Ageing Research Reviews 15 (2014) 100–115

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

Active ingredients against human epidermal aging

Márcio Lorencini[a,b,*], Carla A. Brohem[a], Gustavo C. Dieamant[a], Nilson I.T. Zanchin[b,c], Howard I. Maibach[d]

[a] Grupo Boticário, R&D Department, São José dos Pinhais, PR, Brazil
[b] Universidade Estadual de Campinas (UNICAMP), Department of Genetics and Molecular Biology, Campinas, SP, Brazil
[c] Fundação Oswaldo Cruz, Carlos Chagas Institute, Curitiba, PR, Brazil
[d] University of California San Francisco (UCSF), Department of Dermatology, San Francisco, CA, USA

ARTICLE INFO

Article history:
Received 26 December 2013
Received in revised form 10 March 2014
Accepted 17 March 2014
Available online 25 March 2014

Keywords:
Epidermis
Aging
Skin
Treatment
Active ingredients

ABSTRACT

The decisive role of the epidermis in maintaining body homeostasis prompted studies to evaluate the changes in epidermal structure and functionality over the lifetime. This development, along with the identification of molecular mechanisms of epidermal signaling, maintenance, and differentiation, points to a need for new therapeutic alternatives to treat and prevent skin aging. In addition to recovering age- and sun-compromised functions, proper treatment of the epidermis has important esthetic implications. This study reviews active ingredients capable of counteracting symptoms of epidermal aging, organized according to the regulation of specific age-affected epidermal functions: (1) several compounds, other than retinoids and derivatives, act on the proliferation and differentiation of keratinocytes, supporting the protective barrier against mechanical and chemical insults; (2) natural lipidic compounds, as well as glycerol and urea, are described as agents for maintaining water-ion balance; (3) regulation of immunological pathogen defense can be reinforced by natural extracts and compounds, such as resveratrol; and (4) antioxidant exogenous sources enriched with flavonoids and vitamin C, for example, improve solar radiation protection and epidermal antioxidant activity. The main objective is to provide a functional classification of active ingredients as regulatory elements of epidermal homeostasis, with potential cosmetic and/or dermatological applications.

Contents

1. Introduction

Epidermis, the most exposed skin part, directly contacts the external environment. It is assembled by multiple superposed cell layers that form an effective protection barrier (Baroni et al., 2012; Madison, 2003). As a complex system, which also captures environmental stimuli, epidermis is composed of several cell types such as keratinocytes, melanocytes, Langerhans cells, and Merkel cells (Boulais and Misery, 2008). Keratinocytes are the most abundant cell type constituting 80–95% of epidermal cells (Brohem et al., 2011; Ulmann et al., 2007).

Due to constant desquamation, epidermis needs continuous renewal, which begins with multiplication of proliferative cells

* Corresponding author at: Rua Alfredo Pinto, 1500, São José dos Pinhais, PR 83065-150, Brazil. Tel.: +55 41 3375 9421; fax: +55 41 3375 7600.
E-mail addresses: marciolo@grupoboticario.com.br, marciolorencini@yahoo.com.br (M. Lorencini).

http://dx.doi.org/10.1016/j.arr.2014.03.002
1568-1637/

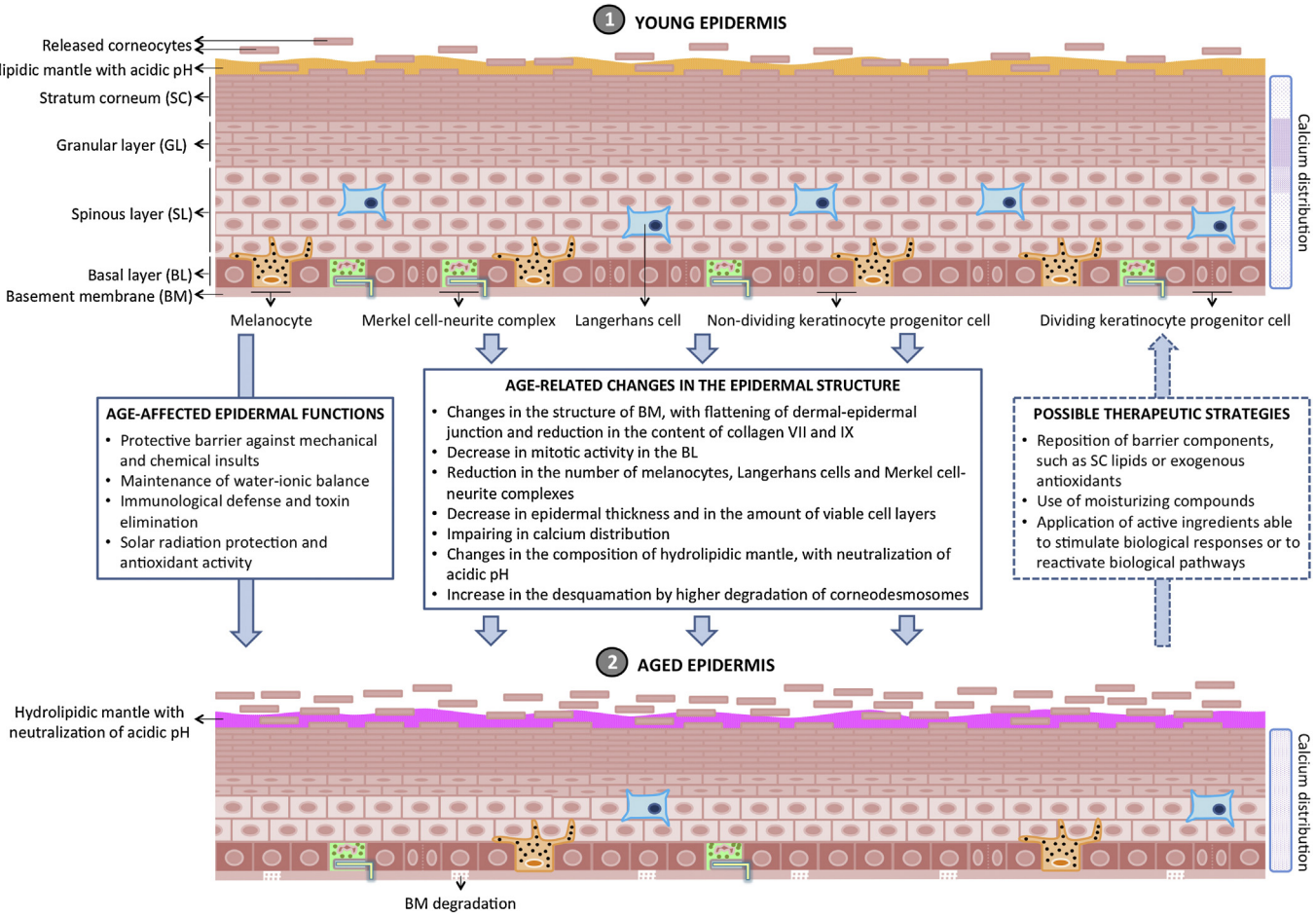

Fig. 1. Molecular, cell and morphological changes associated with epidermal aging. As the epidermis ages, it undergoes a series of structural modifications (Bergman et al., 2000; Choi et al., 2007; Chu and Kollias, 2011; Denda et al., 2003; Hachem et al., 2005; Levakov et al., 2012; Scharffetter-Kochanek et al., 2000; Zouboulis and Makrantonaki, 2011) that directly impact its physiological functions, compromising the natural protective barrier of the organism. Diagram indicating calcium distribution points to a higher ion concentration in the granular layer (GL), darker colored, region in young epidermis (1). In older epidermis (2) calcium gradient is lost and calcium is possibly distributed homogeneously among the skin layers. Possible therapeutic alternatives are different forms of action of active ingredients or compounds capable of helping to recover age-affected physiological functions to an extent that will approximate them as nearly as possible to those in young epidermis.

in the innermost layer, generating keratinocytes that undergo differentiation as they are driven outwards with cell divisions (Fuchs and Raghavan, 2002; Milstone, 2004). Keratinocyte differentiation is marked by molecular, structural, and functional changes, resulting in a stratified epidermis in which the different strata, arranged from the inner to the outer surface, constitute the basal layer (BL), spinous layer (SL), granular layer (GL), and stratum corneum (SC), respectively (Fuchs and Raghavan, 2002; Simpson et al., 2011). The palms and soles possess an additional layer – stratum lucidum (SL) – between GL and SC (Brohem et al., 2011). In SC, keratinocytes reach their highest level of differentiation and are then known as corneocytes – dead, enucleated, and morphologically flat cells composed of protein and lipid blocks bonded to one another and immersed in a lipid matrix (Eckhart et al., 2013).

More than just a barrier for mechanical protection, epidermis is a metabolically active tissue in constant dynamic balance and periodically undergoes complete renewal cycles (Fuchs and Raghavan, 2002). The working of the epidermis seems paradoxical, since it is highly stable in protecting the organism from external aggression and, at the same time, allows its cell components the required flexibility to ensure tissue renewal and capability of response to different stimuli (Simpson et al., 2011). This ability makes the epidermis a decisive component for maintaining body homeostasis. Over the years, however, epidermal primary functions may gradually falter (Elias and Ghadially, 2002). Physiological wear from skin aging is a consequence of damage that accumulates throughout the organism's life and is caused both by intrinsic factors (physiological components and genetic predisposition) and extrinsic factors (external insults, particularly from solar radiation) (El-Domyati et al., 2002; Farage et al., 2008a). Molecular, cell-related, and morphological changes in aged epidermis not only compromise its protective role, but also contribute to the appearance of skin symptoms, including excessive dryness and pruritus (White-Chu and Reddy, 2011), as well as increased predisposition to formation or deepening wrinkles (Kuwazuru et al., 2012), dyspigmentation (Longo et al., 2013), fragility and difficulty to heal injuries (Bourguignon et al., 2013; Calleja-Agius et al., 2007), alteration in skin permeability to drugs (Bourguignon et al., 2013), impaired ability to sense and respond to mechanical stimuli (Wu et al., 2011), skin irritation (Bourguignon et al., 2013), and tumor incidence (Farage et al., 2008b; Wolf et al., 2013) (Fig. 1).

Skin aging involves systemic changes as well as changes in the entire skin (Waller and Maibach, 2006, 2005; for details, refer to Farage et al., 2010). Although most investigations still concern dermis, mainly because of its abundant content in extracellular matrix (ECM), recent studies have targeted epidermal aging and possible therapeutic options. In addition to their health-related implications, epidermal alterations can lead to changes in appearance or image that may have a high esthetic and psychosocial impact (Jiang and DeLaCruz, 2011). Moreover, search for therapeutic alternatives

Table 1
Active ingredients for regulation of epidermal protection barrier against mechanical and chemical insults.

Active ingredients	Action mechanisms	References
Achillea millefolium extract[a]	As the human epidermis ages, expression of receptors of PMOC, a precursor of neuropeptides including ACTH and β-endorphin, gradually diminishes. In human keratinocytes, *A. millefolium* extract increased the synthesis of mRNA and proteins for POMC, MC-2R e MOR-1 receptors. In biopsies of skin in culture, the extract helped to improve the expression of K10, transglutaminase-1 and filaggrin, and to increase epidermal thickness. In vivo, it improved appearance of wrinkles and pores significantly in comparison with placebo	Pain et al. (2011)
Adapalene[a]	Adapalene is a synthetic retinoid commonly used in acne treatment. In vitro and in vivo studies found it active in the regulation of epidermal cell proliferation and differentiation. Action of adapalene on keratinocytes takes place via RAR – specifically γRAR	Jain (2004), Michel et al. (1998)
Alpha-hydroxy acids[a]	AHA's are widely used in chemical peeling and cosmetic formulations as cell renewal stimulants. A lotion containing 25% of AHA promoted a 25% increase in skin thickness as well as a reduction in melanin content, which diminished skin spots. Treatment with glycolic acid increased epidermal cell proliferation rate and thickness in mice, as well as the nuclear volume of keratinocytes in the basal, spinous, and granular layers. Treatment with lactic acid results in increased firmness and thickness of both the epidermis and the dermis, as well as clinical improvement in the softness of the skin and in the appearance of fine lines and wrinkles	Babilas et al. (2012), Bhattacharyya et al. (2009), Ditre et al. (1996), Smith (1996), Yamamoto et al. (2006)
Arotinoid ethyl ester	AEE stimulated cell proliferation in the epidermis of embryonic and adult mice. AEE inhibited epidermal differentiation in embryonic mice and stimulated it in the adult animal	Tsambaos et al. (1985)
Ethyl-α-D-glucoside	α-EG, the main component in Japanese sake, increases loricrin content significantly by acting on keratinocyte differentiation, while reducing the number of SC layers in aged mice, improving their functionality	Nakahara et al. (2007)
Green tea polyphenols	Green tea polyphenols, especially EGCG, were tested on primary human keratinocytes and stimulated their proliferation and differentiation via induction of p57/KIP2, with higher expression of K1 and filaggrin and increased transglutaminase activity. In aged keratinocytes with reduced cell activity rates, treatment with green tea polyphenols renewed DNA synthesis and succinate dehydrogenase activation. EGCG also exhibited a potential for the modulation of caspase 14, a unique regulator of terminal differentiation of keratinocytes associated with cornification	Hsu et al. (2005, 2003)
Hesperidin	Hesperidin is found in orange rind extract. Its topical application on mice stimulated proliferation, differentiation and secretion of lamellar bodies in the epidermis, as well as activation of PPAR-α and PPAR-γ in keratinocytes	Hou et al. (2012)
Hyaluronic acid[a]	HA has been extensively studied in epidermal renewal as a component of formulations, or injected intradermically as an alternative antiage treatment. There are also treatments with active ingredients that induce HA production in the skin, as well as research on the therapeutic potential of HA with different molecular weights. A regimen of topical treatment with low molecular weight HA followed by high molecular weight HA increases proliferation and epidermal thickness, and stimulates cell differentiation in aged mice skin. HA acts on CD44 activation, inducing a series of effects on epidermal processes via Rho GTPase	Bourguignon et al. (2013), Farwick et al. (2011)
Jasmonic acid derivative (LR2412)	Treatment with LR2412 induces hyperplasia in epidermis reconstructed in vitro, with an increase in Ki67-positive cells and in epidermal thickness. LR2412 also stimulates HAS2 and HAS3 expression, as well as HA deposition. Treatment with this compound did not modify the expression of the main proteins involved in late terminal differentiation steps, such as filaggrin e transglutaminase 1, indicating that it is devoid of skin irritant potential	Michelet et al. (2012)
Imiquimod[a]	Therapy using 5% IMI for actinic keratosis results in less compact hyperkeratosis, more homogeneous pattern of epidermal crystals, ordered epidermal proliferation, less sun-damaged melanocytes, and better overall aspect of the skin	Smith et al. (2007)
L-Fucose	Percutaneous application of 1% L-fucose in rats during four weeks results in increased skin thickness in 13% of the test group, in addition to significant improvements in the dermis	Fodil-Bourahla et al. (2003)
Lutein	Lutein, zeaxanthin and astaxanthin induced increased expression of HAS3, with an increase in hyalurinan synthesis. Lutein significantly increased RARE transcript activity. In addition, lutein-derived metabolites were reported to act as RAR ligands in keratinocytes, which makes lutein a potential substitute for retinoids	Sayo et al. (2013)
Myristyl nicotinate[a]	MN, a nicotinic acid derivative, was developed for treating photodamaged skin. Treatment of photodamaged face skin increases the content of NAD in the skin by 25%, in addition to increasing the stratum corneum thickness by 70% and of the whole epidermis by 20%. MN causes the epidermal renewal rate to increase by 6–11% and the TEWL rate to decrease by about 20%. These results indicate that MN improves differentiation and epidermal barrier function, suggesting that MN can play a significant part in the treatment of the progression of skin lesions caused by photoexposure	Jacobson et al. (2007)
Oxysterols	Treatment of primary human keratinocytes with oxysterols induced differentiation, stimulating the expression of involucrin and transglutaminase with an inhibitory effect on cell proliferation. Action pathway of oxysterols in the keratinocytes involves activation of liver X receptor-beta. Similar results have been obtained from topical treatments of mice with oxysterols, indicating increased levels of mRNA and protein for involucrin, loricrin and profilaggrin. The treatment of hyperproliferative epidermis with oxysterols proved capable to restore epidermal homeostasis	Hanley et al. (2000), Kömüves et al. (2002)
p-Dodecylaminophenol	With a more potent antioxidant action than retinoic acid, p-DDAP suppresses MMP expression and stimulates K16 synthesis without causing skin irritation or desquamation. p-DDAP also regulates keratinocyte differentiation, promotes increase in epidermal thickness, and may improve wrinkles and freckles in mice	Takahashi and Fujiu (2010)
Retinyl retinoate[a]	Retinyl retinoate is a less irritating retinol derivative than other retinoids. A study of primary human and mice keratinocyte cultures indicates that retinyl retinoate has a potential for expressing retinoic acid, as well as its receptor CD44 and the enzyme HAS2.TEWL rates induced by retinyl retinoate were lower than the rates induced by retinol, retinoic acid and retinaldehyde. When used in topical formulations, retinyl retinoate decreased wrinkles	Kim et al. (2011, 2010)
Simarouba amara extract[a]	Immunohistochemical analysis of involucrin and activation of transglutaminase in skin fragments treated with this extract demonstrated its potential to increase the expression of these markers. Results were proven with clinical and instrumental methodologies which showed it to have an effect on the improvement of barrier function and skin hydration	Bonté et al. (1996)
Triterpenes[a]	Purified TE's particularly rich in betulin were demonstrated to act on the proliferation, apoptosis and differentiation of human keratinocytes in vitro, ex vivo, and in vivo. TE activity in human keratinocytes occurred by means of increased calcium influx, which led to an increase in the expression of genes such as TRPC6 and several differentiation markers, including K10	Woelfle et al. (2010)

Table 1 (*Continued*)

Active ingredients	Action mechanisms	References
Valproic acid	Application of VPA on lesions in the skin of mice assisted the scarring process by stimulating the expression of β-catenin and terminal differentiation markers in keratinocytes, as well as the expression of proliferation markers such as Ki67. In vitro, VPA increased the mobility of HaCaT-lineage keratinocytes by activating signaling pathways involving Wnt/β-catenin, ERK and PI3-kinase/Akt	Lee et al. (2012)
Vitamin A[a]	Vitamin A or retinoic acid is the most widely studied compound for epidermal renewal because of its effect on the proliferation and differentiation of keratinocytes. However, there have been reports of instability and degradation in cosmetic formulas, and also of incidence of skin irritation, prompting the production of similar compounds to avoid such unwanted effects. Retinoids are lipophilic molecules that penetrate easily in the epidermis; their biologically active forms modulate the expression of genes involved in cell differentiation and proliferation by way of nuclear receptors. Mechanisms of retinoid action include RAR and RXR activation, increased CRABP2 and HBEGF gene expression, enhanced keratinocyte proliferation, and increased epidermal thickness. Their proliferative effect was also noted in human keratinocytes via P2Y2 activation	Babamiri and Nassab (2010), Bellemère et al. (2009), Fujishita et al. (2006), Sorg et al. (2006, 2005), Tur et al. (1995), Wang et al. (2011)
Vitamin B3[a]	Topical application of vitamin B3 (niacinamide or nicotinic acid) has a stabilizing effect on the epidermal barrier function by reducing TEWL and improving the moisture content of the cornified layer. Niacinamide leads to increased synthesis of proteins with keratin, stimulation of ceramide synthesis, acceleration of keratinocyte differentiation, and increased intercellular NADP levels. In skin aging treatments, topical application of niacinamide results in improvement of skin surface structure, softening of wrinkles, and photocarcinogenesis inhibition	Gehring (2004)

[a] Active ingredients with placebo/vehicle controlled studies in vivo in man. α-EG, ethyl-α-D-glucoside; ACTH, adrenocorticotropic hormone; AEE, arotinoid ethyl ester; AHA, alpha-hydroxy acids; Akt, a serine/threonine-specific protein kinase; CD44, cluster of differentiation 44; CRABP2, cellular retinoic-acid-binding protein II; EGCG, epigallocatechin-3-gallate; ERK, extracellular-signal-regulated kinases; HA, hyaluronic acid; HAS, hyaluronan synthase; HBEGF, heparin-binding epidermal growth factor; IMI, imiquimod; K, keratin; Ki67, nuclear protein Ki-67; MC-2R, melanocortin 2 receptor; MMP, matrix metalloproteinases; MN, myristyl nicotinate; MOR-1, μ-opioid receptor; NAD, nicotinamide adenine dinucleotide; NADP, nicotinamide adenine dinucleotide phosphate; P2Y2, P2Y purinoceptor 2; p57/KIP2, cyclin-dependent kinase inhibitor; p-DDAP, p-Dodecylaminophenol; POMC, pro-opiomelanocortin; PPAR, peroxisome proliferator-activated receptor; PI3, phosphatidylinositol 3; RAR, retinoic acid receptors; RARE, retinoic acid responsive element; RXR, retinoid receptor X; SC, stratum corneum; TE, triterpenes; TEWL, transepidermal water loss; TRPC6, transient receptor potential canonical subtype 6; VPA, valproic acid; Wnt, a group of signal transduction pathways.

that include the epidermis is an additional step toward an integrating approach to skin aging treatment and prevention.

This manuscript overviews active ingredients identified for the treatment of skin aging. They are grouped according to their specific activity in the recovery of epidermal functions and include the following major topics: (1) protective barrier against mechanical and chemical insults (Lulevich et al., 2010; Kirschner et al., 2013), (2) maintenance of water-ion balance in the organism (Kirschner et al., 2013; Proksch et al., 2008), (3) immunological defense and toxin elimination (Baroni et al., 2012; Geusau et al., 2001; Polak et al., 2014), and (4) solar radiation protection and antioxidant activity (Shindo et al., 1994; Yamaguchi et al., 2006). Overall, current active ingredients were searched for potential cosmetic and/or dermatological applications, according to their biological and biophysical effects on the regulation of age-impaired epidermal homeostasis.

2. Protective barrier against mechanical and chemical insults

Protection against mechanical and chemical insults depends directly on the structural epidermal integrity – a stratified arrangement of superposed cell layers with keratinocytes bonded by means of intercellular junctions and extracellular matrix components (Ishida-Yamamoto et al., 2011; Kirschner et al., 2013; Lulevich et al., 2010). A primary factor for preserving skin barrier is its capability for cell renewal, affected by the keratinocyte proliferation rate and differentiation (Cangkrama et al., 2013). Distinct mechanical properties of keratinocytes, including their high deformation resistance, which may be up to seventy times that of other cells in the organism, contribute significantly to their protective action (Lulevich et al., 2010). This resistance is largely due to the keratin cytoskeleton acquired along the epidermal cell differentiation process: complete keratin deletion causes significant biomechanical deficiencies in keratinocytes (Bragulla and Homberger, 2009; Kim et al., 2012b; Ramms et al., 2013). Chemical composition of the epidermis, which also plays a part in the protection against mechanical and chemical insults, will be discussed more detailedly in Section 3 due to its high relevance to maintenance of the water-ion balance in the organism.

Reduction in epidermal thickness – one of the morphological characteristics of age-affected skin – results from lower cell renewal rates due both to intrinsic and extrinsic factors (Crisan et al., 2012; Shlivko et al., 2013; Tsugita et al., 2013; Waaijer et al., 2012). The number of layers containing viable cells diminishes with epidermal aging, and keratinocyte proliferation and differentiation are significantly impaired in elderly persons' epidermis (Bourguignon et al., 2013; Levakov et al., 2012; Lock-Andersen et al., 1997). Senescent cell build-up may also play a role in the diminishing regenerative capacity of aged biological tissues, including epidermis (Cordisco et al., 2010). In addition, changes that occur in the cells and extracellular matrix suggest a more porous and less effective structural organization of the aged epidermis as regards its barrier function against external chemical agents (Elias and Ghadially, 2002).

Active ingredients that regulate the protection against mechanical and chemical insults should be capable of restoring cell renewal in aged epidermis and thus ensure integrity in the skin barrier. In addition to the possibilities here identified, physical treatments such as photodynamic (Orringer et al., 2008), high-energy pulsed CO_2 laser (Ratner et al., 1998; Stuzin et al., 1997), and fractional CO_2 laser (Sasaki et al., 2009) therapies are suggested as options for epithelium renewal and keratinocyte proliferation incitement action. Table 1 lists ingredients capable of supporting the protective epidermal barrier against mechanical and chemical insults, including literature-enshrined elements, such as retinoids and their derivatives (for recent review, see Babamiri and Nassab, 2010), as well as alpha-hydroxy acids (AHAs) (for recent review, see Babilas et al., 2012) and several other compounds.

Regarding retinoic acids, a large set of data has already been published describing their effect on the proliferation and differentiation of keratinocytes, that directly affects wrinkles appearance and formation (Bellemère et al., 2009; Skazik et al., 2013). Retinoids are also used for photoaged skin treatment, since they reduce skin hyperpigmentation (Gold et al., 2013; Kircik, 2012) and inhibit metalloproteinases expression (Jurzak et al., 2008). Besides these well-known properties, retinoids have recently been described in the regeneration of hair follicles by promoting functional differentiation of dermal papilla cells (Aoi et al., 2012) and, in association with minoxidil, they prevent apoptosis of dermal papilla cells

(Kwon et al., 2007). Side effects upon use of retinoic acids are related to their potential to cause skin irritation. Another potential inconvenience of retinoic acids involves its instability in topical formulations. Interestingly, these problems have led to the development of retinoid derivatives and similar compounds with superior properties (Kim et al., 2011, 2010). AHAs, such as glycolic and lactic acid, are also used to treat photodamaged skin (Rendl et al., 2001) and to stimulate epidermal renewal, with clinical improvements in skin thickness, firmness, and softness, as well as in the appearance of fine lines and wrinkles (Bhattacharyya et al., 2009; Yamamoto et al., 2006). They reduce the calcium ion concentration in the epidermis and remove calcium ions by chelation, disrupting cell adhesions and resulting in desquamation (Wang, 1999).

3. Maintenance of water-ion balance in the organism

Epidermis plays a fundamental part in sustaining internal homeostasis in the organism by controlling the exchange of substances, especially water and ions, with the external environment (Tzaphlidou, 2004). Hydration also determines the general aspect of the skin; since the entire cell metabolism can be affected by the amount of water it contains (Jiang and DeLaCruz, 2011). To preserve this functionality, in addition to the cell structure discussed previously, epidermis shows an arrangement of biochemical components with selective properties. In SC, for example, the extracellular matrix contains 75–80% of proteins, 5–15% of lipids, and 5–10% of other constituents (Förster et al., 2009). Lipid fraction consists primarily of ceramides, fatty acids, cholesterol, esters, triglycerides, and phospholipids (Lampe et al., 1983). Part of the highly insoluble and resistant SC proteins, such as loricrin and involucrin, corresponds to corneocyte envelope (Hansen et al., 2009; Kalinin et al., 2001; Nishifuji and Yoon, 2013). Moreover, to preserve water and soluble ions, epidermis has differentiated molecular mechanisms, such as natural moisturizing factors (NMFs) derived from profilaggrin proteolysis, which form an intensely hygroscopic mixture composed of peptides, amino acids and their derivatives (such as urocanic acid (UCA) and 2-pyrrolidone-5-carboxylic acid (PCA)), minerals, urea, and sugars (Bouwstra et al., 2008; Kezic et al., 2009; Zhang et al., 2006). Aquaporins (AQPs) are channels that run along epidermal cell membranes to carry water and small molecules of solute, which are essential for maintaining water-ion balance of the cell. Of the thirteen AQP types described in humans, the most extensively studied AQP in the skin is AQP3, found chiefly in epidermal basal cells (Hara and Verkman, 2003; Takata et al., 2004). Recently, AQP10 has also been identified in human epidermis, specifically in SC corneocytes (Boury-Jamot et al., 2006; Jungersted et al., 2013). AQP3 and AQP10 belong to the same aquaglyceroporin subclass; they are known to transport water and glycerol – the latter being an important agent for the hydration, resilience and repair of the skin barrier (Fluhr et al., 2008).

Aging significantly affects the epidermal function of controlling the balance of water and ions in the body. Lipid synthesis diminishes with age, as does the secretion of lamellar bodies in SC which generates an extracellular matrix that is more porous and less efficient in controlling the water-ion balance in the organism (Elias and Ghadially, 2002; Ghadially et al., 1995). Many molecular pathways related to SC lipid metabolism are downregulated in aged skin; and cholesterol seems to be the most affected lipid class (Ghadially et al., 1996; Jarrold et al., 2009). In specific cases, such as solar lentigo (an aging mark in photoexposed skin areas), a reduction occurs in the expression of cornified envelope-related genes, such as filaggrin and involucrin (Aoki et al., 2007). Free amino acid content of NMF's seems lower in the SC of senile epidermis (Jacobson et al., 1990). Expression AQP3 levels diminish with the aging of human epidermis and also in isolated keratinocytes, probably related to the development of xerosis (excessive skin dryness commonly seen in the elderly) (Li et al., 2010).

As therapeutic alternatives for recovering the epidermal function that preserves the water-ion balance in the organism, active ingredients should promote replenishment or stimulate the endogenous synthesis of affected biochemical components. Table 2 lists the most frequently used components for this specific function, such as waxes, natural oils and derivatives, whose lipid composition either mimics that of SC elements or acts complementarily on skin hydration (for critical considerations, see Draelos, 2013), as well as compounds that stimulate endogenous synthesis of epidermal biomolecules, including glycerol and urea (for details, refer to Lodén and Maibach, 1999).

Among the compounds widely used for maintenance of water-ion balance are glycerol and urea, as they are able to sustain the physical properties of hydrated lipid systems under dry conditions (Björklund et al., 2013). Comparison of the effects of these compounds on water distribution in the SC of human skin equivalents suggested distinct patterns of action. While water domains were mainly located in the intercellular regions under urea treatment, water was observed both in intercellular regions and in corneocytes following glycerol treatment (Bouwstra et al., 2012). A fine-tuned regulation of AQPs expression is also involved in the maintenance of water and solute balance in the skin (Hara and Verkman, 2003). It has been shown that mice lacking AQP3 have impaired SC hydration and skin elasticity and a threefold reduction in their glycerol content. However, all these effects were compensated with orally administered glycerol, restoring the epidermal barrier function (Hara and Verkman, 2003). Peptides and standardized plant extracts have already been reported to increase expression of the AQP3 gene in cultures of human keratinocytes, but such studies usually lack consistent clinical trials to confirm their function in vivo.

4. Immunological defense and toxin elimination

Regulation of epidermal defense mechanisms is crucial for local and systemic homeostasis of the organism. Existence of a complex, unified skin defense system, described as a cutaneous neuroimmunoendocrinological system, has been suggested (Brazzini et al., 2003; Misery, 2000; O'Sullivan et al., 1998). Epidermal cells – including keratinocytes, melanocytes, and Langerhans cells – can produce, either constitutionally or by activation, an arsenal of cytokines (Table 3) and thus reinforce the action of epidermis as a tissue that is immunocompetent and active in creating an immunological barrier (Corsini and Galli, 2000; Kupper and Fuhlbrigge, 2004; Williams and Kupper, 1996). Langerhans cells act as sentries for epidermis and ensure the activation of adaptive immune response by presenting antigens to T-cells (Cumberbatch et al., 2003). Epidermis also acts as an adjuvant in the potentiation of inflammatory pathways and in the preparation of more efficient systemic immune responses with improved B- and T-cell activation (Gutowska-Owsiak and Ogg, 2012; Liu et al., 2010). In addition, the epidermal surface exhibits particular properties for a defense strategy against potential pathogens. The strategy includes maintenance of commensal microorganisms capable of producing competitor-inhibiting substances, secretion of antimicrobial peptides named defensins, and maintenance of acid pH levels to hinder the installation and growth of certain microorganisms (Harder et al., 2013; Namjoshi et al., 2008; Niyonsaba et al., 2009). Although scantily reported to date, there are indications that epidermal desquamation helps to eliminate toxins such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) (Geusau et al., 2001).

Table 2
Active ingredients in epidermal regulation for maintenance of water-ion balance in the organism.

Active ingredients	Action mechanisms	References
Ajuga turkestanica hydroalcoholic extract[a]	*A. turkestanica* extract increased AQP3 and filaggrin expression compared with non-treated groups in studies with experimental human keratinocyte models and cocultures of human keratinocytes and fibroblasts. These results led to the application of the extract in formulations; a significant increase hydration was observed in human skin, which strengthens the role of these water channels and small solutes in the skin as a regulation mechanism for the hydration of the skin	Dumas et al. (2007, 2002)
Botryococcus braunii microalgae	Extract of these microalgae increased significantly the AQP3 gene expression in human keratinocyte cultures in vitro. Furthermore, it inhibited hormone-sensitive lipase activity in adipocytes and increased the biosynthesis of collagen I and III in fibroblasts. To an important extent, the extract increased expression of cornified envelope proteins, such as filaggrin and involucrin, and exhibited a powerful antioxidant activity, for example in reducing nitric oxide production	Buono et al. (2012)
Coffea arabica L. seed oil	*C. arabica* L. seed oil induces TGF-β and GM-CSF increase in cell culture; both are associated with increased synthesis of extracellular matrix and recovery of neurological response, and also with increased AQP3 gene expression in culture and ex vivo skin	Velazquez Pereda et al. (2009)
Eucalyptus extract (standardized in macrocarpal A)[a]	Addition of eucalyptus extract to a culture of human keratinocytes increased ceramide levels in a dose-dependent manner, as well as glucosylceramide and sphingomyelin biosynthesis. Topical application of the extract on dry human skin promoted increase in SC ceramide levels, reduction of TEWL, and improved barrier function of the skin. Addition of macrocarpal A, the chief phytochemical in eucalyptus extract, promoted an increase in the amount of ceramide, as well as the expression of acid palmitoyl-transferase, sphingomyelinase, glucosylceramide synthase and glucocerebrosidase. Results indicate a possible therapeutic application of this extract for a variety of skin disorders	Ishikawa et al. (2012)
Glycerol[a]	Glycerol promotes a significant increase of AQP3 and AQP10 gene expression in human keratinocyte culture in vitro. Moreover, in skin exposed to UVB radiation, which reduces the presence of these proteins in the skin, glycerol has been shown to promote the preservation of this expression, contributing to the maintenance of hydric homeostasis in the skin when confronted with this type of environmental aggression	Jungersted et al. (2013), Lodén and Maibach (1999), Xie et al. (2013)
Gypsum fibrosum extract (standardized in 0.3% of $CaSO_4$)	Animals treated with oral doses of 0.3% *G. fibrosum* extract or 0.3% of $CaSO_4$ revealed a significant increase in AQP3 expression relatively to non-treated groups. This shows that both the extract and its main active ingredient by itself are capable of stimulating AQP3 expression, contributing positively to the maintenance of hydric homeostasis in the skin	Ikarashi et al. (2012)
Kanglaite (mixture of extractions of coix seed)	In a photoaging study using different experimental models, including in vitro and skin-equivalent models, kanglaite increased AQP3 gene expression. It was also capable of inhibiting the reduction of the expression of this protein caused by keratinocyte exposure to UVB radiation	Shan et al. (2012)
Lithospermum erythrorhizon aqueous extract	Aqueous gromwell (*L. erythrorhizon*) extract induced more intense keratinocyte and fibroblast migration with increased lipid synthesis in an experimental model that simulates wound healing. Cell groups treated with the extract showed a significant increase in phospholipids, sphingolipids (ceramides and glucosylceramides), and neutral lipids. These findings indicate that the aqueous *L. erythrorhizon* extract has an important mechanism linked to the improvement of barrier function and consequent maintenance of skin hydration	Kim et al. (2012a)
Natural oils, waxes or derivatives[a]	There are countless available possibilities of using natural compounds whose lipid composition mimics SC elements, or else acts as an adjutant in skin hydration. The following stand out: amaranth oil, apricot oil, argan oil, candelilla wax, canola oil, carnauba wax, castor oil, coconut oil, corn oil, jojoba oil, jojoba wax, lanolin, lecithin, olive oil, palm oil, rice bran oil, safflower oil, sesame oil, shea butter, soybean oil, squalane, sunflower oil, sweet almond oil, wheat-germ oil, and yellow beeswax, among others	Budai et al. (2012), de Waroux Yle (2013), Huang et al. (2009)
Piptadenia colubrina extract[a]	*P. colubrina* hydroglycolic extract, standardized for total arabinogalactans, increased AQP3 gene and protein expression in keratinocyte culture and ex vivo skin. Extract also increased the expression of the cornified envelope proteins filaggrin and involucrin. These skin-hydration related results were substantiated with findings from clinical studies, in which formulations containing the extract increased the corneometric indices and reduced TEWL	Pereda et al. (2010)
Rice-derived glucosylceramide	Rice-derived GCFr significantly changed the SC ceramide profile in a human skin-equivalent model. Oral administration of this GCFr fraction in mice (3 and 10 mg/kg/day) reduced TEWL in the group exposed to sodium lauryl sulfate. In the skin fragments, ceramide I had increased, while GlcCer (EOS) and the mixture of the GlcCer + GlcCer A/B complex had diminished. These shifts were followed by an increase in GCSase and glucocerebrosidase expression. On the other hand, the expression of GlcCer (d18:2), ceramides 1 and 2, GlcCer (EOS), and GlcCer A/B increased in skin equivalent and was followed by the expression of GCSase and epidermal maturation markers for these ceramides. These results suggest that oral administration of GCFr counterbalanced epidermal ceramide loss by increasing GlcCer metabolism, which resulted in TEWL reduction and barrier function improvement	Shimoda et al. (2012)
Simarouba amara extract[a]	Immunohistochemical analysis of skin fragments treated with *S. amara* extract demonstrated an increase in involucrin expression and transglutaminase activation. These results were corroborated by clinical and instrumental methodologies which provided evidence of effects related to improvement of barrier function and skin hydration	Bonté et al. (1996)
Urea[a]	Urea was shown to stimulate significantly the expression of AQP3, AQP7 and AQP9, as well as of cornified envelope proteins (filaggrin, loricrin and involucrin), in addition to promoting increase in the activity of transglutaminase-1 and other enzymes involved in skin lipid synthesis	Grether-Beck et al. (2012), Lodén and Maibach (1999)

[a] Active ingredients with placebo/vehicle controlled studies in vivo in man. AQP, aquaporin; GCSase, glucosylceramide synthase; GlcCer, EOS, esterified ω-hydroxy fatty acid and sphingosine [EOS]; GM-CSF, granulocyte-macrophage colony-stimulating factor; GCFr, glucosylceramide fraction; SC, stratum corneum; TGF-β, transformation growth factor β; TEWL, transepidermal water loss; UVB, ultraviolet B.

As the skin ages, agents that stimulate the epidermal immune defense system undergo significant changes: total number of Langerhans cells diminishes, as does their functional capability (Ogden et al., 2011; Xu et al., 2012); secretion level of IL-1 is reduced and affects mitotic capacity and epidermal lipid synthesis (Ye et al., 2002); and SC surface pH tends to become more basic (Choi et al., 2007; Hachem et al., 2005). Furthermore, in addition to activating epidermal immune response, constant exposure to toxins and/or pollutants accelerates skin aging (Vierkötter and Krutmann, 2012). Toxins present in cigarettes damage healing processes, trigger onset of diseases, increase hair loss, and cause premature skin aging and formation of deep wrinkles (Morita et al., 2009). Organic particles released by burning tobacco's smoke induce apoptosis in keratinocytes (Pedata et al., 2012). Exposure to air pollution

Table 3
Cytokines produced by epidermal cells, with constitutive or induced expression.

Cells	Cytokines
Keratinocytes	G-CSF, GM-CSF, IFN-γ, IL-1α, IL-1β, IL-3, IL-6, IL-7, IL-8, IL-10, IL-12, IL-15, IL-18, IP-10, M-CSF, MCP-1, MIP-1α, TGF-α, TGF-β, TNF-α
Langerhans Cells	IFN-γ, IL-1α, IL-1β, IL-6, IL-15, IL-18, MIP-1α, MIP-2, TGF-β
Melanocytes	G-CSF, GM-CSF, IL-1α, IL-1β, IL-6, IL-7, IL-8, IL-10, IL-12, MCSF, MIP-1α, MCP-1, TGF-α, TGF-β, TNF-α

G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, Interferon; IL, interleukin; IP, IFN-γ inducible protein; M-CSF, macrophage colony-stimulating factor; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein; TGF, transformation growth factor; TNF, tumor necrosis factor.

showed significant correlation with signs of aging, such as dark spots and fine lines on the skin of 400 Caucasian women (Vierkötter et al., 2010). Moreover, capacity of response to pollutants has been suggested to diminish with age (Valacchi et al., 2012).

Active ingredients capable of regulating the immune defense function of the epidermis include those that can modulate inflammatory responses or stimulate the synthesis of natural defense compounds, such as antimicrobial peptides. Table 4 covers natural extracts and compounds of various origins which have been described for this type of application, such as resveratrol and its widely studied anti-inflammatory properties (for recent review, see Baur and Sinclair, 2006).

We were unable to identify any effectively proven therapeutic opportunities for epidermal regulation of toxin removal. It is therefore advisable to avoid excessive exposure to polluting or toxic substances and to pursue a healthier lifestyle. An example of this approach is a survey using future projections of the appearance of women who used tobacco led many female volunteers to stop smoking (Grogan et al., 2011). Indeed, cigarette smoking represents an environmental stressor that can damage SC, modifying its lipid composition by increasing the expression of scavenger receptor B1 (SR-B1), related to cholesterol uptake. Resveratrol was recently described as a SR-B1 inhibitor in keratinocytes in a dose-dependent manner, suggesting a skin protective potential against cigarette smoking (Sticozzi et al., 2014). Resveratrol is also able to induce phosphorylation of EGFR (epidermal growth factor receptor), whose signaling pathway regulates the expression of interleukins (IL) by human keratinocytes, such as IL-8 (Pastore et al., 2013). Moreover, in association with its natural precursor polydatin, resveratrol modulates gene expression of IL-6, IL-8 and tumor necrosis factor-alpha (TNF-α), and augments the release of human beta-defensin 2 whose combined action might mediate a positive outcome related to the skin response to toxins (Ravagnan et al., 2013).

5. Solar radiation protection and antioxidant activity

Solar radiation is a leading environmental factor that affects human skin, particularly radiation in the ultraviolet (UV) region of the spectrum, which is divided into UVA (320–400 nm), UVB (280–320 nm) and UVC (100–280 nm, mostly absorbed by the ozone layer) (Hockberger, 2002). In addition to UV rays, infrared radiation (IR, above 800 nm) may also lead to biological changes in living organisms (Polefka et al., 2012). As the amount of energy is inversely proportional to the wavelength, UVB delivers more energy than UVA. However, UVA has a higher penetration rate and reaches the deepest epidermal layers, while UVB affects primarily epidermis and papillary dermis (Hoffmann et al., 2000). UVB is harmful to biological tissues in that it causes direct injury in molecules such as nucleic acids and proteins, whereas the action of UVA is less understood and involves oxidative stress and production of reactive oxygen species (ROS) that may damage different cell components through propagation reactions (Césarini et al., 2003; Dröge, 2002; Hockberger, 2002). ROS may originate from processes such as cell respiration, or from exogenous agents such as UV radiation, which intensify the formation of such oxygen species in the skin (Burke, 2010; Palmer and Kitchin, 2010; Puizina-Ivić et al., 2010; Rahimpour and Hamishehkar, 2012). UV acts as a broad activator of cell surface receptors, inducing multiple downstream signaling pathways that regulate expression of multiple genes (Rittié and Fisher, 2002). Epidermal cells – and keratinocytes in particular – have an internal machinery capable of preventing, to a certain extent, the occurrence of UVB-induced mutations by eliminating ROS and inducing cell cycle arrest for subsequent DNA repair. However, if the levels of accumulated damage in DNA become critical, or ROS amounts come to be excessive, an apoptosis-inducing mechanism is activated to prevent malignant changes from taking place in the cells (Kulms et al., 2002). The closer to BL, the greater the chances for a keratinocyte to undergo a malignant transformation, which is why the epidermis is endowed with additional protective mechanisms, such as pigmentation and higher cell susceptibility to UVB-induced apoptosis (Schäfer et al., 2010).

Endogenous components for the removal of ROS are in place all over the body. Transcription factor Nrf2 (NF-E2-related factor 2) is an important cytoprotector that induces production of enzymatic and non-enzymatic elements for antioxidant defense (Beyer et al., 2007; Schäfer et al., 2010). In human skin, antioxidant capacity of epidermis is much greater than that of dermis. Several antioxidant components in the epidermis have higher (enzymatic) activity or (non-enzymatic) concentration percentages than the corresponding components in dermis: superoxide dismutase (126%), glutathione peroxidase (61%), glutathione reductase (215%), glucose-6-phosphate dehydrogenase (111%), isocitrate dehydrogenase (313%), α-tocopherol (90%), ubiquinol 10 (900%), ascorbic acid (425%), uric acid (488%), reduced glutathione (513%), and total glutathione (471%) (Shindo et al., 1994).

UV radiation effects are the main cause of extrinsic skin aging or photoaging, a condition that may be aggravated when combined with IR exposure (Kligman, 1982; Polefka et al., 2012). Skin defenses against oxidative damage become vulnerable with age (Keogh et al., 1996). Elimination of DNA damage, such as removal of UVB-induced pyridine dimers, is slower in the epidermis of older individuals (Yamada et al., 2006). By the same token, antioxidant capacity of epidermal cells declines with age following reduction of α-tocopherol, ascorbic acid and glutathione concentrations (Rhie et al., 2001). As a result, aged skin shows increasing levels of oxidized proteins that become inactive and accumulate inside the cells (Sander et al., 2002).

Table 5 lists active ingredients described in the literature as capable of acting on the regulation of protection against solar radiation, as well as for their antioxidant activity. Exogenous antioxidant supplementation is currently the most explored therapeutic alternative (for review, see Dreher and Maibach, 2001). Topical and oral antioxidant use may reinforce the action of endogenous molecules in protection against ROS. Cosmetics formulated with antioxidants are among the most popular antiage products in the market worldwide (Palmer and Kitchin, 2010; Stamford, 2012). In addition, the use of sunscreens in cosmetic formulations is a preventive measure to avoid damaging effects of excessive solar radiation (for critical considerations, see Lodén et al., 2011). In view of the ample

Table 4
Active ingredients regulating epidermal immunological defense.

Active ingredients	Action Mechanisms	References
Association of standardized *Pfaffia paniculata*, *Ptychopetalum olacoides* B. and *Lilium candidum* extracts	Association of standardized plant extracts of *P. paniculata*, *P. olacoides* B. and *L. candidum* promotes significant anti-inflammatory action by reducing PGE2, LTB4 and histamine production in a model of cultivated normal human keratinocyte cells stimulated with LPS	Eberlin et al. (2009)
Butea monosperma (Lam.) Taub. flowers extract	Hydroglycolic *B. monosperma* flower extract is capable of reducing secretion of pro-inflammatory cytokines IL-1β, IL-6 and IL-8 in cell culture of normal human keratinocyte by approximately 32, 33 and 18%, respectively. In addition, the extract also inhibits the production of PGE2 and secretion of MMP-1, MMP-2, MMP-9 e MMP-10	Krolikiewicz-Renimel et al. (2013)
Coffea arabica L. seed oil	*C. arabica* L. seed oil induces increase of TGF-β and GM-CSF in keratinocyte cell culture; both are associated with increased extracellular matrix synthesis and immune response recovery	Velazquez Pereda et al. (2009)
Imiquimod	Topical application of imiquimod in a murine model revealed a potential for recovery of the epidermal barrier following treatment with tacrolimus. The potential was determined by stimulating IL-1α production, and also by an increase in the gene expression of mBD3 and CRAMP, two important antimicrobial peptides	Jung et al. (2011)
Korean red ginseng extract	Treatment of human keratinocyte cells with Korean red ginseng extract indicated its capability to control LPS-stimulated inflammatory response with a dose-dependent decrease of TNF-α and IL-8 production	Hong and Lyu (2011)
Leontopodium alpinum extract	*L. alpinum* extract inhibited IL-8, IP-10, MCP-1, GM-CSF, TNF-α, and IFN-γ levels, dose-dependently, in human keratinocyte cell cultures exposed to radiation or LPS. Results demonstrate anti-inflammatory and immunomodulating activities of this extract	Daniela et al. (2012)
Natural extracts of arnica flowers, betel nuts, black elder bark, and mugwort root	Natural extracts of arnica (*Arnica montana*) flowers, betel (*Areca catechu*) nuts, black elder (*Sambucus nigra*) bark, and mugwort (*Artemisia vulgaris*) root stimulated gene expression of defensins (hBD2 and/or hBD3) in a normal human keratinocyte culture model. In some cases or at specific concentrations, the extracts also induced secretion of cytokines, including MIP-3a, IL-8, and IL-1α	Pernet et al. (2005)
Red orange extract	Red orange extract (*Citrus sinensis* varieties: Moro, Tarocco, Sanguinello) has high levels of anthocyanins, flavanones, hydroxycinnamic acids, and ascorbic acid. Its anti-inflammatory activity was assessed in human keratinocytes (lineage NCTC 2544) exposed to IFN-γ and histamine. Treatment with red orange extract at different concentrations inhibited expression of ICAM-1 and secretion of MCP-1 and IL-8	Cardile et al. (2010)
Resveratrol[a]	Resveratrol or its natural precursor, polydatin, on human keratinocytes (lineage HaCaT) promoted the modulation of gene expression of cytokines IL-6, IL-8, and TNF-α, and also stimulated the expression of Hsp70B (important for cytoprotection and cell repair) and hBD2	Baur and Sinclair (2006), Ravagnan et al. (2013)

[a] Active ingredients with placebo/vehicle controlled studies in vivo in man. CRAMP, cathelin related antimicrobial peptide; GM-CSF, granulocyte-macrophage colony-stimulating factor, Hsp, heat shock protein; hBD, human beta defensin; ICAM-1, intercellular adhesion molecule 1; IFN-γ, interferon γ; IL, interleukin; LPS, lipopolysaccharide; LTB4, leukotriene B4; mBD, mouse beta-defensin; MCP-1, monocyte chemoattractant protein-1; MIP-3a, macrophage inflammatory protein 3a; MMP, matrix metalloproteinases; PGE2, prostaglandin E2; TGF-β, transformation growth factor β; Th, T helper cell; TNF-α, tumor necrosis factor α.

exposure of epidermis to sunlight and its fundamental role as the first barrier in the fight against ROS, numerous studies have been investigating and proposing options of active ingredients with this protective function.

Among the widely characterized compounds that are capable of protecting skin from solar radiation are green tea extract and resveratrol (Nichols and Katiyar, 2010). Green tea extract and its main polyphenols – notably epigallocatechin-3-gallate and epicatechin-3-gallate – have shown positive effects against inflammation, oxidative stress and DNA damage, with potential to nullify several biochemical processes induced or mediated by UV radiation, such as erythema and premature skin aging (Nichols and Katiyar, 2010; Türkoğlu et al., 2010). Protective effects of polyphenols were also observed due to inhibition of UVA-induced ROS production, mitogen-activating protein kinase activation, and expression of ciclooxigenase-2 (Chan et al., 2008). However, an evaluation of different commercial green tea extracts, used to enrich cosmetic formulations, revealed that photoprotective properties can be affected by the methodologies employed for production of the herbal mixtures (Silva et al., 2013). Therefore, the use of standardized extracts, at least in terms of polyphenols content, seems to be essential to assure the efficacy of products containing such ingredients. Resveratrol, another well-known antioxidant molecule (Bastianetto et al., 2010), is a phytoalexin isolated mainly from grapes (Jagdeo et al., 2010). As a very promising natural drug, resveratrol has been widely explored in the last years to fight aging and age-associated disturbes with consistent in vivo applications (for recent review, see Baur and Sinclair, 2006) and different mechanisms of action, including: (1) reduction of intracellular hydrogen peroxide-upregulated ROS (Jagdeo et al., 2010), (2) activation of sirtuin – in special SIRT1 that is capable of deacetylate histones promoting increased DNA stability and persistent
survival in mammals–and cellular protection against UV damages via modulation of p53 and JNK pathways (Cao et al., 2009), and (3) significant cancer chemopreventive potential (Qian et al., 2009).

6. Concluding topics and prospects

With the growing lifespan and quality of life of the population worldwide, appearance of skin becomes increasingly important for people to feel safe and confident in their social interactions. Skin products currently in use are based on new standards of personal hygiene and health, in addition to transmitting a significant esthetic appeal. Moreover, skin care represents an additional benefit for the elderly, since it also helps to prevent skin disorders and cancer development (Farage et al., 2008a). In its efforts to meet the escalating demand for treatments, development of products keeps abreast of the rapidly evolving knowledge of skin physiology and its functional deterioration with age. Two work fronts cooperate for these advances in knowledge: (1) identification of new biological mechanisms associated with skin aging, and (2) continuous discoveries of new forms of acting to prevent the appearance of or recover signs of aging.

New active ingredients, formulations and suitable delivery systems that may induce the recovery of biological functions affected by age are being sought both by cosmetic and pharmaceutical industries (Kaur et al., 2007). Moreover, a growing movement is under way to customize treatments by taking specific needs of each individual into account. This is the development of tailored medicine, whereby ingredients and their combinations are optimized in a unique composition intended for a specific

Table 5
Active ingredients for regulation of epidermal protection against solar radiation and antioxidant activity.

Active ingredients	Action mechanisms	References
Astaxanthin[a]	Astaxanthin, derived from the microalga *Haematococcus pluvialis* and administered both orally and topically in humans, provided significant inhibition of melanogenesis in age spots by suppressing oxidative melanocyte polymerization and inflammation of the epidermis. Treatment with astaxanthin also acts by protecting keratinocytes from differentiation and cornification induced by oxidative damage	Tominaga et al. (2012)
Apigenin and luteolin	Apigenin and luteolin jointly inhibited the production of ROS in, and increased the viability of, HaCaT cells irradiated with UVA. Pretreatment of the keratinocytes with these flavonoids also inhibited UVA-induced production of MMP-1 and suppressed the expression of c-jun and c-fos, as well as MAPK phosphorylation. Flavonoids also diminished the calcium influx and Ca^{2+}/CaMKs phosphorylation	Hwang et al. (2011)
β-Carotene	β-Carotene inhibited UVA-induced gene modulation in a HaCaT human keratinocyte lineage. In non-irradiated cells, the gene regulation suggests that β-carotene significantly reduced signs of stress and degradation of the extracellular matrix, in addition to promoting the differentiation of the keratinocytes. These effects occur via singlet oxygen sequestration	Wertz et al. (2005)
Calluna vulgaris extract	Topical application of *C. vulgaris* extract (4 mg polyphenols/cm^2) on mice during 30 min before exposure to UVB radiation, for 10 days, provided protection to the skin, reducing the levels of TNF-α and IL-6 cytokines and pirimidin dimers, and the formation of UVB-induced sunburn cells. Therefore, *C. vulgaris* extract protects the skin from sun-induced DNA damage	Olteanu et al. (2012)
Cocoa powder[a]	Female volunteers who took these flavonoids during 12 weeks showed reduced UV radiation-induced erythema, improved skin appearance and hydration, increased skin layer thickness, and lower TEWL	Heinrich et al. (2006), Katz et al. (2011)
Cynaropicrin	Cynaropicrin prevents photoaging of micel by suppressing photo-induced (especially UVB radiation-induced) transactivation of NF-κB	Tanaka et al. (2013)
Epicatechin-3-gallate	ECG inhibits keratinocyte death induced by UVA and UVB in a dose-dependent manner. For UVA, this mechanism proceeds by inhibiting hydrogen peroxide production. For UVB, ECG inhibited membrane lipid peroxidation in treated cells, in addition to blocking the activation of ERK1/2, p38 and JNK in keratinocytes. Therefore, ECG was demonstrated to have an important antioxidant potential to prevent photodamage	Huang et al. (2007, 2005), Nichols and Katiyar (2010)
Epigallocatechin-3-gallate[a]	EGCG promotes keratinocyte survival and inhibits UV-induced apoptosis with the aid of a dual mechanism: (1) increased Bad phosphorylation through ERK-AKT-dependent pathways; (2) increased Bcl-2/Bax ratio. EGCG treatment of human HaCaT keratinocyte cultures lowered UVB-induced cytotoxicity and also inhibited mRNA expression of apoptosis-regulating genes p53 and p21, and gene c-fos, in addition to blocking the secretion of cytotoxins IL-6 and TNF-α. These data suggest that EGCG may be used for its antiaging effect and as a tumoral inhibitor in human skin. Moreover, EGCG can inhibit/regulate NF-κB action, iNOS gene expression, and NO generation in keratinocytes following UVB exposure. It suggests that EGCG may have an inhibitory effect on photodamage caused by UVB in the epidermis. In human in vivo evaluation, the addition of EGCG to a broad-spectrum sunscreen decreased UV-induced damage compared with sunscreen alone	Chen et al. (1999), Chung et al. (2003), Luo et al. (2006), Matsui et al. (2009), Song et al. (2006), Tobi et al. (2002)
Fucoxantin	Fucoxantin antioxidant activity inhibited vessel formation induced by UVB exposure in a hairless mice model. Expression of VEGF abates with reduction in wrinkle formation, diminishing epidermal hypertrophy caused by UV exposure	D'Orazio et al. (2012), Urikura et al. (2011), Yasuda et al. (1999)
General carotenoids[a]	Raman spectroscopy showed that, as a defense mechanism against harmful irradiation and environmental factors, topical application of carotenoids enhances the defense potential of the human epidermis. In addition, carotenoids are recognized as excellent nutricosmetics, improving skin resilience and hydration	Anunciato and da Rocha Filho (2012), Darvin et al. (2009), Lademann et al. (2011)
Grape seed proanthocyanidins	Human keratinocytes irradiated with UVB and treated with GSP's inhibited formation of UVB-induced hydrogen peroxide, lipid peroxidation, protein oxidation, DNA damage, as well as depletion of antioxidant components, such as glutathione peroxidase, catalase, superoxide dismutase, and glutathione. GSP's also inhibit phosphorylation of ERK1/2, JNK, p38 and proteins of MAPK family, as well as UVB-induced activation of NF-κB/p65. These results suggest that GSP may attenuate UV-induced oxidative stress in human skin	Mantena and Katiyar (2006)
Green tea extract[a]	Green tea extract enhances skin photoprotection through anti-inflammatory, antioxidant, and DNA repair mechanisms. In mice stimulated by psoralen and UVA (a quite common psoriasis treatment), orally-administered green tea extract inhibited c-fos and p53 protein accumulation. In reconstituted skin model, green tea extract inhibited psoralen plus UVA-induced 8-methoxypsoralen-DNA adduct formation and p53 protein accumulation. Topic treatment of human skin with green tea extract lowered UV-induced p53 expression as well as the number of apoptotic keratinocytes	Mnich et al. (2009), Nichols and Katiyar (2010), Zhao et al. (1999)
Jacquez grapes wine extract	Jacquez grapes wine extract efficiently prevents the skin from suffering oxidative damage induced by exposure to UVB radiation. This photoprotective effect is attributed to the rich polyphenol content of the extract. Its application, tested on reconstituted skin, helps to maintain the epidermal redox state even after exposure to radiation	Tomaino et al. (2006)
L-carnosine and *Rhodiola rosea* extract association	This association of extracts modulates β-endorphin, enkephalin, CGRP, substance P, IL-1α, TNF-α and IL-10 levels in normal human keratinocytes in basal conditions, as well as under conditions of acute or chronic exposure to UV radiation	Dieamant et al. (2008)
Lycopene[a]	Employed in several formulations for topical use, lycopene shows hight therapeutic potential to recover epidermal antioxidants lost as a result of UV exposure and, in addition, acts to protect the skin from damage caused by UV. Lycopene was also found to work as a preventive agent by inhibiting the activity of epidermal ornithine decarboxylase, reducing inflammation, maintaining cell proliferation at normal levels and, possibly, preventing damage to DNA from apoptosis blockage (in particular by inhibition of caspase-3), after exposure to UVB	Andreassi et al. (2004), Fazekas et al. (2003)
Mangifera indica L. extract	Mice treated orally with mango (*M. indica* L.) extract exhibited a significant capacity to modulate harmful effects of UV radiation by inhibiting epidermal hypertrophy	Song et al. (2013)
Mangiferin	Mangiferin is a sequestrant of ROS, superoxide radicals, and hidroxyl radicals. In HaCaT human keratinocyte cultures, mangiferin inhibited the induction of MMP-1 generated by hydrogen peroxide, blocking AP-1 DNA binding. In addition, mangiferin inhibited keratinocyte cell death by down-regulating MEK-ERK and SEK-JNK pathways	Chae et al. (2011)
Myricetin	Myricetin inhibits UVB-induced human keratinocyte death in a dose-dependent fashion, by inhibiting hydrogen peroxide build-up and c-jun activation induced by UVB	Huang et al. (2010)
N-acetyl cysteine and genistein[a]	Pretreatment of human skin with N-acetyl cysteine in conjunction with genistein blocked UV-induction of collagenase, indicating a photoprotective potential for this ingredient	Kang et al. (2003)
Naringenin	Treatment of HaCaT human keratinocytes with naringenin extended the long-term survival of the cells after irradiation with UVB. UVB-induced PARP-1 cleavage, caspase activation, and Bax/Bcl2 ratio were modulated after the naringenin treatment, indicating an antiapoptotic effect for this active ingredient. Also, when HaCaT cells are irradiated with UVB, naringenin increases CPD removal, which indicates that the active ingredient has a protective effect against DNA damage	El-Mahdy et al. (2008)

Table 5 (*Continued*)

Active ingredients	Action mechanisms	References
Phenylpropanoid glycosides	Phenylpropanoid glycosides (verbascoside, forsythoside B, echinacoside and campneoside I) induced Nrf2 and cytoprotective enzyme activity, and exhibited antioxidant activity in HaCaT human keratinocyte cultures	Sgarbossa et al. (2012)
Polyphenol-rich pomegranate fruit extract	POMx effect on photoaging and UVB-induced oxidative stress was evaluated on HaCaT human keratinocytes. Pretreatment with POMx modulated UVB effects related to reduction in cell viability and intracellular glutathione content, and increase in lipid peroxidation. POMx was also capable of inhibiting increases in MMP-1, -2, -9, and -7, reduction of TIMP-1, and UV-induced phosphorylation of MAPK and c-jun	Zaid et al. (2007)
Polypodium leucotomos exctract	Oral administration of *P. leucotomos* extract in mice during 5 days prior to UV exposure and 2 days following irradiation reduced the number of proliferating cells in the epidermis by 13%, promoted an increase in p53-positive cells, and increased the antioxidant capacity of plasma by 30%. The beneficial effect of *P. leucotomos* extract is probably due to its antioxidant and anti-ROS properties	Rodríguez-Yanes et al. (2012)
Red orange extract	Red orange extract was able to neutralize UVB-induced response efficiently in HaCaT human keratinocytes and, in particular, some of the events associated with inflammation and apoptosis, such as NF-κB and AP-1 translocation and procaspase-3 cleavage. This activity is probably due to a blockage of events related to cell oxidative stress, showing that red orange extract may be useful for the photoprotection of the skin	Cimino et al. (2007)
Resveratrol[a]	Human skin has specific bonding sites for resveratrol, which has a potential to delay, or even arrest, the normal course of skin aging by blocking apoptotic events and mitochondrial disfunctions in keratinocytes. Studies with the HaCaT human keratinocyte lineage have shown trans-resveratrol to be able to inhibit hydrogen peroxide production. In humans, in addition to providing a protective effect against UVA radiation, trans-resveratrol even improves clinical signs of aging when used in association with β-cyclodextrin excipient	Bastianetto et al. (2010), Baur and Sinclair (2006), Chen et al. (2006), Moyano-Mendez et al. (2013)
Rheum rhaponticum L. rhizome extract	Rhubarb extract (*R. rhaponticum* L.) showed antiradical characteristics and antioxidant properties against lipid peroxidation in vitro; the extract also reduced tirosinase activity. In addition, it inhibited the production of IL-1α, TNF-α, and α-MSH, and the activity of tyrosine kinase in human melanocytes subjected to UV radiation	Silveira et al. (2013)
Sea buckthorn fruit blend	UV-irradiated mice were treated orally with a blend of sea buckthorn fruit extract, blueberry extract and collagen. Oral ingestion of SFB reduced formation of wrinkles and helped to maintain skin thickness. SFC-treated mice showed inhibited TEWL and increased skin moisture content. SFB application reduced MMP-1 and -9 expressions, and regulated SOD activity levels	Hwang et al. (2012)
Silk lutein	Protection against harmful effects of UVB was evaluated for lutein extracted from yellow silk cocoons, in comparison with plant-derived lutein, in primary human keratinocytes or lineage CCD 1102 KERTr. Silk lutein was not cytotoxic for keratinocytes, and also protected the cells that received treatment prior to UVB iradiation, reducing the cytotoxicity and the levels of cell apoptosis	Pongcharoen et al. (2013)
Soybean extract	Soybean extract, rich in isoflavones, inhibited UVB-induced cell death in HaCaT human keratinocytes, as well as p38, JNK and ERK1/2 phosphorylation. In mice, topic application prior to UV irradiation was shown to diminish epidermal thickness and COX-2 and PCNA expression, and also to increase catalase concentration	Chiu et al. (2009)
Tannase-converted green tea extract	Tannase, an enzyme produced by fungi, yeasts and bacteria, hydrolyzes catechin gallates (EGCG and ECG) from green tea and enhance its potential application for elimination of radicals, such as hydrogen superoxide and peroxide. A formulation containing tannase-converted green tea extract was used to inhibit UV-induced oxidative damage in mice epidermis. Formulation acted by preventing glutathione reduction and controlling hydrogen peroxide levels. Mice treated with FTGE displayed a significant reduction in the levels of thiobarbituric acid reactive substances by lipid peroxidation, in comparison with non-UVB-irradiated controls, which indicates that this formulation is effective in protecting the skin against photoaging	Hong et al. (2012)
Tectroside	Tectroside or lactone inhibits UVB-induced production of proinflammatory cytokines (IL-6 and IL-8) in HaCaT human keratinocyte cultures, in a dose-dependent manner. It also inhibits COX-2 expression and JNK phosphorylation. These results suggest that this compound has the potential to protect the skin against UVB-induced inflammation	Kim et al. (2013)
Vitamin C[a]	Vitamin C or ascorbic acid reduces effects of aging, such as deep and superficial wrinkles, and increases skin elasticity, firmness, roughness, and hydration. Evaluation of ascorbic acid and its derivatives, AA 2-phosphate e AAS 2-glucoside, on UVB-induced cytotoxicity in HaCaT human keratinocytes showed that, unlike its derivatives, ascorbic acid was unable to inhibit cytotoxicity	Haftek et al. (2008), Raschke et al. (2004), Yasuda et al. (2004)
Vitamin E[a]	One of the forms of vitamin E, α-tocopherol, is widely known for its antioxidant potential. The inhibitory role of α-tocopherol in the regulation of IL-8 and AP-1 production in human keratinocyte exposed to UVA was assessed and shown to inhibit significantly the activity of NADPH oxidase, which would be responsible for the activation of IL-8 and AP-1; α-tocopherol also inhibited malondialdehyde-thiobarbituric acid formation in cells exposed to UVA radiation	Wu et al. (2008)
Vitis vinifera shoot extract	*V. vinifera* shoot extract shows a higher in vitro antioxidant capability than vitamin C or E. An aquous *V. vinifera* L. tendril extract, applied in human keratinocytes (NCTC 2544) was able to increase the concentration of reduced glutathione and the activity of trans plasma membrane oxido reductase, in a time- and dose-dependent fashion, which demonstrates that the extract has a relevant antioxidant activity	Cornacchione et al. (2007), Fraternale et al. (2011)
Zeaxanthin and lutein[a]	Increased intake of lutein improved the health of the skin when supplemented orally or applied topically (zeaxanthin and lutein), as assessed on the basis of the following five physiological parameters: skin surface lipids, skin hydration, photoprotective activity, skin elasticity, and lipid peroxidation. Oral or topical administration improved such measurements significantly: oral administration resulted in better protection against changes in lipid peroxidation and in photoprotective activity following UV irradiation. Nevertheless, combined oral and topic administration provide a higher degree of protection. Other studies have also demonstrated the protective effect of this combination against epidermal hyperproliferation and inflammation after UVB exposure in mice	Evans and Johnson (2010), González et al. (2003), Palombo et al. (2007)

[a] Active ingredients with placebo/vehicle controlled studies in vivo in man. AKT, protein kinase B; AP-1, activator protein 1; Bad, Bcl-2-associated death promoter; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; c-fos, cellular oncogene fos; c-jun, cellular oncogene jun; CaMKs, calmodulin-dependent protein kinases; CGRP, calcitonin gene-related peptide; COX-2, ciclooxigenase-2; ECG, epicatechin-3-gallate; EGCG, epigallocatechin-3-gallate; ERK, extracellular-signal-regulated kinases; FTGE, tannase-converted green tea extract; GSP, grape seed proanthocyanidins; IL, interleukin; iNOS, inducible nitric oxide synthase; JNK, c-Jun NH2-terminal kinase; MAPK, mitogen-activated protein kinases; MEK, mitogen-activated protein kinase kinase; MMP, matrix metalloproteinases; NF-κB, nuclear factor kappa B; Nrf2, NF-E2-related factor 2; p21, cyclin-dependent kinase inhibitor 1; p53, protein 53; p65, transcription factor p65; PARP-1, Poly [ADP-ribose] polymerase 1; PCNA, proliferating cell nuclear antigen; POMx, polyphenol-rich pomegranate fruit extract; ROS, reactive oxygen species; SEK, stress-activated protein kinase/extracellular signal-regulated kinase; Ser, serine; SFB, sea buckthorn fruit blend; SOD, superoxide dismutase; TEWL, transepidermal water loss; TIMP, tissue inhibitors of metalloproteinases; TNF-α, tumor necrosis factor α; UV, ultraviolet.

person (Rizzo and Maibach, 2012; Squassina et al., 2010). If this movement is to become feasible for skin treatment, it would be highly useful to have an extensive portfolio of active ingredients capable of acting on cells, pathways or specific molecules, in addition to refined skin diagnoses. Lists of potential candidates for epidermal aging treatment were organized according to this innovative concept. Mechanisms of action were discussed for key ingredients, evidencing the importance of in depth scientific assessment for specific compounds before their use, considering not just individual needs, but also specific biological and physicochemical properties, compatibility with intended formulation, as well as the availability of robust pre-clinical and clinical trials.

Another scientific trend is related to a holistic approach for the treatment of skin aging. If the skin is to be viewed as a complex biological system, emergence and advance of research involving different skin layers or cell types are essential for the development of more complete and comprehensive therapies. In this sense, it is important to note that our review was focused on active ingredients available for topic applications, but new opportunities have been described for dietary supplements. Distinct possible applications of ingredients in the treatment of phenotypes like aging gave origin to new terminologies that has been more and more diffused in the market, including cosmeceuticals (topically applied products capable of making changes in the skin status that are not considered drugs, nor cosmetics, that decorate the skin), nutraceuticals (any substance that is a food or part of a food that provides medical or health benefits, including the prevention and treatment of disease), and nutricosmetics (a new concept formed by the intersection of cosmeceuticals and nutraceuticals and referring to oral supplementation of nutrients formulated and marketed specifically for beauty purposes) (Anunciato and da Rocha Filho, 2012). This nomenclature is not aligned across legal regulations in different countries but, independently of the adopted term, it points to a trend that involves the development of interdisciplinary activities focused on health and well-being promotion (Anunciato and da Rocha Filho, 2012; Vranesić-Bender, 2010). A good example of that is the use of probiotics for improvements in the photoprotection capacity of the skin (Guéniche et al., 2009). Supplementation with the oral probiotic bacteria *Lactobacillus johnsonii* (La1) maintains cutaneous immune homeostasis after UV exposure, evidenced through substantial experimental protocols, including randomized, double-blind and placebo controlled clinical trials (Guéniche et al., 2006, 2008; Peguet-Navarro et al., 2008; Yang et al., 2011). If combined with nutriotinal doses of carotenoids, La1 intake reduced early UV-induced skin damage, suggesting a beneficial influence on skin photoaging (Bouilly-Gauthier et al., 2010). Cutaneous carotenoids can be enriched in the skin by nutrition and topically applied antioxidants, indicated for the prevention of cell damage, premature skin aging, and skin cancer (Meinke et al., 2013). Indeed, anti-aging substances derived from food includes different categories of ingredients, but special attention has been dedicated to those with antioxidant properties, such as coenzyme Q10, phytoestrogens, probiotics and omega-3 fatty acids (Vranesić-Bender, 2010).

This work addresses the issues specifically associated with epidermal aging and was conducted with the intention of providing a comprehensive list of therapeutic approaches to complement those that are currently in use and chiefly concerned with the dermis. This scientific scenario is undergoing rapid expansion with opportunities for future developments. Growing advances in research in the fields of molecular biology and skin stem cells are examples of the next steps to be taken by cosmetology and dermatology (Fu and Sun, 2009). For many of actives considered here, well controlled and executed efficacy and safety studies in man are few or none. The integrity of interpretation of these therapeutic and/or preventive actions will – in the end – rest on such information.

Conflict of interest

No conflict of interest was involved in the present work.

Acknowledgements

We are grateful to Frank Hollander for the English revision, and we sincerely apologize to all those colleagues whose important work is not cited because of space considerations. This work was conducted with the support of Grupo Boticário.

References

Andreassi, M., Stanghellini, E., Ettorre, A., Di Stefano, A., Andreassi, L., 2004. Antioxidant activity of topically applied lycopene. J. Eur. Acad. Dermatol. Venereol. 18, 52–55.

Anunciato, T.P., da Rocha Filho, P.A., 2012. Carotenoids and polyphenols in nutricosmetics, nutraceuticals, and cosmeceuticals. J. Cosmet. Dermatol. 11, 51–54.

Aoi, N., Inoue, K., Chikanishi, T., Fujiki, R., Yamamoto, H., Kato, H., Eto, H., Doi, K., Itami, S., Kato, S., Yoshimura, K., 2012. 1α,25-dihydroxyvitamin D3 modulates the hair-inductive capacity of dermal papilla cells: therapeutic potential for hair regeneration. Stem Cells Transl. Med. 1, 615–626.

Aoki, H., Moro, O., Tagami, H., Kishimoto, J., 2007. Gene expression profiling analysis of solar lentigo in relation to immunohistochemical characteristics. Br. J. Dermatol. 156, 1214–1223.

Babamiri, K., Nassab, R., 2010. Cosmeceuticals: the evidence behind the retinoids. Aesthet. Surg. J. 30, 74–77.

Babilas, P., Knie, U., Abels, C., 2012. Cosmetic and dermatologic use of alpha hydroxy acids. J. Dtsch. Dermatol. Ges. 10, 488–491.

Baroni, A., Buommino, E., De Gregorio, V., Ruocco, E., Ruocco, V., Wolf, R., 2012. Structure and function of the epidermis related to barrier properties. Clin. Dermatol. 30, 257–262.

Bastianetto, S., Dumont, Y., Duranton, A., Vercauteren, F., Breton, L., Quirion, R., 2010. Protective action of resveratrol in human skin: possible involvement of specific receptor binding sites. PLoS ONE 5, e12935.

Baur, J.A., Sinclair, D.A., 2006. Therapeutic potential of resveratrol: the in vivo evidence. Nat. Rev. Drug Discov. 5, 493–506.

Bellemère, G., Stamatas, G.N., Bruère, V., Bertin, C., Issachar, N., Oddos, T., 2009. Antiaging action of retinol: from molecular to clinical. Skin Pharmacol. Physiol. 22, 200–209.

Bergman, E., Ulfhake, B., Fundin, B.T., 2000. Regulation of NGF-family ligands and receptors in adulthood and senescence: correlation to degenerative and regenerative changes in cutaneous innervation. Eur. J. Neurosci. 12, 2694–2706.

Beyer, T.A., Auf dem Keller, U., Braun, S., Schäfer, M., Werner, S., 2007. Roles and mechanisms of action of the Nrf2 transcription factor in skin morphogenesis, wound repair and skin cancer. Cell Death Differ. 14, 1250–1254.

Bhattacharyya, T.K., Higgins, N.P., Sebastian, J.S., Thomas, J.R., 2009. Comparison of epidermal morphologic response to commercial antiwrinkle agents in the hairless mouse. Dermatol. Surg. 35, 1109–1118.

Björklund, S., Engblom, J., Thuresson, K., Sparr, E., 2013. Glycerol and urea can be used to increase skin permeability in reduced hydration conditions. Eur. J. Pharm. Sci. 50, 638–645.

Bonté, F., Barré, P., Pinguet, P., Dusser, I., Dumas, M., Meybeck, A., 1996. Simarouba amara extract increases human skin keratinocyte differentiation. J. Ethnopharmacol. 53, 65–74.

Bouilly-Gauthier, D., Jeannes, C., Maubert, Y., Duteil, L., Queille-Roussel, C., Piccardi, N., Montastier, C., Manissier, P., Piérard, G., Ortonne, J.P., 2010. Clinical evidence of benefits of a dietary supplement containing probiotic and carotenoids on ultravioletinduced skin damage. Br. J. Dermatol. 163, 536–543.

Boulais, N., Misery, L., 2008. The epidermis: a sensory tissue. Eur. J. Dermatol. 18, 119–127.

Bourguignon, L.Y., Wong, G., Xia, W., Man, M.Q., Holleran, W.M., Elias, P.M., 2013. Selective matrix (hyaluronan) interaction with CD44 and RhoGTPase signaling promotes keratinocyte functions and overcomes age-related epidermal dysfunction. J. Dermatol. Sci. 72, 32–44.

Boury-Jamot, M., Sougrat, R., Tailhardat, M., Le Varlet, B., Bonté, F., Dumas, M., Verbavatz, J.M., 2006. Expression and function of aquaporins in human skin: Is aquaporin-3 just a glycerol transporter? Biochim. Biophys. Acta 1758, 1034–1042.

Bouwstra, J.A., Groenink, H.W., Kempenaar, J.A., Romeijn, S.G., Ponec, M., 2008. Water distribution and natural moisturizer factor content in human skin equivalents are regulated by environmental relative humidity. J. Invest. Dermatol. 128, 378–388.

Bouwstra, J.A., Nahmoed, N., Groenink, H.W., Ponec, M., 2012. Human skin equivalents are an excellent tool to study the effect of moisturizers on the water distribution in the stratum corneum. Int. J. Cosmet. Sci. 34, 560–566.

Bragulla, H.H., Homberger, D.G., 2009. Structure and functions of keratin proteins in simple, stratified, keratinized and cornified epithelia. J. Anat. 214, 516–559.

Brazzini, B., Ghersetich, I., Hercogova, J., Lotti, T., 2003. The neuro-immuno-cutaneous-endocrine network: relationship between mind and skin. Dermatol. Ther. 16, 123–131.

Brohem, C.A., Cardeal, L.B., Tiago, M., Soengas, M.S., Barros, S.B., Maria-Engler, S.S., 2011. Artificial skin in perspective: concepts and applications. Pigment Cell Melanoma Res. 24, 35–50.

Budai, L., Antal, I., Klebovich, I., Budai, M., 2012. Natural oils and waxes: studies on stick bases. J. Cosmet. Sci. 63, 93–101.

Buono, S., Langellotti, A.L., Martello, A., Bimonte, M., Tito, A., Carola, A., Apone, F., Colucci, G., Fogliano, V., 2012. Biological activities of dermatological interest by the water extract of the microalga Botryococcus braunii. Arch. Dermatol. Res. 304, 755–764.

Burke, K.E., 2010. Photoaging: the role of oxidative stress. G. Ital. Dermatol. Venereol. 145, 445–459.

Calleja-Agius, J., Muscat-Baron, Y., Brincat, M.P., 2007. Skin ageing. Menopause Int. 13, 60–64.

Cangkrama, M., Ting, S.B., Darido, C., 2013. Stem cells behind the barrier. Int. J. Mol. Sci. 14, 13670–13686.

Cao, C., Lu, S., Kivlin, R., Wallin, B., Card, E., Bagdasarian, A., Tamakloe, T., Wang, W.J., Song, X., Chu, W.M., Kouttab, N., Xu, A., Wan, Y., 2009. SIRT1 confers protection against UVB- and H_2O_2-induced cell death via modulation of p53 and JNK in cultured skin keratinocytes. J. Cell. Mol. Med. 13, 3632–3643.

Cardile, V., Frasca, G., Rizza, L., Rapisarda, P., Bonina, F., 2010. Antiinflammatory effects of a red orange extract in human keratinocytes treated with interferon-gamma and histamine. Phytother. Res. 24, 414–418.

Césarini, J.P., Michel, L., Maurette, J.M., Adhoute, H., Béjot, M., 2003. Immediate effects of UV radiation on the skin: modification by an antioxidant complex containing carotenoids. Photodermatol. Photoimmunol. Photomed. 19, 182–189.

Chae, S., Piao, M.J., Kang, K.A., Zhang, R., Kim, K.C., Youn, U.J., Nam, K.W., Lee, J.H., Hyun, J.W., 2011. Inhibition of matrix metalloproteinase-1 induced by oxidative stress in human keratinocytes by mangiferin isolated from Anemarrhena asphodeloides. Biosci. Biotechnol. Biochem. 75, 2321–2325.

Chan, C.M., Huang, J.H., Lin, H.H., Chiang, H.S., Chen, B.H., Hong, J.Y., Hung, C.F., 2008. Protective effects of (−)-epigallocatechin gallate on UVA-induced damage in ARPE19 cells. Mol. Vis. 14, 2528–2534.

Chen, M.L., Li, J., Xiao, W.R., Sun, L., Tang, H., Wang, L., Wu, L.Y., Chen, X., Xie, H.F., 2006. Protective effect of resveratrol against oxidative damage of UVA irradiated HaCaT cells. Zhong Nan Da Xue Xue Bao Yi Xue Ban 31, 635–639.

Chen, W., Dong, Z., Valcic, S., Timmermann, B.N., Bowden, G.T., 1999. Inhibition of ultraviolet B-induced c-fos gene expression and p38 mitogen-activated protein kinase activation by (−)-epigallocatechin gallate in a human keratinocyte cell line. Mol. Carcinog. 24, 79–84.

Chiu, T.M., Huang, C.C., Lin, T.J., Fang, J.Y., Wu, N.L., Hung, C.F., 2009. In vitro and in vivo anti-photoaging effects of an isoflavone extract from soybean cake. J. Ethnopharmacol. 126, 108–113.

Choi, E.H., Man, M.Q., Xu, P., Xin, S., Liu, Z., Crumrine, D.A., Jiang, Y.J., Fluhr, J.W., Feingold, K.R., Elias, P.M., Mauro, T.M., 2007. Stratum corneum acidification is impaired in moderately aged human and murine skin. J. Invest. Dermatol. 127, 2847–2856.

Chu, M., Kollias, N., 2011. Documentation of normal stratum corneum scaling in an average population: features of differences among age, ethnicity and body site. Br. J. Dermatol. 164, 497–507.

Chung, J.H., Han, J.H., Hwang, E.J., Seo, J.Y., Cho, K.H., Kim, K.H., Youn, J.I., Eun, H.C., 2003. Dual mechanisms of green tea extract (EGCG)-induced cell survival in human epidermal keratinocytes. FASEB J. 17, 1913–1915.

Cimino, F., Cristani, M., Saija, A., Bonina, F.P., Virgili, F., 2007. Protective effects of a red orange extract on UVB-induced damage in human keratinocytes. Biofactors 30, 129–138.

Cordisco, S., Maurelli, R., Bondanza, S., Stefanini, M., Zambruno, G., Guerra, L., Dellambra, E., 2010. Bmi-1 reduction plays a key role in physiological and premature aging of primary human keratinocytes. J. Invest. Dermatol. 130, 1048–1062.

Cornacchione, S., Sadick, N.S., Neveu, M., Talbourdet, S., Lazou, K., Viron, C., Renimel, I., de Quéral, D., Kurfurst, R., Schnebert, S., Heusèle, C., André, P., Perrier, E., 2007. In vivo skin antioxidant effect of a new combination based on a specific Vitis vinifera shoot extract and a biotechnological extract. J. Drugs Dermatol. 6, s8–s13.

Corsini, E., Galli, C.L., 2000. Epidermal cytokines in experimental contact dermatitis. Toxicology 142, 203–211.

Crisan, D., Lupsor, M., Boca, A., Crisan, M., Badea, R., 2012. Ultrasonographic assessment of skin structure according to age. Indian J. Dermatol. Venereol. Leprol. 78, 519.

Cumberbatch, M., Dearman, R.J., Griffiths, C.E., Kimber, I., 2003. Epidermal Langerhans cell migration and sensitisation to chemical allergens. APMIS 111, 797–804.

Daniela, L., Alla, P., Maurelli, R., Elena, D., Giovanna, P., Vladimir, K., Roberto, D.T., Chiara de, L., Saveria, P., Liudmila, K., 2012. Anti-inflammatory effects of concentrated ethanol extracts of Edelweiss (*Leontopodium alpinum* Cass.) callus cultures towards human keratinocytes and endothelial cells. Mediators Inflamm. 2012, 498373.

Darvin, M.E., Fluhr, J.W., Caspers, P., van der Pool, A., Richter, H., Patzelt, A., Sterry, W., Lademann, J., 2009. In vivo distribution of carotenoids in different anatomical locations of human skin: comparative assessment with two different Raman spectroscopy methods. Exp. Dermatol. 18, 1060–1063.

de Waroux Yle, P., 2013. The social and environmental context of argan oil production. Nat. Prod. Commun. 8, 1–4.

Denda, M., Tomitaka, A., Akamatsu, H., Matsunaga, K., 2003. Altered distribution of calcium in facial epidermis of aged adults. J. Invest. Dermatol. 121, 1557–1558.

Dieamant, G.C., Velazquez Pereda, M.C., Eberlin, S., Nogueira, C., Werka, R.M., Queiroz, M.L., 2008. Neuroimmunomodulatory compound for sensitive skin care: in vitro and clinical assessment. J. Cosmet. Dermatol. 7, 112–119.

Ditre, C.M., Griffin, T.D., Murphy, G.F., Sueki, H., Telegan, B., Johnson, W.C., Yu, R.J., Van Scott, E.J., 1996. Effects of alpha-hydroxy acids on photoaged skin: a pilot clinical, histologic, and ultrastructural study. J. Am. Acad. Dermatol. 34, 187–195.

D'Orazio, N., Gemello, E., Gammone, M.A., de Girolamo, M., Ficoneri, C., Riccioni, G., 2012. Fucoxantin: a treasure from the sea. Mar. Drugs 10, 604–616.

Draelos, Z.D., 2013. Modern moisturizer myths, misconceptions, and truths. Cutis 91, 308–314.

Dreher, F., Maibach, H., 2001. Protective effects of topical antioxidants in humans. Curr. Probl. Dermatol. 29, 157–164.

Dröge, W., 2002. Free radicals in the physiological control of cell function. Physiol. Rev. 82, 47–95.

Dumas, M., Gondran, C., Barré, P., Sougrat, R., Verbavatz, J.M., Heusèle, C., Schnébert, S., Bonté, F., 2002. Effect of an Ajuga turkestanica extract on aquaporin 3 expression, water flux, differentiation and barrier parameters of the human epidermis. Eur. J. Dermatol. 12, XXV–XXVI.

Dumas, M., Sadick, N.S., Noblesse, E., Juan, M., Lachmann-Weber, N., Boury-Jamot, M., Sougrat, R., Verbavatz, J.M., Schnebert, S., Bonté, F., 2007. Hydrating skin by stimulating biosynthesis of aquaporins. J. Drugs Dermatol. 6, s20–s24.

Eberlin, S., Del Carmen Velazquez Pereda, M., de Campos Dieamant, G., Nogueira, C., Werka, R.M., de Souza Queiroz, M.L., 2009. Effects of a Brazilian herbal compound as a cosmetic eyecare for periorbital hyperchromia ("dark circles"). J. Cosmet. Dermatol. 8, 127–135.

Eckhart, L., Lippens, S., Tschachler, E., Declercq, W., 2013. Cell death by cornification. Biochim. Biophys. Acta 1833, 3471–3480.

El-Domyati, M., Attia, S., Saleh, F., Brown, D., Birk, D.E., Gasparro, F., Ahmad, H., Uitto, J., 2002. Intrinsic aging vs. photoaging: a comparative histopathological, immunohistochemical, and ultrastructural study of skin. Exp. Dermatol. 11, 398–405.

El-Mahdy, M.A., Zhu, Q., Wang, Q.E., Wani, G., Patnaik, S., Zhao, Q., Arafa, el-S., Barakat, B., Mir, S.N., Wani, A.A., 2008. Naringenin protects HaCaT human keratinocytes against UVB-induced apoptosis and enhances the removal of cyclobutane pyrimidine dimers from the genome. Photochem. Photobiol. 84, 307–316.

Elias, P.M., Ghadially, R., 2002. The aged epidermal permeability barrier: basis for functional abnormalities. Clin. Geriatr. Med. 18, 103–120.

Evans, J.A., Johnson, E.J., 2010. The role of phytonutrients in skin health. Nutrients 2, 903–928.

Farage, M.A., Miller, K.W., Berardesca, E., Maibach, H.I., 2008a. Neoplastic skin lesions in the elderly patient. Cutan. Ocul. Toxicol. 27, 213–229.

Farage, M.A., Miller, K.W., Elsner, P., Maibach, H.I., 2008b. Intrinsic and extrinsic factors in skin ageing: a review. Int. J. Cosmet. Sci. 30, 87–95.

Farage, M.A., Miller, K.W., Maibach, H.I., 2010. Textbook of Aging Skin, first ed. Springer, Heidelberg.

Farwick, M., Gauglitz, G., Pavicic, T., Köhler, T., Wegmann, M., Schwach-Abdellaoui, K., Malle, B., Tarabin, V., Schmitz, G., Korting, H.C., 2011. Fifty-kDa hyaluronic acid upregulates some epidermal genes without changing TNF-α expression in reconstituted epidermis. Skin Pharmacol. Physiol. 24, 210–217.

Fazekas, Z., Gao, D., Saladi, R.N., Lu, Y., Lebwohl, M., Wei, H., 2003. Protective effects of lycopene against ultraviolet B-induced photodamage. Nutr. Cancer 47, 181–187.

Fluhr, J.W., Darlenski, R., Surber, C., 2008. Glycerol and the skin: holistic approach to its origin and functions. Br. J. Dermatol. 159, 23–34.

Fodil-Bourahla, I., Bizbiz, L., Schoevaert, D., Robert, A.M., Robert, L., 2003. Effect of L-fucose and fucose-rich oligo- and polysaccharides (FROP-s) on skin aging: penetration, skin tissue production and fibrillogenesis. Biomed. Pharmacother. 57, 209–215.

Förster, M., Bolzinger, M.A., Fessi, H., Briançon, S., 2009. Topical delivery of cosmetics and drugs. Molecular aspects of percutaneous absorption and delivery. Eur. J. Dermatol. 19, 309–323.

Fraternale, D., De Bellis, R., Calcabrini, C., Potenza, L., Cucchiarini, L., Mancini, U., Dachà, M., Ricci, D., 2011. Aqueous extract from *Vitis vinifera* tendrils is able to enrich keratinocyte antioxidant defences. Nat. Prod. Commun. 6, 1315–1319.

Fu, X., Sun, X., 2009. Can hematopoietic stem cells be an alternative source for skin regeneration? Ageing Res. Rev. 8, 244–249.

Fuchs, E., Raghavan, S., 2002. Getting under the skin of epidermal morphogenesis. Nat. Rev. Genet. 3, 199–209.

Fujishita, K., Koizumi, S., Inoue, K., 2006. Upregulation of P2Y2 receptors by retinoids in normal human epidermal keratinocytes. Purinergic Signal. 2, 491–498.

Gehring, W., 2004. Nicotinic acid/niacinamide and the skin. J. Cosmet. Dermatol. 3, 88–93.

Geusau, A., Tschachler, E., Meixner, M., Päpke, O., Stingl, G., McLachlan, M., 2001. Cutaneous elimination of 2,3,7,8-tetrachlorodibenzo-p-dioxin. Br. J. Dermatol. 145, 938–943.

Ghadially, R., Brown, B.E., Hanley, K., Reed, J.T., Feingold, K.R., Elias, P.M., 1996. Decreased epidermal lipid synthesis accounts for altered barrier function in aged mice. J. Invest. Dermatol. 106, 1064–1069.

Ghadially, R., Brown, B.E., Sequeira-Martin, S.M., Feingold, K.R., Elias, P.M., 1995. The aged epidermal permeability barrier. Structural, functional, and lipid biochemical abnormalities in humans and a senescent murine model. J. Clin. Invest. 95, 2281–2290.

Gold, M.H., Kircik, L.H., Bucay, V.W., Kiripolsky, M.G., Biron, J.A., 2013. Treatment of facial photodamage using a novel retinol formulation. J. Drugs Dermatol. 12, 533–540.

González, S., Astner, S., An, W., Goukassian, D., Pathak, M.A., 2003. Dietary lutein/zeaxanthin decreases ultraviolet B-induced epidermal hyperproliferation and acute inflammation in hairless mice. J. Invest. Dermatol. 121, 399–405.
Grether-Beck, S., Felsner, I., Brenden, H., Kohne, Z., Majora, M., Marini, A., Jaenicke, T., Rodriguez-Martin, M., Trullas, C., Hupe, M., Elias, P.M., Krutmann, J., 2012. Urea uptake enhances barrier function and antimicrobial defense in humans by regulating epidermal gene expression. J. Invest. Dermatol. 132, 1561–1572.
Grogan, S., Flett, K., Clark-Carter, D., Gough, B., Davey, R., Richardson, D., Rajaratnam, G., 2011. Women smokers' experiences of an age-appearance anti-smoking intervention: a qualitative study. Br. J. Health Psychol. 16, 675–689.
Guéniche, A., Benyacoub, J., Buetler, T.M., Smola, H., Blum, S., 2006. Supplementation with oral probiotic bacteria maintains cutaneous immune homeostasis after UV exposure. Eur. J. Dermatol. 16, 511–517.
Guéniche, A., Buetler, T., Benyacoub, J., Blum, S., 2008. Lactobacillus johnsonii provides a dose-dependent protection against UVR-induced immunosuppression. Eur. J. Dermatol. 18, 476–477.
Guéniche, A., Philippe, D., Bastien, P., Blum, S., Buyukpamukcu, E., Castiel-Higounenc, I., 2009. Probiotics for photoprotection. Dermatoendocrinology 1, 275–279.
Gutowska-Owsiak, D., Ogg, G.S., 2012. The epidermis as an adjuvant. J. Invest. Dermatol. 132, 940–948.
Hachem, J.P., Man, M.Q., Crumrine, D., Uchida, Y., Brown, B.E., Rogiers, V., Roseeuw, D., Feingold, K.R., Elias, P.M., 2005. Sustained serine proteases activity by prolonged increase in pH leads to degradation of lipid processing enzymes and profound alterations of barrier function and stratum corneum integrity. J. Invest. Dermatol. 125, 510–520.
Haftek, M., Mac-Mary, S., Le Bitoux, M.A., Creidi, P., Seité, S., Rougier, A., Humbert, P., 2008. Clinical, biometric and structural evaluation of the long-term effects of a topical treatment with ascorbic acid and madecassoside in photoaged human skin. Exp. Dermatol. 17, 946–952.
Hanley, K., Ng, D.C., He, S.S., Lau, P., Min, K., Elias, P.M., Bikle, D.D., Mangelsdorf, D.J., Williams, M.L., Feingold, K.R., 2000. Oxysterols induce differentiation in human keratinocytes and increase Ap-1-dependent involucrin transcription. J. Invest. Dermatol. 114, 545–553.
Hansen, S., Naegel, A., Heisig, M., Wittum, G., Neumann, D., Kostka, K.H., Meiers, P., Lehr, C.M., Schaefer, U.F., 2009. The role of corneocytes in skin transport revised–a combined computational and experimental approach. Pharm. Res. 26, 1379–1397.
Hara, M., Verkman, A.S., 2003. Glycerol replacement corrects defective skin hydration, elasticity, and barrier function in aquaporin-3-deficient mice. Proc. Natl. Acad. Sci. U.S.A. 100, 7360–7365.
Harder, J., Schröder, J.M., Gläser, R., 2013. The skin surface as antimicrobial barrier: present concepts and future outlooks. Exp. Dermatol. 22, 1–5.
Heinrich, U., Neukam, K., Tronnier, H., Sies, H., Stahl, W., 2006. Long-term ingestion of high flavanol cocoa provides photoprotection against UV-induced erythema and improves skin condition in women. J. Nutr. 136, 1565–1569.
Hockberger, P.E., 2002. A history of ultraviolet photobiology for humans, animals and microorganisms. Photochem. Photobiol. 76, 561–579.
Hoffmann, K., Kaspar, K., Altmeyer, P., Gambichler, T., 2000. UV transmission measurements of small skin specimens with special quartz cuvettes. Dermatology 201, 307–311.
Hong, C.E., Lyu, S.Y., 2011. Anti-inflammatory and anti-oxidative effects of Korean red ginseng extract in human keratinocytes. Immune Netw. 11, 42–49.
Hong, Y.H., Jung, E.Y., Shin, K.S., Kim, T.Y., Yu, K.W., Chang, U.J., Suh, H.J., 2012. Photoprotective effects of a formulation containing tannase-converted green tea extract against UVB-induced oxidative stress in hairless mice. Appl. Biochem. Biotechnol. 166, 165–175.
Hou, M., Man, M., Man, W., Zhu, W., Hupe, M., Park, K., Crumrine, D., Elias, P.M., Man, M.Q., 2012. Topical hesperidin improves epidermal permeability barrier function and epidermal differentiation in normal murine skin. Exp. Dermatol. 21, 337–340.
Hsu, S., Bollag, W.B., Lewis, J., Huang, Q., Singh, B., Sharawy, M., Yamamoto, T., Schuster, G., 2003. Green tea polyphenols induce differentiation and proliferation in epidermal keratinocytes. J. Pharmacol. Exp. Ther. 306, 29–34.
Hsu, S., Yamamoto, T., Borke, J., Walsh, D.S., Singh, B., Rao, S., Takaaki, K., Nah-Do, N., Lapp, C., Lapp, D., Foster, E., Bollag, W.B., Lewis, J., Wataha, J., Osaki, T., Schuster, G., 2005. Green tea polyphenol-induced epidermal keratinocyte differentiation is associated with coordinated expression of p57/KIP2 and caspase 14. J. Pharmacol. Exp. Ther. 312, 884–890.
Huang, C.C., Fang, J.Y., Wu, W.B., Chiang, H.S., Wei, Y.J., Hung, C.F., 2005. Protective effects of (−)-epicatechin-3-gallate on UVA-induced damage in HaCaT keratinocytes. Arch. Dermatol. Res. 296, 473–481.
Huang, C.C., Wu, W.B., Fang, J.Y., Chiang, H.S., Chen, S.K., Chen, B.H., Chen, Y.T., Hung, C.F., 2007. (−)-Epicatechin-3-gallate, a green tea polyphenol is a potent agent against UVB-induced damage in HaCaT keratinocytes. Molecules 12, 1845–1858.
Huang, J.H., Huang, C.C., Fang, J.Y., Yang, C., Chan, C.M., Wu, N.L., Kang, S.W., Hung, C.F., 2010. Protective effects of myricetin against ultraviolet-B-induced damage in human keratinocytes. Toxicol. In Vitro 24, 21–28.
Huang, Z.R., Lin, Y.K., Fang, J.Y., 2009. Biological and pharmacological activities of squalene and related compounds: potential uses in cosmetic dermatology. Molecules 14, 540–554.
Hwang, I.S., Kim, J.E., Choi, S.I., Lee, H.R., Lee, Y.J., Jang, M.J., Son, H.J., Lee, H.S., Oh, C.H., Kim, B.H., Lee, S.H., Hwang, D.Y., 2012. UV radiation-induced skin aging in hairless mice is effectively prevented by oral intake of sea buckthorn (*Hippophae rhamnoides* L.) fruit blend for 6 weeks through MMP suppression and increase of SOD activity. Int. J. Mol. Med. 30, 392–400.
Hwang, Y.P., Oh, K.N., Yun, H.J., Jeong, H.G., 2011. The flavonoids apigenin and luteolin suppress ultraviolet A-induced matrix metalloproteinase-1 expression via MAPKs and AP-1-dependent signaling in HaCaT cells. J. Dermatol. Sci. 61, 23–31.
Ikarashi, N., Ogiue, N., Toyoda, E., Kon, R., Ishii, M., Toda, T., Aburada, T., Ochiai, W., Sugiyama, K., 2012. Gypsum fibrosum and its major component $CaSO_4$ increase cutaneous aquaporin-3 expression levels. J. Ethnopharmacol. 139, 409–413.
Ishida-Yamamoto, A., Igawa, S., Kishibe, M., 2011. Order and disorder in corneocyte adhesion. J. Dermatol. 38, 645–654.
Ishikawa, J., Shimotoyodome, Y., Chen, S., Ohkubo, K., Takagi, Y., Fujimura, T., Kitahara, T., Takema, Y., 2012. Eucalyptus increases ceramide levels in keratinocytes and improves stratum corneum function. Int. J. Cosmet. Sci. 4, 17–22.
Jacobson, E.L., Kim, H., Kim, M., Williams, J.D., Coyle, D.L., Coyle, W.R., Grove, G., Rizer, R.L., Stratton, M.S., Jacobson, M.K., 2007. A topical lipophilic niacin derivative increases NAD, epidermal differentiation and barrier function in photodamaged skin. Exp. Dermatol. 16, 490–499.
Jacobson, T.M., Yüksel, K.U., Geesin, J.C., Gordon, J.S., Lane, A.T., Gracy, R.W., 1990. Effects of aging and xerosis on the amino acid composition of human skin. J. Invest. Dermatol. 95, 296–300.
Jagdeo, J., Adams, L., Lev-Tov, H., Sieminska, J., Michl, J., Brody, N., 2010. Dose-dependent antioxidant function of resveratrol demonstrated via modulation of reactive oxygen species in normal human skin fibroblasts in vitro. J. Drugs Dermatol. 9, 1523–1526.
Jain, S., 2004. Topical tretinoin or adapalene in acne vulgaris: an overview. J. Dermatol. Treat. 15, 200–207.
Jarrold, B., Mullins, L., Binder, R., Osborne, R., 2009. Expression profiles of stratum corneum lipid metabolism pathways associated with intrinsic and extrinsic aging. J. Am. Acad. Dermatol. 60, AB28.
Jiang, Z.X., DeLaCruz, J., 2011. Appearance benefits of skin moisturization. Skin Res. Technol. 17, 51–55.
Jung, Y.J., Jung, M., Kim, M., Hong, S.P., Choi, E.H., 2011. IL-1α stimulation restores epidermal permeability and antimicrobial barriers compromised by topical tacrolimus. J. Invest. Dermatol. 131, 698–705.
Jungersted, J.M., Bomholt, J., Bajraktari, N., Hansen, J.S., Klærke, D.A., Pedersen, P.A., Hedfalk, K., Nielsen, K.H., Agner, T., Hélix-Nielsen, C., 2013. In vivo studies of aquaporins 3 and 10 in human stratum corneum. Arch. Dermatol. Res. 305, 699–704.
Jurzak, M., Latocha, M., Gojniczek, K., Kapral, M., Garncarczyk, A., Pierzchała, E., 2008. Influence of retinoids on skin fibroblasts metabolism in vitro. Acta Pol. Pharm. 65, 85–91.
Kalinin, A., Marekov, L.N., Steinert, P.M., 2001. Assembly of the epidermal cornified cell envelope. J. Cell Sci. 114, 3069–3070.
Kang, S., Chung, J.H., Lee, J.H., Fisher, G.J., Wan, Y.S., Duell, E.A., Voorhees, J.J., 2003. Topical N-acetyl cysteine and genistein prevent ultraviolet-light-induced signaling that leads to photoaging in human skin in vivo. J. Invest. Dermatol. 120, 835–841.
Katz, D.L., Doughty, K., Ali, A., 2011. Cocoa and chocolate in human health and disease. Antioxid. Redox Signal. 15, 2779–2811.
Kaur, I.P., Kapila, M., Agrawal, R., 2007. Role of novel delivery systems in developing topical antioxidants as therapeutics to combat photoageing. Ageing Res. Rev. 6, 271–288.
Keogh, B.P., Allen, R.G., Pignolo, R., Horton, J., Tresini, M., Cristofalo, V.J., 1996. Expression of hydrogen peroxide and glutathione metabolizing enzymes in human skin fibroblasts derived from donors of different ages. J. Cell Physiol. 167, 512–522.
Kezic, S., Kammeyer, A., Calkoen, F., Fluhr, J.W., Bos, J.D., 2009. Natural moisturizing factor components in the stratum corneum as biomarkers of filaggrin genotype: evaluation of minimally invasive methods. Br. J. Dermatol. 161, 1098–1104.
Kim, H., Kim, J., Park, J., Kim, S.H., Uchida, Y., Holleran, W.M., Cho, Y., 2012a. Water extract of gromwell (*Lithospermum erythrorhizon*) enhances migration of human keratinocytes and dermal fibroblasts with increased lipid synthesis in an in vitro wound scratch model. Skin Pharmacol. Physiol. 25, 57–64.
Kim, H., Koh, J., Baek, J., Seo, Y., Kim, B., Kim, J., Lee, J., Ryoo, H., Jung, H., 2011. Retinyl retinoate, a novel hybrid vitamin derivative, improves photoaged skin: a double-blind, randomized-controlled trial. Skin Res. Technol. 17, 380–385.
Kim, J.E., Kim, B., Kim, H., Kim, H., Lee, J.D., Kim, H.J., Choi, K.Y., Lee, S.H., 2010. Retinyl retinoate induces hyaluronan production and less irritation than other retinoids. J. Dermatol. 37, 448–454.
Kim, J.S., Lee, C.H., Su, B.Y., Coulombe, P.A., 2012b. Mathematical modeling of the impact of actin and keratin filaments on keratinocyte cell spreading. Biophys. J. 103, 1828–1838.
Kim, S.B., Kang, O.H., Joung, D.K., Mun, S.H., Seo, Y.S., Cha, M.R., Ryu, S.Y., Shin, D.W., Kwon, D.Y., 2013. Anti-inflammatory effects of tectroside on UVB-induced HaCaT cells. Int. J. Mol. Med. 31, 1471–1476.
Kircik, L.H., 2012. Safety and efficacy evaluation of tretinoin cream 0.02% for the reduction of photodamage: a pilot study. J. Drugs Dermatol. 11, 83–90.
Kirschner, N., Rosenthal, R., Furuse, M., Moll, I., Fromm, M., Brandner, J.M., 2013. Contribution of tight junction proteins to ion, macromolecule, and water barrier in keratinocytes. J. Invest. Dermatol. 133, 1161–1169.
Kligman, L.H., 1982. Intensification of ultraviolet-induced dermal damage by infrared radiation. Arch. Dermatol. Res. 272, 229–238.
Kömüves, L.G., Schmuth, M., Fowler, A.J., Elias, P.M., Hanley, K., Man, M.Q., Moser, A.H., Lobaccaro, J.M., Williams, M.L., Mangelsdorf, D.J., Feingold, K.R., 2002. Oxysterol stimulation of epidermal differentiation is mediated by liver X receptor-beta in murine epidermis. J. Invest. Dermatol. 118, 25–34.
Krolikiewicz-Renimel, I., Michel, T., Destandau, E., Reddy, M., André, P., Elfakir, C., Pichon, C., 2013. Protective effect of a *Butea monosperma* (Lam.) Taub. flowers

extract against skin inflammation: antioxidant, anti-inflammatory and matrix metalloproteinases inhibitory activities. J. Ethnopharmacol. 148, 537–543.
Kulms, D., Zeise, E., Pöppelmann, B., Schwarz, T., 2002. DNA damage, death receptor activation and reactive oxygen species contribute to ultraviolet radiation-induced apoptosis in an essential and independent way. Oncogene 21, 5844–5851.
Kupper, T.S., Fuhlbrigge, R.C., 2004. Immune surveillance in the skin: mechanisms and clinical consequences. Nat. Rev. Immunol. 4, 211–222.
Kuwazuru, O., Miyamoto, K., Yoshikawa, N., Imayama, S., 2012. Skin wrinkling morphology changes suddenly in the early 30s. Skin Res. Technol. 18, 495–503.
Kwon, O.S., Pyo, H.K., Oh, Y.J., Han, J.H., Lee, S.R., Chung, J.H., Eun, H.C., Kim, K.H., 2007. Promotive effect of minoxidil combined with all-trans retinoic acid (tretinoin) on human hair growth in vitro. J. Korean Med. Sci. 22, 283–289.
Lademann, J., Meinke, M.C., Sterry, W., Darvin, M.E., 2011. Carotenoids in human skin. Exp. Dermatol. 20, 377–382.
Lampe, M.A., Williams, M.L., Elias, P.M., 1983. Human epidermal lipids: characterization and modulations during differentiation. J. Lipid Res. 24, 131–140.
Lee, S.H., Zahoor, M., Hwang, J.K., Min do, S., Choi, K.Y., 2012. Valproic acid induces cutaneous wound healing in vivo and enhances keratinocyte motility. PLoS ONE 7, e48791.
Levakov, A., Vucković, N., Dolai, M., Kaćanski, M.M., Bozanić, S., 2012. Age-related skin changes. Med. Pregl. 65, 191–195.
Li, J., Tang, H., Hu, X., Chen, M., Xie, H., 2010. Aquaporin-3 gene and protein expression in sun-protected human skin decreases with skin ageing. Australas J. Dermatol. 51, 106–112.
Liu, L., Zhong, Q., Tian, T., Dubin, K., Athale, S.K., Kupper, T.S., 2010. Epidermal injury and infection during poxvirus immunization is crucial for the generation of highly protective T cell-mediated immunity. Nat. Med. 16, 224–227.
Lock-Andersen, J., Therkildsen, P., de Fine Olivarius, F., Gniadecka, M., Dahlstrøm, K., Poulsen, T., Wulf, H.C., 1997. Epidermal thickness, skin pigmentation and constitutive photosensitivity. Photodermatol. Photoimmunol. Photomed. 13, 153–158.
Lodén, M., Beitner, H., Gonzalez, H., Edström, D.W., Akerström, U., Austad, J., Buraczewska-Norin, I., Matsson, M., Wulf, H.C., 2011. Sunscreen use: controversies, challenges and regulatory aspects. Br. J. Dermatol. 165, 255–262.
Lodén, M., Maibach, H.I., 1999. Dry Skin and Moisturizers: Chemistry and Function, first ed. CRC Press, New York.
Longo, C., Casari, A., Beretti, F., Cesinaro, A.M., Pellacani, G., 2013. Skin aging: in vivo microscopic assessment of epidermal and dermal changes by means of confocal microscopy. J. Am. Acad. Dermatol. 68, e73–e82.
Lulevich, V., Yang, H.Y., Isseroff, R.R., Liu, G.Y., 2010. Single cell mechanics of keratinocyte cells. Ultramicroscopy 110, 1435–1442.
Luo, D., Min, W., Lin, X.F., Wu, D., Xu, Y., Miao, X., 2006. Effect of epigallocatechin-gallate on ultraviolet B-induced photo-damage in keratinocyte cell line. Am. J. Chin. Med. 34, 911–922.
Madison, K.C., 2003. Barrier function of the skin: "la raison d'être" of the epidermis. J. Invest. Dermatol. 121, 231–241.
Mantena, S.K., Katiyar, S.K., 2006. Grape seed proanthocyanidins inhibit UV-radiation-induced oxidative stress and activation of MAPK and NF-kappaB signaling in human epidermal keratinocytes. Free Radic. Biol. Med. 40, 1603–1614.
Matsui, M.S., Hsia, A., Miller, J.D., Hanneman, K., Scull, H., Cooper, K.D., Baron, E., 2009. Non-sunscreen photoprotection: antioxidants add value to a sunscreen. J. Invest. Dermatol. Symp. Proc. 14, 56–59.
Meinke, M.C., Friedrich, A., Tscherch, K., Haag, S.F., Darvin, M.E., Vollert, H., Groth, N., Lademann, J., Rohn, S., 2013. Influence of dietary carotenoids on radical scavenging capacity of the skin and skin lipids. Eur. J. Pharm. Biopharm. 84, 365–373.
Michel, S., Jomard, A., Démarchez, M., 1998. Pharmacology of adapalene. Br. J. Dermatol. 139, 3–7.
Michelet, J.F., Olive, C., Rieux, E., Fagot, D., Simonetti, L., Galey, J.B., Dalko-Csiba, M., Bernard, B.A., Pereira, R., 2012. The anti-ageing potential of a new jasmonic acid derivative (LR2412): in vitro evaluation using reconstructed epidermis Episkin™. Exp. Dermatol. 21, 398–400.
Milstone, L.M., 2004. Epidermal desquamation. J. Dermatol. Sci. 36, 131–140.
Misery, L., 2000. The neuro-immuno-cutaneous system and ultraviolet radiation. Photodermatol. Photoimmunol. Photomed. 16, 78–81.
Mnich, C.D., Hoek, K.S., Virkki, L.V., Farkas, A., Dudli, C., Laine, E., Urosevick, M., Dummer, R., 2009. Green tea extract reduces induction of p53 and apoptosis in UVB-irradiated human skin independent of transcriptional controls. Exp. Dermatol. 18, 69–77.
Morita, A., Torii, K., Maeda, A., Yamaguchi, Y., 2009. Molecular basis of tobacco smoke-induced premature skin aging. J. Invest. Dermatol. Symp. Proc. 14, 53–55.
Moyano-Mendez, J.R., Fabbrocini, G., De Stefano, D., Mazzella, C., Mayol, L., Scognamiglio, I., Carnuccio, R., Ayala, F., La Rotonda, M.I., De Rosa, G., 2013. Enhanced antioxidant effect of trans-resveratrol: potential of binary systems with polyethylene glycol and cyclodextrin. Drug Dev. Ind. Pharm. (in press).
Nakahara, M., Mishima, T., Hayakawa, T., 2007. Effect of a sake concentrate on the epidermis of aged mice and confirmation of ethyl alpha-D-glucoside as its active component. Biosci. Biotechnol. Biochem. 71, 427–434.
Namjoshi, S., Caccetta, R., Benson, H.A., 2008. Skin peptides: biological activity and therapeutic opportunities. J. Pharm. Sci. 97, 2524–2542.
Nichols, J.A., Katiyar, S.K., 2010. Skin photoprotection by natural polyphenols: anti-inflammatory, antioxidant and DNA repair mechanisms. Arch. Dermatol. Res. 302, 71–83.
Nishifuji, K., Yoon, J.S., 2013. The stratum corneum: the rampart of the mammalian body. Vet. Dermatol. 24, 60–72.
Niyonsaba, F., Nagaoka, I., Ogawa, H., Okumura, K., 2009. Multifunctional antimicrobial proteins and peptides: natural activators of immune systems. Curr. Pharm. Des. 15, 2393–2413.
Ogden, S., Dearman, R.J., Kimber, I., Griffiths, C.E., 2011. The effect of ageing on phenotype and function of monocyte-derived Langerhans cells. Br. J. Dermatol. 165, 184–188.
Olteanu, E.D., Filip, A., Clichici, S., Daicoviciu, D., Achim, M., Postescu, I.D., Bolfa, P., Bolojan, L., Vlase, L., Muresan, A., 2012. Photochemoprotective effect of *Calluna vulgaris* extract on skin exposed to multiple doses of ultraviolet B in SKH-1 hairless mice. J. Environ. Pathol. Toxicol. Oncol. 31, 233–243.
Orringer, J.S., Hammerberg, C., Hamilton, T., Johnson, T.M., Kang, S., Sachs, D.L., Fisher, G., Voorhees, J.J., 2008. Molecular effects of photodynamic therapy for photoaging. Arch. Dermatol. 144, 1296–1302.
O'Sullivan, R.L., Lipper, G., Lerner, E.A., 1998. The neuro-immuno-cutaneous-endocrine network: relationship of mind and skin. Arch. Dermatol. 134, 1431–1435.
Pain, S., Altobelli, C., Boher, A., Cittadini, L., Favre-Mercuret, M., Gaillard, C., Sohm, B., Vogelgesang, B., André-Frei, V., 2011. Surface rejuvenating effect of Achillea millefolium extract. Int. J. Cosmet. Sci. 33, 535–542.
Palmer, D.M., Kitchin, J.S., 2010. Oxidative damage, skin aging, antioxidants and a novel antioxidant rating system. J. Drugs Dermatol. 9, 11–15.
Palombo, P., Fabrizi, G., Ruocco, V., Ruocco, E., Fluhr, J., Roberts, R., Morganti, P., 2007. Beneficial long-term effects of combined oral/topical antioxidant treatment with the carotenoids lutein and zeaxanthin on human skin: a double-blind, placebo-control study. Skin Pharmacol. Physiol. 20, 199–210.
Pastore, S., Lulli, D., Maurelli, R., Dellambra, E., De Luca, C., Korkina, L.G., 2013. Resveratrol induces long-lasting IL-8 expression and peculiar EGFR activation/distribution in human keratinocytes: mechanisms and implications for skin administration. PLoS ONE 8, e59632.
Pedata, P., Boccellino, M., La Porta, R., Napolitano, M., Minutolo, P., Sgro, L.A., Zei, F., Sannolo, N., Quagliuolo, L., 2012. Interaction between combustion-generated organic nanoparticles and biological systems: in vitro study of cell toxicity and apoptosis in human keratinocytes. Nanotoxicology 6, 338–352.
Peguet-Navarro, J., Dezutter-Dambuyant, C., Buetler, T., Leclaire, J., Smola, H., Blum, S., Bastien, P., Breton, L., Gueniche, A., 2008. Supplementation with oral probiotic bacteria protects human cutaneous immune homeostasis after UV exposure-double blind, randomized, placebo controlled clinical trial. Eur. J. Dermatol. 18, 504–511.
Pereda, M.C., Dieamant, G.C., Eberlin, S., Werka, R.M., Colombi, D., Queiroz, M.L., Di Stasi, L.C., 2010. Expression of differential genes involved in the maintenance of water balance in human skin by Piptadenia colubrina extract. J. Cosmet. Dermatol. 9, 35–43.
Pernet, I., Reymermier, C., Guezennec, A., Viac, J., Guesnet, J., Perrier, E., 2005. An optimized method for intensive screening of molecules that stimulate beta-defensin 2 or 3 (hBD2 or hBD3) expression in cultured normal human keratinocytes. Int. J. Cosmet. Sci. 27, 161–170.
Polak, M.E., Thirdborough, S.M., Ung, C.Y., Elliott, T., Healy, E., Freeman, T.C., Ardern-Jones, M.R., 2014. Distinct molecular signature of human skin langerhans cells denotes critical differences in cutaneous dendritic cell immune regulation. J. Invest. Dermatol. 134, 695–703.
Polefka, T.G., Meyer, T.A., Agin, P.P., Bianchini, R.J., 2012. Effects of solar radiation on the skin. J. Cosmet. Dermatol. 11, 134–143.
Pongcharoen, S., Warnnissorn, P., Lertkajornsin, O., Limpeanchob, N., Sutheerawattananonda, M., 2013. Protective effect of silk lutein on ultraviolet B-irradiated human keratinocytes. Biol. Res. 46, 39–45.
Proksch, E., Brandner, J.M., Jensen, J.M., 2008. The skin: an indispensable barrier. Exp. Dermatol. 17, 1063–1072.
Puizina-Ivić, N., Mirić, L., Carija, A., Karlica, D., Marasović, D., 2010. Modern approach to topical treatment of aging skin. Coll. Antropol. 34, 1145–1153.
Qian, Y.P., Cai, Y.J., Fan, G.J., Wei, Q.Y., Yang, J., Zheng, L.F., Li, X.Z., Fang, J.G., Zhou, B., 2009. Antioxidant-based lead discovery for cancer chemoprevention: the case of resveratrol. J. Med. Chem. 52, 1963–1974.
Rahimpour, Y., Hamishehkar, H., 2012. Liposomes in cosmeceutics. Expert Opin. Drug Deliv. 9, 443–455.
Ramms, L., Fabris, G., Windoffer, R., Schwarz, N., Springer, R., Zhou, C., Lazar, J., Stiefel, S., Hersch, N., Schnakenberg, U., Magin, T.M., Leube, R.E., Merkel, R., Hoffmann, B., 2013. Keratins as the main component for the mechanical integrity of keratinocytes. Proc. Natl. Acad. Sci. U.S.A. 110, 18513–18518.
Raschke, T., Koop, U., Düsing, H.J., Filbry, A., Sauermann, K., Jaspers, S., Wenck, H., Wittern, K.P., 2004. Topical activity of ascorbic acid: from in vitro optimization to in vivo efficacy. Skin Pharmacol. Physiol. 17, 200–206.
Ratner, D., Viron, A., Puvion-Dutilleul, F., Puvion, E., 1998. Pilot ultrastructural evaluation of human preauricular skin before and after high-energy pulsed carbon dioxide laser treatment. Arch. Dermatol. 134, 582–587.
Ravagnan, G., De Filippis, A., Cartenì, M., De Maria, S., Cozza, V., Petrazzuolo, M., Tufano, M.A., Donnarumma, G., 2013. Polydatin, a natural precursor of resveratrol, induces β-defensin production and reduces inflammatory response. Inflammation 36, 26–34.
Rendl, M., Mayer, C., Weninger, W., Tschachler, E., 2001. Topically applied lactic acid increases spontaneous secretion of vascular endothelial growth factor by human reconstructed epidermis. Br. J. Dermatol. 145, 3–9.
Rhie, G., Shin, M.H., Seo, J.Y., Choi, W.W., Cho, K.H., Kim, K.H., Park, K.C., Eun, H.C., Chung, J.H., 2001. Aging- and photoaging-dependent changes of enzymic and nonenzymic antioxidants in the epidermis and dermis of human skin in vivo. J. Invest. Dermatol. 117, 1212–1217.

Rittié, L., Fisher, G.J., 2002. UV-light-induced signal cascades and skin aging. Ageing Res. Rev. 1, 705–720.
Rizzo, A.E., Maibach, H.I., 2012. Personalizing dermatology: the future of genomic expression profiling to individualize dermatologic therapy. J. Dermatol. Treat. 23, 161–167.
Rodríguez-Yanes, E., Juarranz, Á., Cuevas, J., Gonzalez, S., Mallol, J., 2012. Polypodium leucotomos decreases UV-induced epidermal cell proliferation and enhances p53 expression and plasma antioxidant capacity in hairless mice. Exp. Dermatol. 21, 638–640.
Sander, C.S., Chang, H., Salzmann, S., Müller, C.S., Ekanayake-Mudiyanselage, S., Elsner, P., Thiele, J.J., 2002. Photoaging is associated with protein oxidation in human skin in vivo. J. Invest. Dermatol. 118, 618–625.
Sayo, T., Sugiyama, Y., Inoue, S., 2013. Lutein, a nonprovitamin A, activates the retinoic acid receptor to induce HAS3-dependent hyaluronan synthesis in keratinocytes. Biosci. Biotechnol. Biochem. 77, 1282–1286.
Sasaki, G.H., Travis, H.M., Tucker, B., 2009. Fractional CO_2 laser resurfacing of photoaged facial and non-facial skin: histologic and clinical results and side effects. J. Cosmet. Laser Ther. 11, 190–201.
Schäfer, M., Dütsch, S., auf dem Keller, U., Werner, S., 2010. Nrf2: a central regulator of UV protection in the epidermis. Cell Cycle 9, 2917–2918.
Scharffetter-Kochanek, K., Brenneisen, P., Wenk, J., Herrmann, G., Ma, W., Kuhr, L., Meewes, C., Wlaschek, M., 2000. Photoaging of the skin from phenotype to mechanisms. Exp. Gerontol. 35, 307–316.
Sgarbossa, A., Dal Bosco, M., Pressi, G., Cuzzocrea, S., Dal Toso, R., Menegazzi, M., 2012. Phenylpropanoid glycosides from plant cell cultures induce heme oxygenase 1 gene expression in a human keratinocyte cell line by affecting the balance of NRF2 and BACH1 transcription factors. Chem. Biol. Interact. 199, 87–95.
Shan, S.J., Xiao, T., Chen, J., Geng, S.L., Li, C.P., Xu, X., Hong, Y., Ji, C., Guo, Y., Wei, H., Liu, W., Li, D., Chen, H.D., 2012. Kanglaite attenuates UVB-induced down-regulation of aquaporin-3 in cultured human skin keratinocytes. Int. J. Mol. Med. 29, 625–629.
Shimoda, H., Terazawa, S., Hitoe, S., Tanaka, J., Nakamura, S., Matsuda, H., Yoshikawa, M., 2012. Changes in ceramides and glucosylceramides in mouse skin and human epidermal equivalents by rice-derived glucosylceramide. J. Med. Food 15, 1064–1072.
Shindo, Y., Witt, E., Han, D., Epstein, W., Packer, L., 1994. Enzymic and non-enzymic antioxidants in epidermis and dermis of human skin. J. Invest. Dermatol. 102, 122–124.
Shlivko, I.L., Petrova, G.A., Zor'kina, M.V., Tchekalkina, O.E., Firsova, M.S., Ellinsky, D.O., Agrba, P.D., Kamensky, V.A., Donchenko, E.V., 2013. Complex assessment of age-specific morphofunctional features of skin of different anatomic localizations. Skin Res. Technol. 19, e85–e92.
Silva, A.R., Seidl, C., Furusho, A.S., Boeno, M.M., Dieamant, G.C., Weffort-Santos, A.M., 2013. In vitro evaluation of the efficacy of commercial green tea extracts in UV protection. Int. J. Cosmet. Sci. 35, 69–77.
Silveira, J.P., Seito, L.N., Eberlin, S., Dieamant, G.C., Nogueira, C., Pereda, M.C., Di Stasi, L.C., 2013. Photoprotective and antioxidant effects of Rhubarb: inhibitory action on tyrosinase and tyrosine kinase activities and TNF-α, IL-1α and α-MSH production in human melanocytes. BMC Complement. Altern. Med. 13, 49.
Simpson, C.L., Patel, D.M., Green, K.J., 2011. Deconstructing the skin: cytoarchitectural determinants of epidermal morphogenesis. Nat. Rev. Mol. Cell Biol. 12, 565–580.
Skazik, C., Amann, P.M., Heise, R., Marquardt, Y., Czaja, K., Kim, A., Rühl, R., Kurschat, P., Merk, H.F., Bickers, D.R., Baron, J.M., 2013. Downregulation of STRA6 expression in epidermal keratinocytes leads to hyperproliferation-associated differentiation in both in vitro and in vivo skin models. J. Invest. Dermatol. (in press).
Smith, K., Hamza, S., Germain, M., Skelton, H., 2007. Does imiquimod histologically rejuvenate ultraviolet radiation-damaged skin? Dermatol. Surg. 33, 1419–1428.
Smith, W.P., 1996. Epidermal and dermal effects of topical lactic acid. J. Am. Acad. Dermatol. 35, 388–391.
Song, J.H., Bae, E.Y., Choi, G., Hyun, J.W., Lee, M.Y., Lee, H.W., Chae, S., 2013. Protective effect of mango (*Mangifera indica* L.) against UVB-induced skin aging in hairless mice. Photodermatol. Photoimmunol. Photomed. 29, 84–89.
Song, X.Z., Bi, Z.G., Xu, A.E., 2006. Green tea polyphenol epigallocatechin-3-gallate inhibits the expression of nitric oxide synthase and generation of nitric oxide induced by ultraviolet B in HaCaT cells. Chin. Med. J. (Engl.) 119, 282–287.
Sorg, O., Antille, C., Kaya, G., Saurat, J.H., 2006. Retinoids in cosmeceuticals. Dermatol. Ther. 19, 289–296.
Sorg, O., Kuenzli, S., Kaya, G., Saurat, J.H., 2005. Proposed mechanisms of action for retinoid derivatives in the treatment of skin aging. J. Cosmet. Dermatol. 4, 237–244.
Squassina, A., Manchia, M., Manolopoulos, V.G., Artac, M., Lappa-Manakou, C., Karkabouna, S., Mitropoulos, K., Del Zompo, M., Patrinos, G.P., 2010. Realities and expectations of pharmacogenomics and personalized medicine: impact of translating genetic knowledge into clinical practice. Pharmacogenomics 11, 1149–1167.
Stamford, N.P., 2012. Stability, transdermal penetration, and cutaneous effects of ascorbic acid and its derivatives. J. Cosmet. Dermatol. 11, 310–317.
Sticozzi, C., Belmonte, G., Cervellati, F., Muresan, X.M., Pessina, F., Lim, Y., Forman, H.J., Valacchi, G., 2014. Resveratrol protects SR-B1 levels in keratinocytes exposed to cigarette smoke. Free Radic. Biol. Med. 69, 50–57.
Stuzin, J.M., Baker, T.J., Baker, T.M., Kligman, A.M., 1997. Histologic effects of the high-energy pulsed CO2 laser on photoaged facial skin. Plast. Reconstr. Surg. 99, 2036–2050.
Tanaka, Y.T., Tanaka, K., Kojima, H., Hamada, T., Masutani, T., Tsuboi, M., Akao, Y., 2013. Cynaropicrin from *Cynara scolymus* L. suppresses photoaging of skin by inhibiting the transcription activity of nuclear factor-kappa B. Bioorg. Med. Chem. Lett. 23, 518–523.
Takahashi, N., Fujiu, Y., 2010. Effects of the aminophenol analogue p-Dodecylaminophenol on mouse skin. J. Invest. Dermatol. 130, 1258–1267.
Takata, K., Matsuzaki, T., Tajika, Y., 2004. Aquaporins: water channel proteins of the cell membrane. Prog. Histochem. Cytochem. 39, 1–83.
Tobi, S.E., Gilbert, M., Paul, N., McMillan, T.J., 2002. The green tea polyphenol, epigallocatechin-3-gallate, protects against the oxidative cellular and genotoxic damage of UVA radiation. Int. J. Cancer 102, 439–444.
Tomaino, A., Cristani, M., Cimino, F., Speciale, A., Trombetta, D., Bonina, F., Saija, A., 2006. In vitro protective effect of a Jacquez grapes wine extract on UVB-induced skin damage. Toxicol. In Vitro 20, 1395–1402.
Tominaga, K., Hongo, N., Karato, M., Yamashita, E., 2012. Cosmetic benefits of astaxanthin on humans subjects. Acta Biochim. Pol. 59, 43–47.
Tsambaos, D., Stadler, R., Hilt, K., Zimmermann, B., Orfanos, C.E., 1985. Effects of arotinoid ethyl ester on epithelial differentiation and proliferation. Ciba Found. Symp. 113, 97–116.
Tsugita, T., Nishijima, T., Kitahara, T., Takema, Y., 2013. Positional differences and aging changes in Japanese woman epidermal thickness and corneous thickness determined by OCT (optical coherence tomography). Skin Res. Technol. 19, 242–250.
Tur, E., Hohl, D., Jetten, A., Panizzon, R., Frenk, E., 1995. Modification of late epidermal differentiation in photoaged skin treated with topical retinoic acid cream. Dermatology 191, 124–128.
Türkoğlu, M., Uğurlu, T., Gedik, G., Yılmaz, A.M., Süha Yalçin, A., 2010. In vivo evaluation of black and green tea dermal products against UV radiation. Drug Discov. Ther. 4, 362–367.
Tzaphlidou, M., 2004. The role of collagen and elastin in aged skin: an image processing approach. Micron 35, 173–177.
Ulmann, L., Rodeau, J.L., Danoux, L., Contet-Audonneau, J.L., Pauly, G., Schlichter, R., 2007. Trophic effects of keratinocytes on the axonal development of sensory neurons in a coculture model. Eur. J. Neurosci. 26, 113–125.
Urikura, I., Sugawara, T., Hirata, T., 2011. Protective effect of Fucoxanthin against UVB-induced skin photoaging in hairless mice. Biosci. Biotechnol. Biochem. 75, 757–760.
Valacchi, G., Sticozzi, C., Pecorelli, A., Cervellati, F., Cervellati, C., Maioli, E., 2012. Cutaneous responses to environmental stressors. Ann. N.Y. Acad. Sci. 1271, 75–81.
Velazquez Pereda, M.C., Dieamant, G.C., Eberlin, S., Nogueira, C., Colombi, D., Di Stasi, L.C., de Souza Queiroz, M.L., 2009. Effect of green *Coffea arabica* L. seed oil on extracellular matrix components and water-channel expression in in vitro and ex vivo human skin models. J. Cosmet. Dermatol. 8, 56–62.
Vierkötter, A., Krutmann, J., 2012. Environmental influences on skin aging and ethnic-specific manifestations. Dermatoendocrinology 4, 227–231.
Vierkötter, A., Schikowski, T., Ranft, U., Sugiri, D., Matsui, M., Krämer, U., Krutmann, J., 2010. Airborne particle exposure and extrinsic skin aging. J. Invest. Dermatol. 130, 2719–2726.
Vranesić-Bender, D., 2010. The role of nutraceuticals in anti-aging medicine. Acta Clin. Croat. 49, 537–544.
Waaijer, M.E., Gunn, D.A., Catt, S.D., van Ginkel, M., de Craen, A.J., Hudson, N.M., van Heemst, D., Slagboom, P.E., Westendorp, R.G., Maier, A.B., 2012. Morphometric skin characteristics dependent on chronological and biological age: the Leiden Longevity Study. Age (Dordr.) 34, 1543–1552.
Waller, J.M., Maibach, H.I., 2005. Age and skin structure and function, a quantitative approach (I): blood flow, pH, thickness, and ultrasound echogenicity. Skin Res. Technol. 11, 221–235.
Waller, J.M., Maibach, H.I., 2006. Age and skin structure and function, a quantitative approach (II): protein, glycosaminoglycan, water, and lipid content and structure. Skin Res. Technol. 12, 145–154.
Wang, X., 1999. A theory for the mechanism of action of the alpha-hydroxy acids applied to the skin. Med. Hypotheses 53, 380–382.
Wang, Z., Coleman, D.J., Bajaj, G., Liang, X., Ganguli-Indra, G., Indra, A.K., 2011. RXRα ablation in epidermal keratinocytes enhances UVR-induced DNA damage, apoptosis, and proliferation of keratinocytes and melanocytes. J. Invest. Dermatol. 131, 177–187.
Wertz, K., Hunziker, P.B., Seifert, N., Riss, G., Neeb, M., Steiner, G., Hunziker, W., Goralczyk, R., 2005. beta-Carotene interferes with ultraviolet light A-induced gene expression by multiple pathways. J. Invest. Dermatol. 124, 428–434.
White-Chu, E.F., Reddy, M., 2011. Dry skin in the elderly: complexities of a common problem. Clin. Dermatol. 29, 37–42.
Williams, I.R., Kupper, T.S., 1996. Immunity at the surface: homeostatic mechanisms of the skin immune system. Life Sci. 58, 1485–1507.
Woelfle, U., Laszczyk, M.N., Kraus, M., Leuner, K., Kersten, A., Simon-Haarhaus, B., Scheffler, A., Martin, S.F., Müller, W.E., Nashan, D., Schempp, C.M., 2010. Triterpenes promote keratinocyte differentiation in vitro, ex vivo and in vivo: a role for the transient receptor potential canonical (subtype) 6. J. Invest. Dermatol. 130, 113–123.
Wolf, J., Harris, R., Ferris, L.K., 2013. Screening for melanoma in aging patients. Cutis 91, 81–86.
Wu, M., Fannin, J., Rice, K.M., Wang, B., Blough, E.R., 2011. Effect of aging on cellular mechanotransduction. Ageing Res. Rev. 10, 1–15.
Wu, S., Gao, J., Dinh, Q.T., Chen, C., Fimmel, S., 2008. IL-8 production and AP-1 transactivation induced by UVA in human keratinocytes: roles of D-alpha-tocopherol. Mol. Immunol. 45, 2288–2296.

Xie, H., Liu, F., Liu, L., Dan, J., Luo, Y., Yi, Y., Chen, X., Li, J., 2013. Protective role of AQP3 in UVA-induced NHSFs apoptosis via Bcl2 up-regulation. Arch. Dermatol. Res. 305, 397–406.

Xu, Y.P., Qi, R.Q., Chen, W., Shi, Y., Cui, Z.Z., Gao, X.H., Chen, H.D., Zhou, L., Mi, Q.S., 2012. Aging affects epidermal Langerhans cell development and function and alters their miRNA gene expression profile. Aging (Albany, NY) 4, 742–754.

Yamada, M., Udono, M.U., Hori, M., Hirose, R., Sato, S., Mori, T., Nikaido, O., 2006. Aged human skin removes UVB-induced pyrimidine dimers from the epidermis more slowly than younger adult skin in vivo. Arch. Dermatol. Res. 297, 294–302.

Yamaguchi, Y., Takahashi, K., Zmudzka, B.Z., Kornhauser, A., Miller, S.A., Tadokoro, T., Berens, W., Beer, J.Z., Hearing, V.J., 2006. Human skin responses to UV radiation: pigment in the upper epidermis protects against DNA damage in the lower epidermis and facilitates apoptosis. FASEB J. 20, 1486–1488.

Yamamoto, Y., Uede, K., Yonei, N., Kishioka, A., Ohtani, T., Furukawa, F., 2006. Effects of alpha-hydroxy acids on the human skin of Japanese subjects: the rationale for chemical peeling. J. Dermatol. 33, 16–22.

Yang, J., Li, W., Sun, R., Li, B., 2011. The effect of Lactobacillus johnsonii Ncc533 (La1) on the balance of Th1/Th2 cells in BALB/c mice. Clin. Invest. Med. 34, E254.

Yasuda, M., Ohzeki, Y., Shimizu, S., Naito, S., Ohtsuru, A., Yamamoto, T., Kuroiwa, Y., 1999. Stimulation of in vitro angiogenesis by hydrogen peroxide and the relation with ETS-1 in endothelial cells. Life Sci. 64, 249–258.

Yasuda, S., Tada, M., Yamada, K., Takahata, K., 2004. Suppressive effects of ascorbate derivatives on ultraviolet-B-induced injury in HaCaT human keratinocytes. In Vitro Cell Dev. Biol. Anim. 40, 71–73.

Ye, J., Garg, A., Calhoun, C., Feingold, K.R., Elias, P.M., Ghadially, R., 2002. Alterations in cytokine regulation in aged epidermis: implications for permeability barrier homeostasis and inflammation. I. IL-1 gene family. Exp. Dermatol. 11, 209–216.

Zaid, M.A., Afaq, F., Syed, D.N., Dreher, M., Mukhtar, H., 2007. Inhibition of UVB-mediated oxidative stress and markers of photoaging in immortalized HaCaT keratinocytes by pomegranate polyphenol extract POMx. Photochem. Photobiol. 83, 882–888.

Zhang, G., Moore, D.J., Mendelsohn, R., Flach, C.R., 2006. Vibrational microspectroscopy and imaging of molecular composition and structure during human corneocyte maturation. J. Invest. Dermatol. 126, 1088–1094.

Zhao, J.F., Zhang, Y.J., Jin, X.H., Athar, M., Santella, R.M., Bickers, D.R., Wang, Z.Y., 1999. Green tea protects against psoralen plus ultraviolet A-induced photochemical damage to skin. J. Invest. Dermatol. 113, 1070–1075.

Zouboulis, C.C., Makrantonaki, E., 2011. Clinical aspects and molecular diagnostics of skin aging. Clin. Dermatol. 29, 3–14.