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Selected Medicinal Herbs and Functional Peptides for Protection against Photoaging of the Skin

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Abstract

Photoaging is an accelerating aging process of the skin due to prolonged exposure to UV from the Sun or other sources. Herbal extracts, natural compounds, and bioactive polypeptides have widely used in cosmetic agents for protection of the skin against photoaging. This mini review briefly summarizes topical use of selected most common medicinal herbs, naturopathic chemicals, and bioactive peptides examined for skin protection.

Keywords

Photoaging, Herbal Extract, Bioactive Peptides, Skincare

1. Introduction

Cumulative cutaneous exposure to solar or artificial ultraviolet (UV) radiation results in premature aging changes of the skin, *i.e.*, photoaging, which is directly superimposed on the aging changes of the skin beyond the chronological intrinsic senescence, and accounts for the majority of age-related skin problems [1]. Besides pathophysiological impacts on the skin health, skin aging directly deteriorates the appearance and affects people's behavior and interpersonal interactions. Everyone perhaps is keen to have a youthful-looking skin. Since the chrono-aging process is inevitable, to protect the skin cosmetically from photoaging lesions is critical to slow down the overall aging process. There are numerous cosmetic and dermatological products on the market or on the way being developed. These products may be formulated with biochemicals (such as peptides and growth factors), phytochemicals, traditional herbal extracts, and other ma-

terials. This mini review discusses benefits and undergoing challenges for combined cosmetic use of functional peptides and extracts from selected traditional Chinese medicine (TCM) herbs for anti-photoaging.

2. Molecular Pathology of Skin Photoaging

Photoaging of the skin is also known as dermatoheliosis. The early changes of photoaging in the human skin includes patchy or spotted pigmentation, dryness, wrinkling, laxity (looseness), sagging/droopy, and so on. Photoaging directly results from the loss of structural integrity of the dermal architecture due to lesions in the dermal extracellular matrix (ECM), particularly the destruction of collagens and elastic fibers, which provide strength and resilience to the skin [2]. These pathologic lesions take decades to develop and are different from sunburn and tanning changes, which usually develop in hours to days. As the largest organ of the human body, skin consists of three layers, *i.e.*, the epidermis, the dermis, and the hypodermis or subcutis, from the outmost to the innermost layer [3]. The epidermis is the primary protective structure and is further divided into the acellular stratum corneum and the variable epidermis that is composed of nucleated cells including about 95% keratinocytes and is devoid of blood capillaries and sensory nerve termini. The dermis and subcutis are a supporting fibrous layer and a subcutaneous layer that is made principally of fat and connective cells/tissues underneath, respectively. In addition to the major structural proteins, collagen and elastin, the dermis contains most active cells including various types of immune cells such as macrophages, lymphocytes, mast cells, dermal dendritic cells, and other functional structures, which may include sweat glands, sebaceous glands, hair follicles, nerve termini, lymphatic vessels and as well as blood capillaries. When the skin is exposed to the UV in sunray or from an artificial source, its structures and associated function can be impaired at different levels through multiple approaches.

As briefly summarized in the schematic in **Figure 1**, directly exposed to sunlight the skin may capture about 5% - 10% UVB and 90% - 95% UVA from the solar radiation, while the rest of solar UV including all UVC is filtered by atmosphere (ozone). Once reached to the skin, the UV radiation energy may directly break DNA strands, disrupt structures of nucleotides and proteins/enzymes to cause mutations and changes in metabolism in cells, and overproduction of reactive oxygen species (ROS) [4], which further contributes to the damage of DNA and proteins, lipid peroxidation, depletion of endogenous antioxidants, and other lesions relevant to the oxidative stress [5] [6]. UV (especially UVB) energy directly induces the formation of pyrimidine-pyrimidone and/or thymine-thymine dimers [7] [8]. In addition to the UV, studies suggest a role of infrared (IR) A (wavelength = 760 nm - 1440 nm) in the development of oxidative stress enhancing UV-induced damage through completely different mechanisms in skin cells [9] [10], although there is experimental evidence showing that far-IR suppresses UVB-induced photoaging process [11].

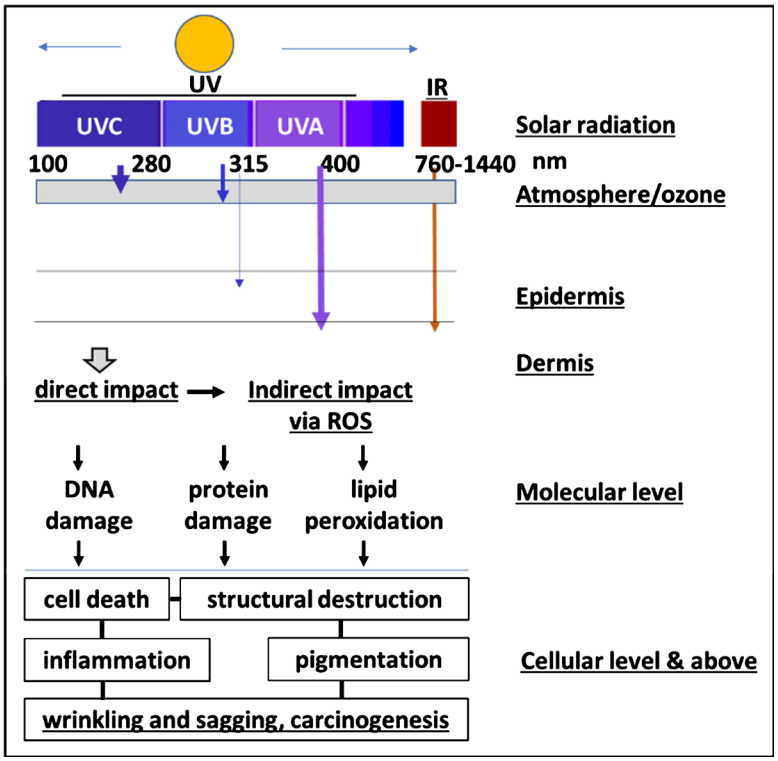

Figure 1. Schematic summary of skin damage induced by solar radiation. Ultraviolet (UV) is a part of the solar radiation with a wavelength from 100 nm to 400 nm and makes up an estimated 10% of the total light output of the Sun. It is further divided into UVA (315 - 400 nm), UVB (280 - 315 nm), and UVC (100 - 280 nm). The atmosphere blocks all UVC and about 90% of UVB. When the rest of UVB and UVA light hits our skin, it can penetrate the epidermis and dermis layers inducing biomolecule damage and subsequent photoaging changes.

Elevation of ROS levels in the skin following photooxidative stress drives production of lipofuscin, a mixed end-product of intracellular lipid peroxidation and oxidized proteins, which is also called as "ceroid" or "age pigment", once it becomes visible in the skin in old people with the naked eye [12]. Protein oxidation leads to abnormal protein degradation due to failure of the ubiquitin-proteasomal as well as the lysosomal-endosomal systems [13] [14]. As a result, oxidized proteins have high propensity form aggregates to build up amyloid deposits inside and/or outside cells [15] [16] [17] [18]. Voluminous evidence suggests that the formation of amyloid deposits be widely implicated in aging as well as many age-related diseases [19] [20], though it is unclear about the precise role that the oxidized protein aggregation plays in the process of skin photoaging. Moreover, oxidative stress promotes the genesis of glycotoxins, advanced glycation end products (AGEs), a highly heterogeneous group of compounds that result from the non-enzymatic glycation of proteins, lipids, and nucleic acids [21]. Accumulation of AGEs in specific tissues has been implicated in multiple diseases and age-related lesions such as diabetes and macular degeneration [21] [22]. Cutaneous buildup of AGEs is known as a feature of skin aging [23].

AGEs severely damage dermis through the AGE receptor (RAGE)-mediated impairments in keratinocytes and other components [23].

The immediate consequence of UV-induced lesions in DNA, protein, and lipid molecules is the dysfunction of these biomolecules and activation of related signal transduction pathways leading to further damage at both subcellular/organellular and cellular levels [24] [25]. UV radiation trims telomeres and UV-induced formation of thymine-thymine dimers activates the signal transduction pathways of P53 protein, a tumor suppressor gene product that plays a crucial role in DNA repair, programmed cell death, and tumorigenesis [26] [27], while increased ROS abundance triggers multiple signal transduction pathways including redox factor 1 (Ref-1), hypoxia-inducible factor-1 (HIF-1) in response to oxidative stress [28] [29]. Other pathways involved in the photooxidative stress also include multiple transcription factors and kinases such as the nuclear factor-kappa B (NF-κB)/P65, AP-1, JAK/STAT, Nrf2, the mitogen-activated protein kinase (MAPK), the extracellular signal-regulated kinase (ERK), PI3K, JNK and so on (see reviews) [6] [30].

UV radiation-induced activation of the multiple pathways accounts for subsequent cell loss, inflammation, immunosuppression, and a series of oxidative stress-mediated modifications on cell structures as well as ECM in the skin. Histologically, UV exposures cause apoptosis in both fibroblasts and keratinocytes, abnormal proliferation at or a loss of their proliferating potency to repair lesions [31] [32] [33]; UV-activated inflammatory response consists of an infiltration of various inflammatory cells mainly including neutrophils, monocytes/macrophages [34]; and both residential mast cells and dendritic cells also play an essential role in the pathogenesis of the photoaging process [35] [36] [37]. Changes in the intracellular signal transduction pathways are further followed by remodeling of the ECM due to the reconstruction of collagen (fragmentation) and elastin (elastosis) as a result of alterations in the matrix metalloproteinase (MMP) network [38]. Taken together, all these changes at molecular and cellular levels contribute to the development of photoaging appearance: coarseness, irregular epidermal thickness, sagging, uneven pigmentation, telangiectasia or spider veins, wrinkling, and cutaneous malignancies [39].

3. Strategies for Anti-Photoaging—The Use of Herbs

The best way to protect our skin from photoaging is to avoid over-exposure to solar radiation or other UV sources. But in fact, photoaging is very commonly seen in a dermatologic clinic and remains as an unsolved problem for us. Nevertheless, antioxidants are considered as main therapeutic elements for combating both photoaging and natural aging [40]. Due to the presence of abundant antioxidant ingredients in plants, the use of medicinal herbs and/or herbal extracts for skincare has had a long history since ancient times, and it is significantly active in the dermatologic and cosmetic practice [41] [42] [43]. In addition, herbal extracts are natural, relatively stable, and safe to use, if original

plants have been commonly used in traditional medicines [41]. Many herbal extracts or purified phytochemicals used for skin protection also have strong potency of UV adsorption, anti-inflammation, and/or hydrating, which reduces or blocks UV exposure, attenuates the inflammatory process and apoptotic cell death, and facilitates wound healing [44] [45] [46]. A large number of herbal blend or formulations have been extensively used for anti-skin aging including photoaging in natural medicines such as TCM in personal care [46] [47] [48]. Depending on the differences between herbs, derived crude extracts and/or purified phytochemical(s) may be used alone or combined with other skin protective agents [49] [50]. The leaves, fruits, seeds, barks, stems, and/or roots of these plants contain alkaloids, flavonoids, polyphenols, polysaccharides, proteins, and/or other nutrient molecules (**Table 1**). For instance, the root of Astragalus (*Radix astragali*, huangqi) and ginseng (*Panax ginseng,* renshen) are the two best-known Chinese herbs, which are used traditionally to strengthen the immune system, boost the energy, and promote skin health, other popular herbs such as aloe leaf, tea-tree seed oil, reishi mushroom, safflower and more are widely used in TCM for similar purpose [51].

Most herbal medicines consist of many different ingredients, of which some of these provide benefits and some of other components may be toxic and give risk to our health when used in vivo [77]. Many herbs and derived preparations are phototoxic and/or photogenotoxic to cells [78]. Topical use of these phototoxic phytochemicals may result in allergy, inflammatory reaction, cell death, and/or skin cancer [79] [78]. In this regard, purified photostable phytochemicals

Table 1. Selected TCM herbs and herbal extracts commonly used for anti-photoaging.

Component	Main source	Known leading bioactive components	References
Extracts	*Aloe vera* (aloe, *luhui*) leaf	Anthraquinones, auxins, gibberellins	[52] [53] [54] [55]
Essential oil	*Boswellia sacra* (frankincense, *ruxiang*)	Boswellic acids	[56]
Essential oil/extracts	*Camellia* (tea tree, *cha*) seed, leaf	Catechins, alkaloids	[57] [58]
Extracts	*Carthamus tinctorius (safflower, honghua)*	Flavonoids, alkaloids	[59]
Essential oil	*Commipora myrrha (moyao)*	Guggulsterone, sesquiterpenes	[60] [61]
Extracts	*Ganoderma lucidum* (*reishi*, *lingzhi*)	Polysaccharides, dietary fibers, oligosaccharides	[62] [63]
Extracts	*Glycine max* (soybean, *dadou*) seed	phenolic acids, flavonoids, isoflavonoids	[64]
Essential oil/extracts	*Hippophae rhamnoides* (sea-buckthorn, *shaji*) fruit, leaf	Phytosterols, flavonoids, phenolic acids	[65]
Extracts	*Leonuri cardiacae herba* (motherwort, *yimucao*)	Hyperoside, flavonoids, phenolic acids	[66]
Extracts	*Lithospermum erythrorhizon* (gromwell, *zicao*) root	Shikonin	[67] [68] [69]
Extracts	*Panax ginseng* (ginseng, *renshen*) root, leaf	Ginsenosides	[70] [71] [72]
Extracts	*Panax notogensing (*sanchi gingseng, *sanqi)*	Ginsenoside C-Mx, saponins	[73] [74]
Essential oil	*Radix Angelica* (*danggui*)	m-Creso, osthole	[75]
Extracts	*Salvia miltiorrhiza* BUNGE (red sage, *danshen*) root	Magnesium lithospermate B, tanshinones,cryptotanshinone	[76]

are more widely used in cosmetic formulations for skin protection against photoaging [30], as potential phototoxic ingredients in mixtures of herbal extracts have been screened out. Table 2 lists a group of selected phytochemicals which are commonly found in popular TCM herbs and demonstrate potent efficacy as an antioxidant, an anti-inflammatory or other cytoprotective agent as described.

4. The Use of Peptides for Anti-Photoaging

Beyond herb-related substances, bioactive peptides have been developed for the purpose of skin protection from natural aging as well as photoaging. Peptides are involved in many physiological processes including cell death, immune response and inflammatory process, skin structural remodeling, and wound healing though modulating related signal transduction pathways and related metabolism [105] [106]. As listed in Table 3, peptides may be grouped as ECM-, growth factor-, neurotransmitter-, enzyme inhibitor-, antioxidant-, cytokine-, and carrier-related peptides. Topical uses of cosmeceutical peptides are expected to stimulate collagen synthesis, inhibit the release of neurotransmitters and inflammatory cytokines in order to attenuate UV radiation-induced lesions and to prevent the development of fine lines and wrinkles as a result of photoaging as well as natural aging [107]. In most cases, in fact, a specific peptide usually has multiple targets and results complex efficacy. For example, topical use of an ECM protein-derived tetrapeptide PKEK boosts formation of ECM and also modulates skin pigmentation resulting in skin whitening effects [108] [109]. As of today, a public database, the TopicalPdb (http://crdd.osdd.net/raghava/topicalpdb/) has currently included 657 entries for the peptides that can be topically delivered [110].

Table 2. Selected herbal compounds/phytochemicals commonly used for anti-photoaging.

Extract	Main source	Known pharmacological efficacy	References
Baicalein	*Radix Scutellariae*	UV adsorption, antioxidant, anti-inflammatory	[80] [81] [45]
Boswellic acids	*Boswellia sacra* (frankincense, *ruxiang*) gum resin	Anti-inflammatory	[82] [83]
Kaempferol	Common fruits such as apples, grapes	Antioxidant, suppress carcinogenesis	[84]
Morin	Members of the Moraceae family	Antioxidant, anti-inflammatory, antibacterial	[85] [86]
Myricetin	Berries, fruits, vegetables	Antioxidant, anti-inflammatory	[87] [88] [89]
Naringenin	Grapefruit, bergamot, sour orange	Antioxidant, apoptotic inhibition	[90] [91]
Nobiletin	Citrus	Antioxidant, anti-inflammatory	[92]
Paeoniflorin	Paeonia (*moutan*)	Anti-inflammatory	[93] [94]
Pycnogenol	French maritime pine bark	Antioxidant, anti-wrinkle	[95] [96]
Quercetin	Common fruits and food such as apples, grapes	Antioxidant, anti-inflammatory	[97] [98]
Rutin	Buckwheat, asparagus	UV adsorption, antioxidant	[99] [100] [45]
Salidroside	*Rhodiola rosea* root	Antioxidant, anti-wrinkle, anti-carcinogenesis	[101] [102]
Wogonin	*Radix Scutellariae*	Antioxidant, anti-inflammatory	[103] [104]

Table 3. Selected polypeptides topically used in cosmetics for anti-photoaging.

Type of Peptide	Name of Peptides	References
ECM-related peptides	Carnosine, tripeptide-10 citrulline, collagen tripeptide, acetyl tetrapeptides (-5, -9, -11), tetrapeptide PKEK, GEKG (tetrapeptide-21), hexapeptide, hexapeptide-11, palmitoyl polypeptides (-pentapeptide-4, -tripeptide-1, -tripeptide-5, -tetra-peptide-7, -hexapeptide-12), oligopeptide-1, pentamide-6	[107] [111]
Growth factor-related peptides	sh-oligopeptide-1, epidermal growth factor (EGF), fibroblast growth factor (FGF), insulin-like growth factor (IGF-1), transforming growth factor (TGF-β, vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF-A), GHK tripeptide, palmitoyl pentapeptide-3 (pal-KTTKS), KTTKS pentapeptide	[112] [113]
Neurotransmitter inhibiting peptides	Acetylhexapeptide-3, pentapeptide-3, pentapeptide-18, tripeptide-3, hexapeptide-8 (Argireline),	[107]
Enzyme inhibiting peptides	Pro-collagen C peptide (YYRADDA), black rice oligopeptides, glutathione (GSH), melanocyte stimulating hormone (MSH), soybean peptide, silk fibroin peptide, AcTP-1, AcTP-2, T10-C,	[114] [107] [115]
Cytokines & other peptides	Interferon-α, heat shock protein-70, peptamide-6, keratin	[114] [115]
Carrier peptides	Copper tripeptide, manganese tripeptide-1	[114] [107]

Combined use of herbal extracts/phytochemicals and functional peptides for skin protection against photoaging

It used to be assumed that, because of the skin barrier, peptides with the molecular weight over 500 Daltons would not be able to pass the barrier [116]. But recent experimental evidence has shown that bigger protein molecules can still pass through the skin barrier, especially in the case of the skin which is stressed and aged and/or injured [117]. Importantly, the skin penetration potency of synthetic peptides can be further modulated by various factors, which directly modify skin permeability, increase the ligand-receptor binding and stability and solubility [109] [118]. Combined use of herbal extracts or phytochemical with functional peptides has been shown to boost the efficacy of bioactive peptides, as herbal components such as polyphenols and flavonoids bind to peptides promoting their penetration to the skin, increasing the lifetime of peptides, and thereby significantly enhance the protection efficacy against UV-induced damage as well as natural aging [119]. Studies demonstrate that topical application of herbal extracts or phytochemicals such as apigenin or hesperidin dramatically enhances epidermal permeability and modifies the barrier function of the skin in animal studies [120] [121] [122]. We also observed that combined topical use of polypeptide mixtures and herbal extracts markedly enhanced proliferation of epidermal cells in SKH-1 hairless mice following UV-induced photoaging (**Figure 2**).

In spite of the advantages of synergistic interaction between herbal ingredients and bioactive peptides, there are still open questions about combined topical use of naturopathic components and functional peptides. The important questions would be how two different groups of components interact with each other to enhance the transdermal process, to affect their pharmacological efficacy as well as other pharmacokinetic issues. Mixing one or multiple types of herbal compounds

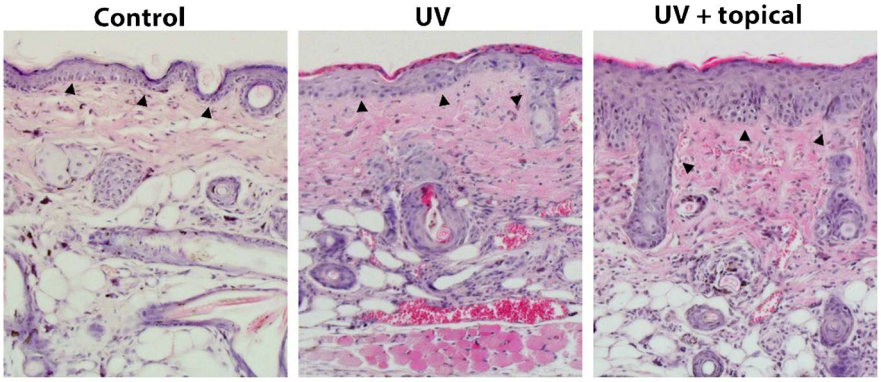

Figure 2. Combined topical use of herbal extracts and bioactive peptides shows evident protection against UV-induced photoaging in SHK-1 hairless mice (*unpublished observations*). SHK-1 mice were exposed to UV light (×6 days) and given topically (daily) blank lotion (UV) or lotion containing polypeptides (a mixture of oligopeptide-1, palmitoyl pentapeptide, and carnosine) and herbal extracts of *S. miltiorrhiza, P. ginseng, P. notoginseng,* and *G. lucidum* (UV + topical). Following conventional hematoxylin-eosin (H & E) staining of the back skin sections prepared from the mice, light microscopic images (20 × 10) demonstrate photoaging changes in UV-exposed mice given blank lotion (UV) compared to the Control (arrowheads), while those given herbal and peptide mixtures (UV + topical) manifest enhanced epidermis proliferation.

with peptides is not simple addition. In addition to directly binding with peptides/proteins through either a specific or a non-specific manner resulting in a change in their bioactivities [123] [124], a variety of herbal compounds such as polyphenols and flavonoids act on membrane lipids and change cell membrane properties affecting epidermal permeability [125]. In fact, in some cases these types of interactions lead to an antagonistic result [126]. Therefore, this is an important issue for cosmetics to consider. Mutual interactions between herbal compounds and polypeptides following combination may occur and change their original pharmacological properties. Answers to these questions will lead to the development of new preventive and therapeutic drugs and/or formulations for both cosmetic and pharmaceutical industries.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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