulea*), which is used for commercial CH preparation¹⁴¹. CH exhibits many biological activities such as antioxidant, anti-inflammatory, anti-aging, antibacterial, anti-angiogenic and anticarcinogenic¹⁴². CH demonstrated an inhibitory effect on the protein and mRNA expression of MMP-1 in NHDF (ref.¹¹⁹). CH pretreatment attenuated UVA-induced damage to HaCaT, especially the reduction of cell viability, ROS production, caspase-3 activation and COX-2 protein level. CH also inhibited JNK phosphorylation and mildly attenuated p38 and ERK1/2 phosphorylation¹⁴³. Although CH was photostable in the UVA and VIS range, it exhibited phototoxic potential in the 3T3 neutral red uptake phototoxicity test¹³¹.

Dihydromyricetin

The flavanonol dihydromyricetin (DHM, 3,5,7-trihydroxy-2-(3,4,5-trihydroxyphenyl)-2,3-dihydrochromen-4-one) is also known as ampelopsin (Fig. 2). It is found in the *Ampelopsis* species, and Chinese vine tea (*Ampelopsis grossedentata*) is used for DHM isolation. DHM possesses numerous pharmacological activities, including antioxidant, anticancer, antimicrobial and hepatoprotective¹⁴⁴. The consumption of DHM was found to reduce UVB-induced photoaging in mice¹⁴⁵.

The DHM pre-treatment of HaCaT attenuated UVA-induced ROS generation, mitochondrial membrane potential decrease, lipid peroxidation, GPx protein decrease and the phosphorylation of histone γ -H2AX, a sensitive biomarker for DNA damage. DHM also reduced the mRNA level of IL-1 β , IL-6, COX-2 and Bax, increased the expression of the anti-apoptotic proteins Bcl-2 and Bcl-xL, and decreased the expression of the pro-apoptotic protein Bax as well as the activation of caspase-3. Additionally, DHM treatment also prevented the nuclear translocation of NF- κ B/p65 and phosphorylation of c-Jun (ref.¹⁴⁶).

Genistein

The isoflavone genistein (GE, 5,7,4'-trihydroxyisoflavone; 5,7-dihydroxy-3-(4-hydroxyphenyl)chromen-4-one, Fig. 2) is abundantly found in soy and other legumes. GE also exists in the glycosylated form genistin. GE acts as a selective estrogen receptor modulator. Several *in vitro* and *in vivo* studies demonstrated the beneficial effects of GE on skin, e.g., for the treatment of keloid scars, stimulation of collagen biosynthesis, acceleration of wound healing or protection of UVB-induced photodamage¹⁴⁷.

As for UVA light, GE suppressed 8-OH-dG formation in purified UVA-irradiated DNA (ref.¹⁴⁸). The application of GE significantly decreased psoralen and UVA-induced (PUVA) photodamage in hairless mice, especially skin thickening, cutaneous erythema and ulceration, inflammatory changes throughout the epidermis and PCNA-positive cells, and completely inhibited the cleavage of poly (ADP-ribose) polymerase and caspase-3 (ref.¹⁴⁹).

Hesperidin

Hesperidin (HE, (3',5,7-trihydroxy-4'-methoxyflavanone-7-rutinoside) is a flavanone glycoside, comprised of the aglycone hesperetin and the disaccharide rutinose (Fig. 2). HE is isolated in large amounts from the rinds of the ordinary orange *Citrus aurantium* L., *Citrus sinensis*, *Citrus unshiu* and other species of the genus *Citrus* (family Rutaceae). It has been reported to occur in many plants other than Citrus, such as in the families *Fabaceae*, *Betulaceae*, *Lamiaceae* and *Papilionaceae*. HE has been reported to possess significant antioxidant, anti-inflammatory, analgesic, immunomodulatory and wound healing effects¹⁴⁷. Several reports also demonstrated a UVB-protective potential of HE *in vitro*^{151,152} and *in vivo*^{153,154}.

HE significantly prevented UVA-induced oxidative damage, in particular increased cell viability and SOD activity and reduced MDA level in HaCaT. Also a decrease in TNF- α , IL-1 β and IL-6 protein and mRNA was observed¹⁵⁵.

Chrysanthemin

Chrysanthemin is one of the most common anthocyanins, also known as kuromanin or cyanidin-3-O-glucoside and cyanidin-3-O- β -glucopyranoside (CG; Fig. 2) CG is found in a variety of fruits and vegetables, including strawberries, blackberries, blueberries, raspberries, cherries, pomegranate, pigmented oranges, red cabbage, black rice, black beans or purple sweet potatoes¹⁵⁶. CG is a potent antioxidant and protects against oxidative damage¹⁵⁷. CG was also reported to reduce UVB-induced damage *in vitro*¹⁵⁸⁻¹⁶⁰ and *in vivo*^{161,162}.

The CG pretreatment of HaCaT cells inhibited the UVA-induced formation of apoptotic cells and DNA fragmentation as well as hydrogen peroxide production¹⁵⁷. CG increased cell viability, Bcl-2 expression, Bcl-2/Bax ratio and ERK phosphorylation and decreased ROS production and the levels of caspase-3 and phosphorylated p38 in UVA-irradiated NHDF (ref.¹⁶³).

Resveratrol

Resveratrol (RE, trans-3,5,4'-trihydroxystilbene, Fig. 2) is a polyphenol belonging to the stilbenoid class. It is a phytoalexin synthesized mainly in grapes, with higher quantities in the red varieties. Other plant sources include peanuts, hops, cacao and berries (blueberries, bilberries, and cranberries) (ref.¹⁶⁴). RE is an effective antioxidant and anti-inflammatory agent. *In vitro* studies demonstrated its antiproliferative activity in various skin cancer cells.

Several *in vitro* and *in vivo* studies have also demonstrated the UVB photoprotective activity of RE (ref.^{164,165}).

In retinal pigment epithelial (RPE) cells, RE reduced the UVA-provoked decrease in cell viability, the generation of intracellular hydrogen peroxide and COX-2 expression. RE also lowered the UVA-induced activation of ERK, JNK and p38 kinase in RPE cells¹⁶⁶. The pre- and post-treatment of HaCaT cells with RE resulted in an increase in cell viability, and a reduction in lipid peroxidation and ROS production. Moreover, RE facilitated Nrf2 accumulation in the nucleus; as a result, the activities of the antioxidant enzymes GST and SOD were also enhanced. Kelch-like ECH-associated protein 1 (Keap1), a repressor of Nrf2 in the cytoplasm, was clearly reduced by RE treatment while the level of Keap1 mRNA was still increased¹⁶⁷. A derivative of RE, oxyresveratrol (oxyRE), increased cell viability and suppressed intracellular ROS when cells were pre-treated before UVA exposure. Post-treatment with oxyRE reduced nitrotyrosine, 8-OH-dG and CPDs formation and stimulated p53 expression¹⁶⁸.

On the other hand, the pre-treatment of HaCaT and NHEK with RE caused a massive increase in oxidative stress in mitochondria, leading to a decrease in the mitochondrial membrane potential and consequently to apoptosis of the keratinocytes¹⁶⁹. Another study showed that RE potentiates the production of 8-OH-dG in UVA-irradiated genomic DNA. Moreover, the combination of RE with UVA significantly enhanced the production of DNA strand breaks and the cell death of HaCaT (ref.¹⁷⁰). In NHEK, RE enhanced the response stimulated by UVA+UVB (10:1), as it had a synergistic effect on the activation of the aryl hydrocarbon receptor pathway, cytochrome P450 1A1 transcription and IL-8 expression, as well as on NFκB activation and the nuclear translocation of the epidermal growth factor receptor¹⁷¹. These suggest that RE might have a potentially hazardous effect when topically applied to the skin, especially on regions exposed to sunlight.

Ellagic acid

Ellagic acid (EA, 2,3,7,8-tetrahydroxy-chromeno[5,4,3-cde]-chromene-5,10-dione; 4,4',5,5',6,6'-hexahydroxydiphenic acid 2,6,2',6'-dilactone, Fig. 2) is a polyphenol, present in several fruits, vegetables, nuts, and a wide variety of berries, including blackberries, raspberries, strawberries, cranberries and pomegranates. EA was demonstrated to eliminate ROS, activate specific endogenous antioxidant enzymes and suppresses specific genes responsible for inflammation. It also possesses antimutagenic and anticancer properties¹⁷². EA was shown to reduce UVB-induced damage in terms of inflammatory response¹⁰⁴.

EA pre-treatment markedly increased HaCaT cell viability and suppressed UVA-induced ROS generation and lipid peroxidation. Moreover, EA pre-treatment reduced single-strand break formation and apoptosis by reducing DNA fragmentation, mitochondria dysfunction, endoplasmic reticulum stress, caspase-3 activation, and Bcl-2/Bax deregulation in irradiated cells. The antioxidant

potential of EA was demonstrated as the downregulation of Keap1 and the augmented nuclear translocation and transcriptional activation of Nrf2 both with and without UVA irradiation, and increased the expression of HO-1 and SOD (ref.¹⁷³).

Carnosic acid

Carnosic acid (CAR, (4aR,10aS)-5,6-dihydroxy-1,1-dimethyl-7-propan-2-yl-2,3,4,9,10,10a-hexahydrophenanthrene-4a-carboxylic acid) also called salvia or sage, is a phenolic diterpene (Fig. 2) found mainly in salvia (*Salvia officinalis* L.) and rosemary (*Rosmarinus officinalis* L.) from the Lamiaceae family. Several studies have demonstrated diverse biological effects of CAR that include anti-inflammatory, anticancer, hepatoprotective and anti-adipogenic activities. CAR is also widely used as a cosmetic and dental hygiene ingredient due to its strong antioxidant and antimicrobial properties¹⁷⁴. CAR also has UVB protective potential¹⁷⁵.

The pre-treatment of NHDF with CAR suppressed the MMP-1 mRNA elevation stimulated by UVA irradiation¹⁷⁶. In UVA-exposed Hs68 human skin fibroblasts, CAR not only reduced the mRNA expression of MMP-1, but also of MMP-3 and MMP-9 (ref.¹⁷⁵).

Ursolic acid

Ursolic acid (UA, 3-β-hydroxyurs-12-en-28-oic acid) is a lipophilic pentacyclic triterpenoid carboxylic acid (Fig. 2). UA is the major component of some fruits and traditional medicinal herbs e.g., apple peels, blueberry (*Vaccinium* spp.), cranberry (*Vaccinium macrocarpon*), heather flower (*Calluna vulgaris*), labrador tea (*Ledum groenlandicum* Retzius), olive (*Olea europaea*), pear (*Pyrus pyrifolia*), basil (*Ocimum basilicum*), thyme (*Thymus*), oregano (*Origanum vulgare*), sage (*Salvia officinalis* L.) or rosemary (*Rosmarinus officinalis* L.). UA exerts various biological effects, including anti-inflammatory, anti-atherosclerosis and anticancer. UA also reduces ROS level and increases the activity of antioxidant enzymes¹⁷⁷. The pre-treatment of HaCaT with UA decreased UVA-induced ROS production, lipid peroxidation, activity and the protein level of MMP-2 and p53 (ref.¹⁷⁸).

Asiatic acid

Asiatic acid (AA, 2α,23-dihydroxyursolic acid), also known as dammarolic acid, is a pentacyclic triterpenoid (Fig. 2). It is abundantly present in many edible and medicinal plants including *Centella asiatica*, which is a renowned herb in many traditional medicine formulations¹⁷⁵. The herb grows in the tropical regions of Asia, Oceania, Africa and America. In traditional Asian medicine, the herb has been used for hundreds of years to improve the healing of small wounds, scratches, burns, and hypertrophic wounds. Previous studies demonstrated that AA could be also used for wound healing and various dermal applications^{180,181}. AA exhibited numerous pharmacological activities such as antioxidant, anti-inflammatory, hepatoprotective, cardioprotective, neuroprotective, and anticancer properties¹⁷⁹. The pre-treatment of HaCaT

with AA decreased UVA-induced ROS production, lipid peroxidation, MMP-2 activity and protein level and p53 protein expression¹⁷⁸.

Zerumbone

Zerumbone (ZER, (2E,6E,10E)-2,6,9,9-tetramethyl-2,6,10-cycloundecatrien-1-one), a monocyclic sesquiterpene with three double bonds (Fig. 2), is obtained from *Zingiber zerumbet* Smith (Zingiberaceae). Its rhizomes are the richest in ZER, followed by the leaves. ZER has various biomedical properties. Several studies have shown its selective anti-proliferative effect on various cancer cells (e.g., colon, breast, cervix, and liver). ZER also exhibits antioxidant, anti-inflammatory, immunomodulatory or antimicrobial activity¹⁸². ZER was also demonstrated to prevent chemically-induced tumour initiation and promotion in mouse skin¹⁸³.

ZER pre-treatment substantially suppressed UVA-induced HaCaT cell death and LDH release, ROS production, DNA single-strand breaks, DNA fragmentation and a dysregulated Bax/Bcl-2 ratio. ZER cytoprotective properties were associated with an increased nuclear translocation of Nrf2 and elevated ARE luciferase activity. The activation of Nrf2/ARE signalling was accompanied by the induction of HO-1 and γ -GCL catalytic subunit genes. ZER-induced Nrf2 transcriptional activation was mediated by the p38 MAPK, phosphoinositide 3-kinase/protein kinase B (AKT) and PKC signalling cascades. In the UVA-treated skin of nude mice, ZER pre-treatment significantly ameliorated UVA cytotoxicity via increased nuclear Nrf2 translocation and Nrf2-dependent antioxidant gene expression (HO-1 and γ -GCL catalytic subunit) (ref.¹⁸⁴).

beta-Carotene

β -Carotene (β -CAR) is a tetraterpenoid that consists of eight isoprene units (40 carbon atoms) in a core structure of conjugated double bonds substituted with two β -ionone rings (Fig. 2). β -CAR is a strongly red-orange pigment that occurs in many different fruits and vegetables such as mango, papaya, orange, apricot, watermelon, cantaloupe, pumpkin, carrot, red pepper, tomato and sweet potato. The colour of β -CAR in some bright green leafy vegetables is masked by chlorophyll, e.g. in spinach, kale, lettuce, broccoli or cabbage^{185,186}. A number of studies investigated the effect of β -CAR on the prevention of solar erythema formation with contradictory results. The literature analysis implies that doses of about 10 mg/day are required to provide UVB photoprotection¹⁸⁶.

As for UVA radiation, β -CAR inhibits JNK activation and the mRNA and protein expression of TNF- α , IL-1 β , and IL-10 in UVA-exposed HaCaT (ref.¹⁸⁷). In the same cells, β -CAR suppressed the UVA-induced mRNA level of MMP-1, MMP-3, and MMP-10, three major MMPs involved in photoaging¹⁸⁸. Microarray analysis in irradiated HaCaT showed that β -CAR inhibited UVA-induced extracellular matrix degradation and enhanced UVA-stimulated tanning-associated protease-activated receptor 2 (ref.¹⁸⁹). The application of β -CAR to NHDF reduced the level of mtDNA mutagenesis provoked by repeated UVA expo-

sure¹⁹⁰. β -CAR pre-treatment resulted in suppression of the UVA-induced transcriptional activation of HO-1 in normal human FEK4 fibroblasts¹⁹¹ and induced the mRNA and protein level of pro-inflammatory IL-6 as well as the protein level of HO-1 in human skin HFP-1 fibroblasts¹⁹². The application of β -CAR to rat kidney fibroblasts prior to UVA exposure significantly increased the activities of CAT and SOD, while the level of TBARS was reduced¹⁹³.

On the other hand, the pre-treatment of C3H10T1/2 fibroblasts with β -CAR increased UVA-induced DNA damage. The combination of β -CAR with flavonoids (naringin > RU > QE) significantly suppressed the photo-oxidative effect of β -CAR (ref.¹¹⁸). In another study, β -CAR increased membrane damage, stimulated HO-1 expression and induced caspase-3 activity in NHDF exposed to UVA light¹⁹⁴. Similarly, in UVA-irradiated HFP-1 fibroblasts, β -CAR pre-treatment strongly enhanced HO-1 mRNA and protein expression. The level of this oxidative stress marker was suppressed by the concomitant addition of vitamin E, but only moderately by vitamin C (ref.¹⁹⁵). These effects may be associated with the photodecomposition of β -CAR stimulated by UVA radiation that was shown *in vitro*. The rapid decomposition of β -CAR was further accelerated by sulphide and reduced by radical scavengers (dithiothreitol, thiourea) (ref.¹⁹⁶).

Astaxanthin

Astaxanthin (AST, 3',3'-dihydroxy- β , β -carotene-4,4'-dione) is a red-orange lipophilic xanthophyll carotenoid, which is structurally similar to β -CAR but possesses an additional hydroxyl and ketone group on each β -ionone ring (Fig. 2). AST is a ubiquitous secondary metabolite naturally synthesized by a number of plants as well as bacteria, yeasts, microalgae crustaceans and salmonids. The commercial production of AST has traditionally been by chemical synthesis, but the microalga *Haematococcus pluvialis* seems to be the most promising source for its industrial biological production. AST has several essential biological functions in marine animals, including pigmentation, stress tolerance, reproductive capacity, protection against UV light effects, immune response and protection against the oxidation of macromolecules. From several studies including clinical trials, beneficial effects of AST on skin physiology and pathology are well documented including antioxidant, anti-inflammatory and UVB photoprotective action¹⁹⁷.

The pre-treatment of NHDF with AST reduced the disruption of cell membrane integrity, level of intracellular ROS, amount of TBARS, number of apoptotic cells as well as the activity of caspase-3. AST also counteracted the decrease in CAT and SOD activity and reduced the mRNA and protein level of HO-1. The application of AST to rat kidney fibroblasts before UVA irradiation increased the activities of CAT and SOD and reduced the level of TBARS. AST was much more effective than the other carotenoids (β -CAR and lutein) (ref.¹⁹³). AST also reduced oxidative DNA damage to human neuroblastoma and rat trachea epithelial cells exposed to UVA radiation¹⁹⁸. Synthetic AST and an algal extract (14% of AST) de-

creased UVA-induced DNA alterations to 1BR-3 human skin fibroblasts, a human melanocyte cell line and human intestinal CaCo-2 cells. The algal extract exhibited a comparable UVA protection to 10 μ M AST on all three of the above cell types. Further, in 1BR-3 cells, the synthetic AST and algal extract prevented UVA-induced alterations to SOD activity and GSH content. Similarly, AST and the extract prevented the depletion of GSH in CaCo-2 cells¹⁹⁹. The addition of AST to NHDF immediately after UVA exposure significantly attenuated the induction of MMP-1 and neutral endopeptidase expression at the gene and protein level as well as reducing MMP-1 and skin fibroblast elastase activity and IL-6 secretion²⁰⁰. Dietary AST reduced features of chronic UVA exposure such as TEWL and wrinkle formation in female hairless mice. AST treatment also reduced the mRNA level of epidermal (lympho-epithelial Kazal-type related inhibitor, steroid sulfatase and aquaporin 3) and dermal (MMP-13) markers increased by chronic UVA irradiation²⁰¹.

Lycopene

Lycopene (LY, (6E,8E,10E,12E,14E,16E,18E,20E,22E,24E,26E)-2,6,10,14,19,23,27,31-octamethyldotriacont-2,6,8,10,12,14,16,18,20,22,24,26,30-tridecaene) is a bright red linear unsaturated tetraterpene composed of eight isoprene units (Fig. 2). The major sources for LY are tomatoes and tomato products, although red carrot, apricot, papaya, pink grapefruit, guava and watermelon also contain LY in considerable amounts²⁰². The pharmacological properties of LY are linked mainly to its antioxidant activity that was demonstrated in many *in vitro*, *ex vivo* and *in vivo* studies¹⁸⁶.

In a placebo-controlled, double-blind, randomized crossover study, the oral treatment of healthy volunteers with LY-rich tomato nutrient complex inhibited UVA1 (340-400 nm) and UVA/B induced the upregulation of HO-1, intercellular adhesion molecule 1 (ICAM-1) and MMP-1 mRNA level²⁰³.

On the other hand, LY enrichment enhanced UVA-induced HO-1 expression and strongly induced DNA damage in UVA-irradiated C3H10T1/2 mouse embryo fibroblasts²⁰⁴. Similarly, LY pre-treatment of NHDF potentiated the UVA-induced elevation of MMP-1 and HO-1 mRNA levels¹⁷⁶.

Lutein

Lutein (LT, 4-[18-(4-hydroxy-2,6,6-trimethyl-1-cyclohexenyl)-3,7,12,16-tetramethyloctadeca-1,3,5,7,9,11,13,15,17-nonaenyl]-3,5,5-trimethyl-cyclohex-2-en-1-ol or (3R,3'R,6R)-4,5-didehydro-5,6-dihydro- β , β -carotene-3,3'-diol) is a member of the xanthophyll family of carotenoids containing hydroxyl groups that make LT more polar than carotenoids, such as LY and β -CAR (Fig. 2). LT is widespread in nature, abundantly present in leafy green vegetables such as spinach, lettuce and kale, but also in apricot, cucumber or red pepper¹⁸⁸. LT is highly concentrated in the human retina and is responsible for central vision and high visual acuity. LT is the second most prevalent carotenoid in human serum. LT

is also found in significant quantities in human skin²⁰⁵. The biological effects of LT are linked to its ability to filter the high-energy wavelengths of visible light and to protect against ROS formation. Animal studies have provided evidence of significant efficacy against light-induced skin damage²⁰⁶. The oral and topical administration of LT provides multiple benefits to the human skin²⁰⁷.

The application of LT to rat kidney fibroblasts prior to UVA exposure protected the cells against UVA-induced decrease in CAT and SOD and increase in TBARS level¹⁹³. LT also reduced oxidative DNA damage in human neuroblastoma and rat trachea epithelial cells exposed to UVA radiation¹⁹⁸. In a placebo-controlled, double-blind, randomized crossover study, the oral treatment of healthy volunteers with LT completely inhibited UVA1 (340-400 nm) and UVA/B induced the mRNA upregulation of HO-1, ICAM-1 and MMP-1 (ref.²⁰³).

Zeaxanthin

Zeaxanthin (ZEA, 4-[18-(4-hydroxy-2,6,6-trimethyl-1-cyclohexenyl)-3,7,12,16-tetramethyl-octadeca-1,3,5,7,9,11,13,15,17-nonaenyl]-3,5,5-trimethyl-cyclohex-3-en-1-ol or (3R,3'R)- β , β -carotene-3,3'-diol) is another member of the xanthophyll family of carotenoids. ZEA is isomeric with LT, differing only in the localization of one double bond (Fig. 2). ZEA is present in high concentrations in green leafy vegetables such as spinach and kale, but also in others e.g., green pepper, corn or wolfberries. Like LT, ZEA is also highly concentrated in the human retina. ZEA is also found in significant quantities in human skin. ZEA works as a filter of the blue light wavelengths and as an antioxidant^{186,206}. Topical and oral treatment with ZEA provides multiple benefits to the human skin^{207,208}. Dietary ZEA supplementation also protects the skin against UVB-induced photoaging and photocarcinogenesis in mice²⁰⁹.

The application of ZEA reduced oxidative DNA damage in human neuroblastoma and rat trachea epithelial cells exposed to UVA radiation¹⁹⁸.

On the other hand, the rapid decomposition of ZEA stimulated by UVA radiation was demonstrated *in vitro*. The photodecomposition of ZEA was more rapid than that of β -CAR due to the presence of hydroxyl groups. The decomposition was accelerated by sulphide and reduced in the presence of dithiothreitol or thiourea¹⁹⁶.

L-Ergothioneine

The low-molecular-weight thiol-based antioxidant L-ergothioneine (EGT, 2-mercaptohistidinetrिमethylbetaine) is a derivative of the amino acid histidine. EGT has two functional groups: an L-thiol (SH) group and a quaternary ammonium group $N^+-(CH_3)_3$ (Fig. 2). Despite apparently being exclusively synthesized in fungi, cyanobacteria and mycobacteria, EGT is ubiquitously present in most cells and the tissues of plants and mammals. Some foods were found to possess particularly high levels of EGT, for example certain species of mushrooms, black and red beans, red meat, liver, kidney and grains. Numerous *in vitro* assays have demonstrated the antioxi-

dant and cytoprotective capabilities of EGT against a wide range of cellular stressors, including UV and gamma radiation²¹⁰.

In UVA-exposed NHDF, EGT reduced the protein and mRNA level of MMP-1 (ref.²¹¹). The EGT treatment of HaCaT prior to UVA exposure significantly prevented LDH leakage into the medium. UVA-induced ROS formation and DNA oxidative damage was remarkably suppressed by EGT, with a parallel inhibition of apoptosis. Furthermore, EGT alleviated UVA-induced mitochondrial dysfunction. A dose-dependent increase in the antioxidant proteins HO-1, NQO-1 and γ -GCL, and reduced GSH produced by EGT was associated with an upregulated Nrf2 and downregulated Keap-1 level²¹². EGT enhanced the level of reduced GSH and protected NHDF from the induction of photoaging-associated mtDNA damage (mutation and deletion) (ref.²¹³).

CONCLUSION

The exposure of human skin to solar radiation intensifies skin aging commonly known as photoaging and escalates the probability of developing skin cancer. Although skin protection against solar radiation has been studied for decades, research was focused on UVB, and UVA was mostly ignored. The plant kingdom represents the main conventional source of new candidates with photoprotective activity. In this review, phytochemicals and plant extracts with UVA-protective potency are summarized. As documented, there is a range of phytochemicals that possess UVA protective properties, many of them also protect against UVB photons and thus may be useful in the protection and treatment of UV light-caused damage; alone or in combination with traditional UV filters. However, most of the compounds and extracts listed in this review were only tested in very simple *in vitro* or possibly *ex vivo* systems. This fact results from the prohibition of animal use for this purpose in many countries around the world. The safety of new photoprotective phytochemicals may be based on their long-term use in traditional medicine. However, clinical trials are needed to validate the effectiveness of new candidates for photoprotective preparations. The demanding nature and ethical limits of studies on human volunteers is most likely the most restrictive step in the rapid introduction of new photoprotective agents for practical use.

Search strategy and selection criteria

The aim of our research strategy was to evaluate well documented studies on the UVA photoprotective properties of phytochemicals and plant extracts. The articles from 1998 to 2019 were searched using the PubMed and Web of Science databases. All searches were up-to-date since January 2020. The search terms used included "UVA photoprotection", "UVA protection", "plant and UVA protection", "polyphenols and UVA protection". Only articles in English were reviewed.

ABBREVIATIONS

AA, Asiatic acid; AKT, Protein kinase B; AP, Apigenin; ARE, Antioxidant responsible element; AST, Astaxanthin; BE, Bilberry extract; β -CAR, β -Carotene; CA, Caffeic acid; CAR, Carnosic acid; CAT, Catalase; CG, Chrysanthemin; CH, Chrysin; CIN, Cinnamic acid; COX-2, Cyclooxygenase 2; CPD, Cyclobutane-pyrimidine dimers; CUR, Curcumin; DHM, Dihydromyricetin; DHSB, 2,3-Dehydrosilybin; EA, Ellagic acid; EC, (-)-epicatechin; ECG, (-)-epicatechin-3-gallate, (-)-epigallocatechin; EGCG, (-)-epigallocatechin-3-gallate; ERK, Extracellular signal-regulated kinases; EGT, L-Ergothioneine; FA, Ferulic acid; γ -GCL, γ -Glutamate-L-cysteine ligase; GE, Genistein; GPx, Glutathione peroxidase; GSH, Glutathione; GSR, Glutathione reductase; GSSG, Oxidized glutathione; GST, Glutathione S-transferase; HaCaT, Spontaneously transformed aneuploid immortal human skin keratinocyte cell line; NHDF, Normal human dermal fibroblasts; HE, Hesperidin; 4-HNE, 4-Hydroxynonenal; HO-1, Heme oxygenase-1; HPRT, Hypoxanthine-guanine phosphoribosyl transferase; HSP 70, Heat shock protein 70; ICAM-1, Intercellular adhesion molecule 1; IL-6, Interleukin-6; ISB, Isosilybin; JNK, c-Jun N-terminal kinase 1/2; Keap1, Kelch-like ECH-associated protein 1; Ki-67, Protein associated with cellular proliferation and ribosomal RNA transcription; LDH, Lactate dehydrogenase; LT, Lutein; LU, Luteolin; LY, Lycopene; MMP, Matrix metalloproteinases; MAPK, Mitogen-activated protein kinases; MDA, Malondialdehyde; MeOEC, 3'-O-Methyl epicatechin; MMP-1, Collagenase; MMP-3, Stromelysin; MMP-9, Gelatinase; mTOR, Serine-threonine kinase involved in cell growth; NF- κ B, Nuclear factor kappa B; NQO1, NADPH quinone oxidoreductase-1; NHEK, Normal human epidermal keratinocytes; Nrf2, Nuclear factor erythroid-2 related factor 2; 8-OH-dG, 8-Hydroxydeoxyguanine; oxyRE, Oxyresveratrol; PCNA, Proliferating cell nuclear antigen; PKC, Protein kinase C; QE, Quercetin; RA, Rosmarinic acid; RE, Resveratrol; RNS, Reactive nitrogen species; ROS, Reactive oxygen species; RPE, Retinal pigment epithelial cells; RU, Rutin; SB, Silybin; SC, Silychristin; SD, Silydianin; SM, Silymarin; SOD, Superoxide dismutase; TBARS, Thiobarbituric acid reactive substances; Trx, Thioredoxin; TEWL, Transepidermal water loss; TIMP-1, Tissue inhibitors of MMP-1; TIMP-2, Tissue inhibitors of MMP-2; TNF- α , Tumour necrosis factor alpha; TrxR, Trx reductase; UA, Ursolic acid; UV, Ultraviolet; ZEA, Zeaxanthin; ZER, Zerumbone.

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