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REVIEW ARTICLE

Topical Retinoids: Therapeutic Mechanisms in the Treatment of Photodamaged Skin

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Abstract Retinoids are a group of substances comprising vitamin A and its natural and synthetic derivatives. Retinoids were first used in dermatology in 1943 by Straumfjord for acne vulgaris. Since that time, retinoids have been utilized in the management and treatment of various skin conditions, including photoaging. Photodamage of the skin occurs as a consequence of cumulative exposure to solar ultraviolet radiation (UVR) and is characterized by deep wrinkles, easy bruising, inelasticity, mottled pigmentation, roughness, and telangiectasias. The mechanism of UVR-induced photodamage is multifactorial. Retinoids have demonstrated efficacy in the treatment of photoaged skin. Indeed, understanding the pathophysiology of photoaging and the molecular mechanism of retinoids can not only provide insight into the effects retinoids can exert in treating photoaging but also provide the rationale for their use in the treatment of other dermatologic diseases.

Key Points

Vitamin A and its derivatives have a role in the treatment of photoaging.

Topical retinoids are safe and effective in the management and treatment of photodamaged skin.

Further understanding of skin aging and retinoids may provide the opportunity to create new therapeutic options.

1 Introduction

Retinoids are a group of substances comprising vitamin A and its natural and synthetic derivatives [1–3]. Retinoids were first used in dermatology in 1943 by Straumfjord for acne vulgaris [1]. Topical retinoids have expanded to treat various skin conditions including acne, photoaging, and actinic keratosis [1, 3–25]. Impairment in retinoid metabolism and signaling has been noted in various diseases such as atopic dermatitis and psoriasis [1].

Interest in therapies to prevent or reverse signs of skin aging has led to research regarding the mechanisms by which aging occurs. Indeed, the integument has been utilized as a model for evaluating the effects of exogenous factors in the process of aging [11–13]. Ultraviolet radiation (UVR) has been demonstrated to play a major role as an environmental factor which leads to premature aging of the skin, with long-term exposure causing altered pigmentation and wrinkle formation [11–13]. Studies continue to demonstrate UVR-induced photodamage is caused by a

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complex interaction involving degradation of matrix proteins, nuclear and mitochondrial damage, and formation of reactive oxygen species (ROS) [4–27].

The use of retinoids in ameliorating signs of photodamage has been demonstrated [11–14, 28–34]. Studies to elucidate the precise mechanisms in which retinoids reverse or palliate signs of photodamage have been performed [2, 4, 5, 11, 14]. Understanding the mechanism of action of retinoids provides insight into the complex pathways involved in retinoid signaling. The aim of this review is to discuss the mechanisms of known topical retinoids in the treatment of photodamaged skin [17–19].

2 Methods

A comprehensive search of PubMed was conducted evaluating papers published from 1997 to 2015. Search terms included dermatoheliosis, dermatoporosis, mechanism, metabolism, photoaging, photodamage, retinal, retinoids, retinoic acid, retinol, wrinkle, wrinkling, vitamin A. Articles that were not related to photoaging and vitamin A were excluded.

3 Vitamin A and Retinoid Metabolism

3.1 Vitamin A: Retinal, Retinoic Acid and Retinol

Vitamin A comprises a group of naturally occurring biologic compounds. These fat-soluble vitamins cannot be synthesized in vivo by humans and dietary absorption requires bile salts, dietary fat, and pancreatic lipase [28]. The main dietary forms of pro-vitamin A include beta-carotene and retinyl esters; they are cleaved and absorbed by the intestine in chylomicrons. These compounds are then transported to the liver and stored as retinyl esters. The normal liver storage can satisfy vitamin A requirements for 2 years [1, 28].

Vitamin A is synonymous with retinol; metabolites of vitamin A include retinal and retinoic acid. These lipophilic organic compounds are important for epithelial differentiation, immune regulation, reproduction, and vision [3, 5]. Retinal is important for visual function; it combines with the rod pigment opsin to form rhodopsin, an agent necessary for visual dark adaptation [1]. The main transport form of vitamin A in the body is retinol, while retinoic acid is the biologically active form of vitamin A [1].

Retinol is hydrophobic and requires transportation in the serum by a complex of retinol-binding protein (RBP) and transthyretin (prealbumin) [1, 35]. Bound retinol prevents damage to cell membranes and also facilitates the transportation and delivery to target organs [35]. Retinol is taken up into cells, where it binds to cytosolic retinol-binding protein (CRBP). CRBP then delivers retinol to the appropriate enzymes; retinol can either become oxidized to form the active form, retinoic acid (RA), or converted to retinyl esters (the storage form) via lecithin retinol acyltransferase (LRAT) [1]. Keratinocytes convert and store a majority of vitamin A as retinyl esters in the skin [34]. The homeostasis of vitamin A is regulated by the expression of LRAT, CYP26, and other RA-induced genes to provide a response system and prevent retinoid toxicity [36].

Vitamin A acts through a complex pathway that involves several different targets [37]. Retinoids exert their effects by activating nuclear receptors to regulate gene transcription (Fig. 1) [1–33]. RA is transported to the nucleus by cytosolic RA-binding protein (CRABP) [1]. CRABPII is the predominant binding protein in skin [1]. In the nucleus, retinoids bind to nuclear RA receptors (RAR), retinoid X receptors (RXR) and fatty acid-binding protein 5 [1]. Isomerization of RA to 9-*cis* RA allows for binding to RXR. Previous studies established that all-*trans* RA does not bind RXR; however, more recent reports suggest that it is possible and may play a role in the function of retinoids [38–44]. RA furthermore activates kinases that phosphorylate RAR and other transcription factors [37]. RAR and RXR form heterodimers; RXR can also homodimerize or form heterodimers with vitamin D or thyroid hormone receptors [4]. These dimers bind to RA response elements (RAREs) to change gene expression through activation and repression [37].

RAR and RXR each have three different receptor subtypes (α, β and γ); various topical retinoids have demonstrated selectivity to particular subtypes [1–3]. RAR-γ is predominantly expressed in the epidermis while RAR-β is found in dermal fibroblasts [1]. RAR-α is expressed at a higher level in embryonic skin and is important in cell growth and differentiation. RAR-α agonists have been demonstrated to decrease expression of all-*trans* RA synthesis enzymes and retinoid target genes, similar to RAR and RXR antagonists [2]. RAR-γ agonists demonstrate induction of genes involved in barrier function and epidermal hyperproliferation [2]. Indeed, mRNA of heparin-binding epidermal growth factor (HB-EGF), postulated to result in the epidermal hyperplasia seen in retinoid use, was decreased with RAR-α agonists and increased with RAR-γ agonists [2].

3.2 Cytokine and Ligand Properties

Additionally, vitamin A can function as a cytokine by activating STRA6 (stimulated by retinoic acid 6) to regulate gene transcription [37]. RA serves as a ligand for peroxisome proliferator-activated receptor β/δ (PPAR β/δ),

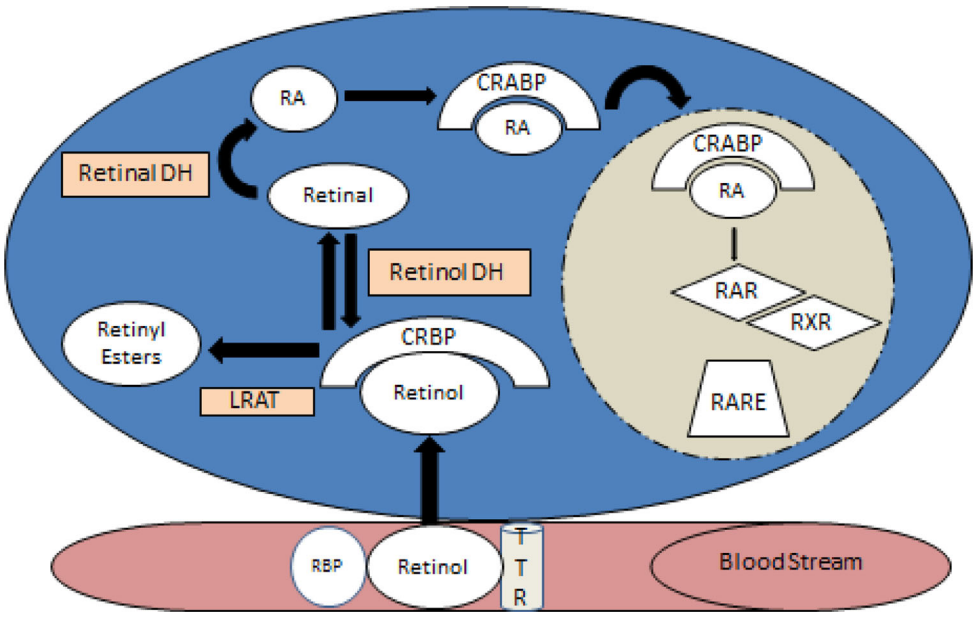

Fig. 1 Overview of retinoid metabolism (Note: Retinol is oxidized to retinoic acid in two steps: retinol is reversibly oxidized by retinol dehydrogenase to give retinal, then retinal is irreversibly oxidized by retinal dehydrogenase to give retinoic acid) [1–31]. *CRABP* cytosolic retinoic acid binding protein, *CRBP* cytosolic retinol binding protein, *LRAT* lecithin retinol acyltransferase, *RA* retinoic acid, *RAR* retinoic acid receptor, *RARE* retinoic acid response element, *RBP* retinol-binding protein, *Retinal DH* retinal dehydrogenase, *RXR* retinoid X receptor, *TTR* transthyretin

which induces genes involved in cell proliferation and prevention of apoptosis [1, 39].

4 Ultraviolet Radiation-Induced Photoaging

4.1 Definition

Photodamage, also termed dermatoheliosis, occurs as a consequence of cumulative exposure to solar UVR. It is characterized by easy bruising, deep wrinkles, inelasticity, mottled pigmentation, roughness, and telangiectasias [8, 11]. The effects of UVR-induced photodamage are often superimposed with chronological aging.

The term 'dermatoporosis' has been used to describe the constellation of functional, morphological, and histological features of photodamaged skin as it ages and loses its protective mechanical function [8, 11, 45]. The clinical manifestations can include senile purpura, skin atrophy, and stellate pseudoscars. The functional fragility of the skin results in impaired would healing, frequent skin lacerations, and subcutaneous bleeding from minor trauma. While the condition may first appear in the sixth decade, the disease typically progresses with age and long-term sun exposure [45].

Concerns about the appearance of photoaged skin can significantly impact employment, personal relationships, and the individual's self-esteem [13]. This is highlighted by the 10-billion-dollar anti-aging product market [26]. While prevention and sun protection are key, treatment options such as retinoids may have a role to improve appearance of aged skin and reverse skin damage [26, 27, 34].

4.2 Histologic Changes

Photodamaged skin demonstrates various histological changes (Table 1) [3–20]. These changes are characterized by degeneration of collagen with disorganization of fibrils, deposition of abnormal elastotic material, keratinocyte atypia, and loss of polarity of keratinocytes [12–14]. There is a decrease in collagen types I, III, and VII with decreased level of cross-linking and collagen precursors [12–14, 25]. Fibrillin microfibrils and elastic fiber-associated protein fibulin-5 are lost in the papillary dermis early in the process of photoaging [12]. With skin atrophy, the epidermis and dermis may thin, with loss of rete ridges [45]. An increase in inflammatory cells, such as eosinophils, mast cells, and mononuclear cells, may also be present [27].

4.3 Pathogenesis

The mechanism of UVR-induced photodamage is multifactorial (Table 2) [1–20, 25]. Photodamaged skin initially demonstrates acanthosis and increased glycosaminoglycan synthesis (GAG). UVR-induced acanthosis is a product of increased proliferation of, and irregularities in, basal keratinocytes due to inflammatory cytokines [5, 14, 20]. Despite increased synthesis, GAGs are deposited in abnormal elastotic material; this renders them unable to bind water and provide hydration [20]. The clinical effect of these changes is thickened, leathery skin that is dry and coarse. With chronic UVR exposure, direct UVB absorption by DNA and ROS-mediated damage to important cellular structures results in apoptosis of not only basal cells, but also other keratinocytes [4]. The resulting loss of

Table 1 Histologic changes observed in photodamaged skin [3−20]

Clinical appearance	Histological correlation
Epidermis	
Atrophied skin (late)	Injury to and decreased number of basal cells with reduction in keratinocyte production
Coarse skin (early)	Acanthosis (hyperplasia)
Development of pre-cancerous and cancerous lesions	Epidermal nuclear atypia
Pigmentary alterations	Initially reactive hyperplasia of melanocytes; over time, a decrease in number
NCC	Decreased number of Langerhans cells
BMZ	
Fragility/increased susceptibility of skin tearing	Decreased anchoring fibrils (type VII collagen)
	Decreased microvillous projections of basal cells into the BMZ
Dermis	
Rough texture	Increased GAG accumulating in abnormal elastotic material
Wrinkled skin	Disorganization of collagen fibrils; reduced collagen I and III; increased ratio of type III to I
Vascular fragility	Decreased small blood vessels; absent or decreased veil cells
	Ectatic blood vessels with thickened or atrophic walls
Sebaceous hyperplasia	Hyperplasia of sebaceous glands
NCC	Increased perivascular histiocytes and lymphocytes

BMZ basement membrane zone, *GAG* glycosaminoglycan, *NCC* no clinical correlation

cells clinically presents as atrophic, thinned epidermis. The skin may also become fragile from loss of the extracellular matrix and hyaluronate [45]. UVR has also been shown to reduce retinoid receptors, essentially producing a retinoid deficient state [4, 20].

4.4 Dyschromia

Dyschromia from excessive UVR is characterized by pigmentary abnormalities and development of ephelides and lentigines. The UVR-induced tanning response signals through the melanocortin-1 receptor (MC1R) pathway, leading to increased cellular cyclic adenosine monophosphate (cAMP) and downstream activation of microphthalmia-associated transcription factor (MITF) [20, 29]. Increased tyrosinase activity causes melanin production and dispersion of melanin-containing granules. UVR has also been shown to cause hyperplasia of melanocytes [4, 20]. Post-inflammatory pigmentary alterations from inflammation and subsequent dermal melanophages can complicate excessive UVR exposure.

4.5 Skin Elasticity and Wrinkling

UVR-induced skin inelasticity and wrinkling occur due to destruction, imperfect repair, and decreased recycling of dermal matrix proteins. Collagen comprises the bulk of the protein in the dermis and is essential in providing structure and strength to the dermis [25]. The regulation of collagen synthesis and turnover is complex. Kang et al. have reported that activator protein-1 (AP-1) (composed of dimers of fos and jun proteins) and transforming growth factor-β (TGF-β) are important regulators of collagen synthesis [25]. TGF-β signaling leads to binding of Smad 2, 3, and 4 to form a transcription factor that stimulates collagen gene transcription [25].

UVR induces Smad 7, which interferes with the TGF-β signaling pathway [26]. AP-1 counteracts the production of collagen by inhibiting the Smad 2,3,4 complex, decreasing TGF-β receptors, and antagonizing RA actions [25, 26]. UVR-activated cysteine-rich protein 61 (CCN1), a regulator of collagen synthesis, induces AP-1, which directly inhibits collagen gene expression [25–27, 46]. Intrinsically aged skin demonstrates increased production of c-Jun occurring as a result of stress-activated mitogen-activated protein (MAP) kinases [14]; AP-1 is similar to c-Jun as they both interfere with procollagen transcription [4, 16].

4.6 Destruction of Dermal Matrix Proteins

UVR increases the destruction of dermal matrix proteins while also decreasing the synthesis of replacement collagen. UVA radiation decreases collagen recycling by down regulation of both prolidase, an enzyme involved in collagen synthesis, and mannose receptor C type 2 (MRC2), a collagen recycling receptor, resulting in decreased internalization of collagen 1 [47]. Increased destruction with

Table 2 Mechanisms of UVR-induced photodamage [1−20, 25, 27, 36, 40, 46−50]

Clinical appearance	Mechanism
Atrophied skin (late)	UVB and ROS mediated damage to keratinocytes and basal cells with resulting apoptosis; net decrease in epidermal keratinocytes [1–20]
	UVR-induced decrease in mRNA for RAR-γ and RXR-α [4]
Coarse and fine wrinkling	UVR-induced increase in AP-1 and NF-kB with upregulation of MMPs, with loss of collagens I, III, VII, and fibrillin [1–20]
	AP-1 suppression of collagen gene transcription [25]
	c-Jun mediated inhibition of procollagen 1 synthesis [4, 15, 16]
	UVR decreased collagen recycling by down regulation of prolidase and MRC2 [47]
	ROS inducing MAP kinase-mediated signal transduction with increased AP-1and c-jun [11, 25]
	Downregulation of TGF-β expression and Smad signaling leading to decreased procollagen synthesis [1, 5]
	Direct UVB absorption and ROS-mediated oxidation of cysteine-rich components of elastic fibers [12, 13]
	Mast-cell recruitment of inflammatory cells leading to local tissue damage [20]
	Leukotriene-mediated low grade chronic inflammation [20]
	NF-kB activation by UVR with increased production of TNF-α, IL-1β, and IL-8 leading to PMN recruitment and subsequent production of elastase and MMP-8 [25, 46, 48, 49]
	UVR activates CCN1 which induces IL-1, ultimately inhibits collagen 1 and upregulates MMP1 [36, 39, 48]
	UVR causing nerve release of substance P and CGRP, leading to mast cell degranulation [20]
Development of pre-cancerous and cancerous lesions	UVR-induced production of free radicals, oxidative stress, and changes in DNA structure causing constitutive expression of proto-oncogenes [20]
Dyschromia	UVR-induced synthesis and release of α-MSH with subsequent binding to MC1R; binding increases production of cAMP leading to downstream activation of MITF [20]
	Reactive hyperplasia of melanocytes secondary to UVR-induced stimulation [4, 20]
	Apoptosis of melanin-laden keratinocytes with pigmentary dropout [2–10, 20]
Inelasticity	Alteration and degradation of elastic fibers by MMPs, direct UVB absorption, and ROS-mediated oxidation [2–10, 20, 45]
	Mast-cell production of fibroblast growth factors with abnormal or disorganized production of elastic fibers [20]
Fragility/skin tearing	Decrease in collagen VII due to UVR-induced increase in MMPs [1–20, 45, 46]
Thickened skin (early)	Acanthosis as a result of increased proliferation due to inflammatory cytokines [5, 14, 20]
	Abnormal increase in GAG deposited in abnormal elastotic material [5, 25]
Vascular ectasia	Destruction of the connective-tissue matrix providing stability to small cutaneous vessels [13, 14, 20]
	Production of angiogenic factors leading to abnormal vessels [20, 27, 50]

α-MSH alpha melanocyte-stimulating hormone, *AP-1* activator protein-1, *cAMP* cyclic adenosine monophosphate, *CCN1* cysteine-rich protein 61, *CGRP* calcitonin gene-related peptide, *GAG* glycosaminoglycan, *IL* interleukin, *MAP* mitogen-activated protein, *MC1R* melanocortin 1 receptor, *MITF* microphthalmia-associated transcription factor, *MMP* matrix metalloproteinase, *MRC2* mannose receptor C type 2, *NF-kB* nuclear factor kappa B, *PMN* polymorphonuclear cells, *ROS* reactive oxygen species, *RAR* retinoic acid receptors, *RXR* retinoid X receptors, *TGF-β* transforming growth factor beta, *TNF-α* tumor necrosis factor-alpha, *UVB* ultraviolet B, *UVR* ultraviolet radiation

decreased production and recycling of collagen leads to a decrease in dermal matrix proteins.

4.7 Metalloproteinases

Exposure to UVR, even in doses below that which can cause erythema, has been shown to up-regulate the transcription factors AP-1 and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) [14, 25]. Both transcription factors stimulate the metalloproteinase genes, leading to increased production of matrix metalloproteinases (MMPs) [11–14, 25]. AP-1 leads to production of MMPs 1, 2, 3, 7, 9, 12, and 13 [1, 12, 14, 27], while NF-kB increases MMP 9 [14]. Chronological aging also upregulates MMP 1, 2, and 3 with downregulation of the tissue inhibitor of MMP 1 [45, 48]. Interleukin (IL)-1β also upregulates MMP 1 [49]. The increased production and imbalance of MMPs within keratinocytes and fibroblasts leads to degradation of collagen

and elastin in the epidermis and dermal matrix [11–15, 45]. Subsequent repair of the matrix can result in imperfections known as solar scars [14].

4.8 Elastic Fibers

Elastic fibers in the dermis are susceptible to direct damage from UVR. In particular, the cysteine-rich fibrillin microfibril portion of the elastic fiber system in the dermis, including fibrillins, fibulins, and TGF-β-binding proteins, are UVB chromophores [12]. These structures share a cysteine-rich motif which is the target for UVB [14].

4.9 Free Radical Production

Photodamage can manifest as the result of free radical production [27, 45]. UVR creates ROS which activates NF-kB, a transcription factor that increases expression of inflammatory cytokines such as IL-1 [27]. IL-1 plays an essential role in the activation of MAP kinases; signal transduction of MAP kinases leads to AP-1 and c-Jun production [4, 20]. Ultimately, UVA exposure with subsequent production of free radicals damages DNA and the matrix structures, including collagen and elastic fibers [15, 27].

4.10 Chronic Inflammatory Response

UVR causes a chronic inflammatory response with release of inflammatory mediators and recruitment of polymorphonuclear cells (PMNs). Cutaneous nerves release calcitonin gene-related peptide (CGRP) and substance P in response to UVR; these substances stimulate mast cells to release inflammatory mediators and chemotactic agents [20]. NF-κB activation by UVR leads to increased production of tumor necrosis factor-α (TNF-α), IL-1β, IL-8, and EGF [27]. CCN1 also increases IL-1β [46, 48, 49]. UVR-induced angiogenesis leads to hyperpermeable vessels, allowing inflammatory markers to escape and recruit inflammatory cells [27, 50]. Prostaglandins, converted by cyclooxygenase enzymes from the release of arachidonic acid from oxidative membrane lipids, also recruit inflammatory cells. This recruitment contributes to the destruction of matrix protein from degranulation and release of proteinases [25, 26, 45].

5 Treatment of Photodamaged Skin: Retinoid Mechanisms

5.1 Initial Observations and Subsequent Studies

The use of topical retinoids in the treatment of photoaging was discovered by reports of improvement in periorbital wrinkling in women using tretinoin for facial acne [4]. Since this initial observation, there has been an interest in the mechanisms of retinoids in the amelioration of aging and photodamage. Studies performed to investigate the effects of retinoids in the treatment of photodamaged skin have provided insight into the pathways in which retinoids can reverse photodamage (Table 3) [1, 2, 4, 5, 8, 9, 11, 14, 15, 21–24].

5.2 Vitamin A and UVR Protection

Vitamin A is found in increasing density from the stratum basale to the stratum granulosum. Retinoids have a critical role in the differentiation of keratinocytes and epidermal regeneration. Retinyl esters in the epidermis offer a protective role secondary to their long conjugated double bond system that absorb and filter UVR [34]. As UVB is absorbed, a functional deficiency of vitamin A may occur secondary to decreased expression of RARα and RARγ [51, 52, 54].

5.3 Dyschromia

UVR-induced dyschromia of the skin is characterized by pigmentary irregularities. Use of topical retinoids has been demonstrated to improve discoloration through various mechanism including direct inhibition of tyrosinase, reduced melanosome transfer, and increase shedding of melanin-containing keratinocytes [1, 11, 14]. The application of a topical retinoid facilitates improved penetration of other topical bleaching agents, including hydroquinone [17]. Decreased production of melanin and increased cell turnover of pigment-containing keratinocytes can lead to improvements in abnormal pigmentation.

5.4 Wrinkling

Improvement in fine and coarse wrinkling has been observed in topical retinoid users [4, 11, 13, 14, 21–25]. UVR-induced wrinkling occurs as a result of increased destruction of dermal matrix proteins and reduced procollagen synthesis. Use of topical retinoids has been shown to counteract the destruction of collagen and elastic fibers by blocking transcription of MMPs and increasing levels of tissue inhibitor of metalloproteinase (TIMP) [28]. Retinoids also increase MRC2 and prolidase to improve collagen 1 recycling [47]. These mechanisms improve the production of procollagen and elastic fiber components which leads to restoration of dermal matrix proteins and improves not only wrinkling but also skin laxity [1–4, 11, 14, 21, 25, 28].

Table 3 Mechanism of action of retinoids in the treatment of photodamaged skin [1, 2, 4, 5, 8, 9, 11, 14, 15, 21–25, 26, 28, 29, 46]

Effect	Mechanism
Dyschromia	Direct inhibition of tyrosinase activity [11, 14]
	Dispersion of melanin granules [1]
	Reduced melanosome transfer [11, 14]
	Increased epidermal cell turnover, leading to increased shedding of melanin-laden keratinocytes [1, 14]
Improvement in wrinkling	Inhibition of UVR-induced c-Jun expression which would lead to decreased procollagen synthesis [11, 16]
	Blocking of UV-induced AP-1 binding to DNA, preventing an increase in AP-1 induced transcription of MMPs [13, 25]
	Increase in prolidase and MRC2, improving collagen internalization and recycling [40]
	Inhibitory effect on the release of proteolytic enzymes by neutrophils [28]
	Reduced degranulation of phagocytic cells [28]
	Retinoid-receptor complex-mediated antagonism of NF-IL6
	Reduced TNF-α production and subsequent synthesis of IL-1,6,8, and GM-CSF leading to net decrease in recruitment of inflammatory cells [28]
	Decreased CCN1, leading to decreased IL-β [46]
	Reduced production of IFN-γ and leukotriene B4 [26]
	Increased production of TIMP [1, 28]
	Increased production of fibrillin in the papillary dermis [4]
	Increased type 1 collagen synthesis, possibly from increased TGF-β [11, 14, 21, 25]
Improvement in texture	HB-EGF activation of ErbB receptors via RAR-dependent paracrine loop mediating epidermal hyperplasia [3, 21]
	Increase in CD44 and increased expression of hyaluronate-polymerizing enzymes leading to increased epidermal and dermal intercellular mucin deposition [3, 11, 29]
	Increased filaggrin, involucrin, and loricrin [2]
Improved elasticity	Inhibition of MMPs via various mechanisms leading to decreased degradation of elastic fibers [1–4, 28]
	Increased fibrillin production [4]
Decreased fragility/skin tearing	Increased synthesis of collagen type VII and decreased degradation leading to net increase in anchoring fibrils to attach BMZ to dermis
	Increased fibrillin microfibrils providing superficial and deep layers a physical link [12]
Improved healing	Increased cutaneous blood flow and angiogenesis [11, 29]
	Increased dermal fibroblasts [14]

AP-1 activator protein-1, *BMZ* basement membrane zone, *CCN1* cysteine-rich protein 61, *GM-CSF* granulocyte–macrophage colony-stimulating factor, *HB-EGF* heparin binding-epidermal growth factor, *INF-* γ interferon gamma, *IL* interleukin, *MMP* matrix metalloproteinase, *MRC2* mannose receptor C type 2, *NF-IL6* nuclear factor interleukin-6, *RAR* retinoic acid receptors, *TGF-β* transforming growth factor beta, *TIMP* tissue inhibitor of metalloproteinase, *TNF-α* tumor necrosis factor-alpha, *UVR* ultraviolet radiation

5.5 Inflammation

Anti-inflammatory effects of topical retinoids are a useful mechanism in acne treatment. In addition, they are also beneficial in decreasing inflammation in photodamaged skin [28]. Reduced production of pro-inflammatory cytokines leads to decreased influx of inflammatory cells and reduced release of both proteolytic enzymes and destructive granules [28].

5.6 Skin Texture

Improvement in skin texture with retinoid use is related to epidermal hyperplasia and increased mucin deposition [3, 11, 21, 29]. Indeed, it has been demonstrated that HB-EGF activation leads to epidermal hyperplasia, leading to improvement in atrophic, photoaged skin [3, 21]. It is hypothesized that an increase in CD44, with upregulation of hyaluronate-polymerizing enzymes, accounts for the increased mucin production observed histologically on retinoid-treated skin [3, 11, 29, 45]. Furthermore, upregulation of filaggrin by some retinoids (such as tazarotene) leads to increased natural moisturizing factors; subsequently, increased hydration of the epidermis and dermis can result in improved skin texture. Retinoids also prevent damage by increasing p53, a tumor suppressor transcription factor, and inhibiting AP-1 and NF-kB [34]. In addition, retinol peels, paired with Vitamin C, increase sebum

secretion which may alleviate dry skin and promote the skin's barrier function [53].

5.7 Skin Fragility

Photodamaged skin can demonstrate fragility and easy shearing or tearing. Intrinsically aged skin also exhibits some of these characteristics; therefore, it is suspected that decreased basement membrane zone proteins, epidermal atrophy, and increased blood vessel fragility contribute to these changes [13, 14, 20]. Topical retinoids have been shown to increase type VII collagen (anchoring fibrils) and fibrillin microfibrils, providing increased physical connection between the epidermis and dermis. In addition, increased angiogenesis and cutaneous blood flow can improve healing time in photodamaged skin [11, 14, 29].

6 Topical Retinoids for Treating Photodamaged Skin

6.1 Adapalene (Differin®, Galderma Laboratories)

Adapalene is a derivative of napthoic acid; it was the first synthetic topical retinoid used in the treatment of acne [5]. The medication is available as a 0.3 % gel or a 0.1 % gel, cream, or lotion. Adapalene's mechanism of action is similar to retinoid acid; however, it is selective for RAR-β and RAR-γ receptors and does not bind RXRs [5]. While adapalene does not bind CRABP II, it does have retinoid activity in skin. It exhibits potent anti-inflammatory activity through inhibition of 5-lipoxygenase and 15-lipoxygenase; it has been shown to inhibit neutrophil chemotaxis [1].

Adalpalene has been demonstrated to reduce actinic keratoses and lighten solar lentigines [5]. Herane and coauthors report that adapalene reduced forehead, perioral, and periorbital wrinkles and improved hydration of the skin [30]. While adapalene shows promise for use in photoaging due to its excellent tolerability, more studies are needed to evaluate and compare it to other retinoids.

6.2 Alitretinoin (Panretin®, Eisai Inc.)

Alitretinoin, available in 0.05 and 0.1 % gel, is the only FDA-approved topical agent for cutaneous Kaposi's sarcoma. It has also been demonstrated to be efficacious in the treatment of recalcitrant chronic hand dermatitis [5]. A 2005 study by Baumann et al. demonstrated improvement in actinic keratosis, seborrheic keratosis, and signs of photoaging with topical alitretinoin [8].

Alitretinoin is composed of 9-*cis* retinoic acid, and differs from other retinoids by its high affinity binding for all RARs and RXRs. Alitretnoin exerts anti-inflammatory, anti-proliferative, and apoptotic effects [54]. The precise mechanism of action in the treatment of Kaposi's sarcoma is unknown; it is hypothesized that downregulation of IL-6 and alteration of virally encoded oncogenes are responsible for inhibiting the growth of Kaposi's sarcoma cells in vitro [1]. The postulated mechanism of alitretinoin in the treatment of photodamaged skin stems from the binding and activation of both RARs and RXRs [8].

6.3 All-*Trans* Retinol

All-*trans* retinol is the natural alcohol form of vitamin A that is transported in the bloodstream from storage in the liver to peripheral target tissues. Topically applied all-*trans* retinol is subsequently oxidized to form all-*trans* retinoic acid (tretinoin), while excess topical retinol is stored as retinyl esters via acyl CoA: retinol acyltransferase (ARAT) [1, 3].

Once converted to retinoic acid, the cellular mechanisms of retinoid receptor binding have been shown to increase procollagen and glycosaminoglycan synthesis [7]. Topical retinol has been shown to have less skin irritation than retinoic acid [3, 7, 55]. Retinol 0.4 % was comparable to tretinoin 0.1 % cream expression of CRABPII mRNA, a marker of retinoid activity [3, 5, 7].

Retinol is clinically and histologically comparable to tretinoin [53, 54]. Although the exact conversion between retinol and tretinoin has not been established, retinol has been postulated to be ten times less potent as tretinoin. Using this conversion factor, studies comparing retinol and tretinoin have shown similar clinical results in photodamaged skin [55–58].

6.3.1 All-Trans Retinol Derivatives

Retinol derivatives include retinyl esters such as retinyl acetate, retinyl palmitate, and retinyl propionate. These compounds are available as non-prescription preparations for anti-aging and skin rejuvenation. In contrast with topical retinol, retinyl propionate cream did not demonstrate any statistically significant improvement in photoaging; however, it did decrease actinic keratoses in some patients [9].

Other derivatives of retinoids include bio-engineered molecules such as ethyl lactyl retinoate, which combines alpha hydroxy acid and retinoids. There are limited studies regarding their use. However, investigators have suggested that these combinations have a synergistic effect with regards to treating photodamaged skin [59].

6.3.2 Retinaldehyde

Retinaldehyde requires transformation to retinoic acid to exert its biologic activity [5]. Retinaldehyde has been demonstrated to improve fine and deep wrinkles when compared with 0.05 % tretinoin [3, 5]. In addition, retinaldehyde is less irritating than tretinoin [3, 5].

6.4 Bexarotene (Targretin®, Valeant Pharmaceuticals North America)

Bexarotene is a synthetic topical retinoid used as an alternative topical-directed therapy for cutaneous T cell lymphoma (CTCL) stage IA and IB [1]. It selectively binds RXRs, leading to decreased expression of cyclin D with inhibition of G1, G2, and M phase of the cell cycle [1]. Bexarotene has been demonstrated to increase TIMP, which may prevent metastasis [1].

The postulated mechanism of bexarotene in CTCL includes increased apoptosis through activation of caspase-3 and reduction of survivin [1]. Bexarotene has also been reported to be effective in alopecia, chronic hand dermatitis, lymphomatoid papulosis, and psoriasis [1, 10]. To the best of our knowledge, no studies in the use of bexarotene in the treatment of photoaging have been performed.

6.5 Isotretinoin

Topical isotretinoin, available in 0.05 and 0.1 % cream, has been demonstrated to improve coarse and fine wrinkles [3]. However, isotretinoin appears to be less effective than topical tretinoin in the treatment of photoaging [3]. Comparative studies of isotretinoin with other topical retinoids are lacking.

Oral isotretinoin has been shown to improve signs of skin aging leading to comparative studies of oral isotretinoin versus topical retinoids. Bagatin and coauthors compared low-dose oral isotretinoin with 0.05 % tretinoin for the treatment of photoaging and found no significant difference [31]. Another recent study by Bravo et al. assessed 20 pre-menopausal women, ages 45–50 years, treated with isotretinoin 20 mg 3 days a week for 12 weeks and found improvement, both clinically and histologically, of their skin quality [60]. While there was no control group, histologic analysis showed an increase in both collagen and elastic fiber density. Therefore, while oral isotretinoin may have a role in protecting against photoaging, further studies are needed to clarify its role in photoaging.

6.6 Seletinoid G

Seletinoid G is a fourth generation retinoid and demonstrates receptor selectivity for RAR-γ. Seletinoid G has been demonstrated to improve photo-aged and intrinsically aged skin similarly to topical tretinoin [5, 32, 61]. A potential advantage of seletinoid G is that it produces minimal irritation, even under an occlusive dressing [61]. More studies are needed to evaluate the efficacy of this product for treatment of photodamaged skin.

6.7 Tazarotene (Avage®, Allergan, Inc.)

Tazarotene is a third generation synthetic retinoid available as a cream, foam, or gel (0.05 and 0.1 %). The prodrug tazarotene is hydrolyzed to form the active metabolite tazarotenic acid. It binds to all RAR subtypes with the highest affinity for RAR-γ. Tazarotene also binds and activates RAR-β [62]. It has been demonstrated to strongly antagonize AP-1, inhibit ornithine decarboxylase (elevated in hyperplastic epidermis and a marker of hyperproliferation), and activate tazarotene-inducible genes (*TIG*) [1].

TIG1 is a tumor suppressor gene that promotes activation of G protein-coupled receptor kinase 5 (GRK5); it has also been shown to inhibit prostaglandin E2 [63]. *TIG2*, which is expressed at high levels in nonlesional psoriatic skin and lower levels in the psoriatic lesion, is up-regulated in psoriatic lesions after topical application of tazarotene [64]. *TIG3* is a tumor suppressor gene reduced in hyperproliferative disorders [65]. Duvic and coauthors suggest not only that *TIG3* is suppressed in basal cell carcinomas but also that treatments which increase *TIG3* expression may be effective for chemoprevention of this skin cancer [66].

Tazarotene has been demonstrated to be efficacious in the treatment of photodamaged skin. Indeed, studies demonstrate improvements in fine and coarse wrinkling, pigmentary mottling, and skin texture [5, 11, 17, 22–24]. Tazarotene, when compared with tretinoin, showed a faster onset of improvement in signs of photodamage [24]. In addition, some authors report that tazarotene 0.1 % cream has greater improvement in signs of photodamage when compared with tretinoin 0.05 % cream [5]; however, long-term (>24 weeks) use of both tazarotene 0.1 % cream and tretinoin 0.05 % cream demonstrated similar improvements in photodamaged skin [24].

6.8 Tretinoin

Tretinoin is the oxidized form of all-trans retinol and the biologically active form of vitamin A. Tretinoin is

available in various strengths and vehicles and is distributed mainly in keratinocytes with minimal uptake in the dermis [1]. Tretinoin binds all subtypes of RARs and can isomerize to 9-*cis* retinoic acid which binds to RXRs [1].

The potential of tretinoin in the treatment of photoaging was first recognized in the 1980s [5]. Tretinoin is perhaps the best studied topical retinoid in the treatment of photoaging. Numerous studies have been performed to evaluate the efficacy and tolerability of tretinoin in the treatment of photoaging. Short-term and long-term studies on tretinoin use in photoaging demonstrate clinical and histologic improvements in signs of photodamage [5, 11, 14, 21, 22, 24].

Tretinoin 0.05 % cream has long-term efficacy and safety in the treatment of photoaging [5, 21]. In addition, the use of low-strength tretinoin has been proposed with studies demonstrating 0.025 and 0.1 % tretinoin leading to significant and similar improvements in signs of photoaging [5, 32]. Other multi-center, randomized studies have demonstrated that tretinoin 0.02 % cream is effective in treatment of photodamaged skin while being more tolerable than higher strength tretinoin [11, 33]. However, tretinoin 0.01 % cream did not demonstrate any improvements in photoaging [11]. Long-term maintenance with retinoids may be continued with tretinoin 0.05 % cream three times a week [11].

Tretinoin may be incorporated with nanoparticles or liposomes in an attempt to improve drug photostability, skin delivery, and efficacy, while decreasing skin irritation [67, 68]. Tretinoin incorporated with nanoparticles has been suggested to be more bioeffective and effective [68]. Clinically, the incorporation resulted in higher efficacy in treating acne vulgaris [69]. However, clinical trials are needed to look specifically at photoaging.

7 Topical Retinoids: Management

Topical retinoids are available. The choice of retinoid in treatment of photoaging requires knowledge of tolerability, desired effect, and speed of onset. The most common side effects of topical retinoids include erythema, dryness, and pruritus [70]. In elderly populations or in situations where less irritation is desired, topical retinol or tretinoin 0.02 % can be used to improve photoaging [2–10, 21–25, 28–32, 70]. Although less data is available, adapalene may be utilized for photoaging when tolerability is an issue.

More aggressive therapy for prevention and amelioration of photodamage includes tretinoin 0.5 or 0.1 % cream and tazarotene 0.1 % cream [21–25]. Tazarotene 0.5 % cream was demonstrated to be similar to tazarotene 0.1 % and tretinoin 0.05 % in treatment of wrinkling; however, the overall global assessment score was less for tazarotene 0.05 % cream. Kang and coauthors found that the onset of tazarotene was faster than tretinoin [24]. Therefore, tazarotene may be utilized in patients who can tolerate the medication and desire faster results.

7.1 Topical Retinoids: New Uses

7.1.1 Chemotherapy-Induced Hand-Foot Syndrome

While topical retinoids have been demonstrated to be efficacious in the treatment of acne and photoaging, new uses for topical retinoids have been reported. Inokuchi and coauthors report treating a patient with capecitabine-induced hand-foot syndrome with adapalene [18]. The authors note that HB-EGF elevation is the mechanism of chemotherapy resistance to capecitabine [18]. The authors speculate that adapalene can induce HB-EGF in the skin of the hands when applied topically, effectively causing resistance to the chemotherapy. Further investigation regarding the use of topical retinoids in the treatment of chemotherapy-induced hand-foot syndrome is warranted [18].

7.1.2 Alopecia Areata

Rajiv and Singh describe topical bexarotene gel as a possible—yet costly—treatment option for alopecia areata [10]. It was noted in previous studies that bexarotene was associated with hair regrowth in patients with folliculotropic mycosis fungoides [10]. Studies of bexarotene in the treatment of alopecia areata have been performed and demonstrate clinical efficacy. This preliminary study suggests that additional investigation of alopecia areata with topical bexarotene is warranted.

8 Conclusion

An understanding of intrinsic and extrinsic aging is important, especially since the elderly population is increasing. Signs of photodamage may have a negative impact on an individual's self-esteem. In addition, excessive sun exposure poses risk to individuals owing to the potential development of precancerous and cancerous lesions. Dermatologists can have a crucial role in educating patients about the risks of excessive sun exposure while providing options for therapy of photoaged skin.

Topical retinoids are safe and effective agents that can be used in the treatment of photodamaged skin. Current studies provide insight into complex mechanisms by which retinoids treat photodamaged skin [2, 4, 5, 11, 14]. This knowledge can be utilized in creating novel therapeutic options to prevent or treat not only extrinsic but also intrinsic aging.

Compliance with Ethical Standards

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