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Retinal and Cutaneous Epigenetics: Retinal Technology + associations that promote cell renewal and rejuvenation up to 3 times more effective than retinoic acid.

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Abstract: *Retinaldehyde (or retinal) is a vitamin A derivative with increasing application in dermatology and aesthetics due to its clinical efficacy and excellent skin tolerance. Acting as a direct precursor of retinoic acid, it provides benefits similar to the most potent retinoids, but with fewer side effects and high tolerance. This review article presents the molecular mechanisms of Retinaldehyde, its main clinical indications and its comparison with retinol and retinoic acid in terms of efficacy, safety and tolerability. The methodology used was a narrative review of the literature based on articles published between 2000 and 2024 in the PubMed, Scielo and ScienceDirect databases.*

Key Word*: **Key words**: Dermatological treatments, dermatology, Retinaldehyde. Retinal. Retinoids. Retinoic acid, Skin aging, collagen, MMPs, TGF -β*

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I. Introduction

The search for improved skin texture, characterized by smoother, more uniform, firmer skin tone, has remained one of the main demands in contemporary aesthetics in recent years. This interest reflects the appreciation of the biomechanical and biophysical characteristics of healthy skin, often associated with youth, overall health and psychosocial well-being (Quan, 2023).

Structural changes in skin tissue such as loss of elasticity, roughness, roughness and irregularities in the epidermal surface are directly related to intrinsic aging, exposure to environmental factors (especially ultraviolet radiation) and the degradation of dermal support and support structures, such as collagen and elastin. In this context, professional aesthetics is a sector in constant expansion, driven by the development of non-invasive and minimally invasive technologies, advanced dermocosmetics and biostimulating topical actives.

The growing demand for interventions capable of restoring the structural and functional integrity of the skin therefore represents a significant opportunity for scientific advancement and the consolidation of evidence-based clinical practices, promoting integrated approaches for skin rejuvenation and revitalization with greater safety for patients.

In view of the growing demand for effective and well-tolerated interventions to improve skin texture, Retinaldehyde (Retinal) stands out as a promising first-generation Retinoid in the field of aesthetics and dermatology. As a direct precursor of retinoic acid, Retinal offers a more efficient and rapid conversion, promoting significant clinical benefits with less irritant potential compared to retinoic acid (Mohuuddin, 2019).

SKIN AGING

Skin aging is a complex, gradual and inevitable biological process, characterized by the progressive alteration of the morphological, functional and structural properties of the skin. This phenomenon results from the interaction between genetic (endogenous) and environmental (exogenous) factors, culminating in changes such as loss of elasticity, irregular texture of the epidermis, appearance of wrinkles, sagging, dryness and changes in pigmentation (GANCEVICI, 2020).

Two main types of skin aging can be distinguished: intrinsic aging, also called chronological, and extrinsic, or environmental, aging.

Intrinsic aging is genetically determined and gradually involves the natural physiological decline of cellular functions over time. Chronological aging is associated with cellular senescence, reduced keratinocyte renewal, decreased collagen synthesis by dermal fibroblasts, and reduced vascularization of the dermis (FISCHER et al., 2022).

These changes result in thinner, drier, duller, devitalized skin with fine wrinkles and sometimes associated with pigmentary disorders. Extrinsic aging is the result of prolonged exposure to harmful environmental agents, such as ultraviolet (UV) radiation, air pollution, smoking, a diet rich in inflammatory components, and oxidative stress. Chronic exposure to solar radiation leads to photoaging, which is responsible for significant histological changes such as degradation of protein fibers, macro and micromolecules of the extracellular matrix, abnormal deposition of elastin (solar elastosis), hyperpigmentation, and accentuation of furrows and wrinkles (KANG et al., 2019).

Although both types of aging share similar cellular mechanisms: such as increased production of reactive oxygen species (ROS) and activation of matrix metalloproteinases (MMPs), photoaging is more aggressive and earlier, and can be mitigated through preventive and therapeutic interventions (GANCEVICI, 2020).

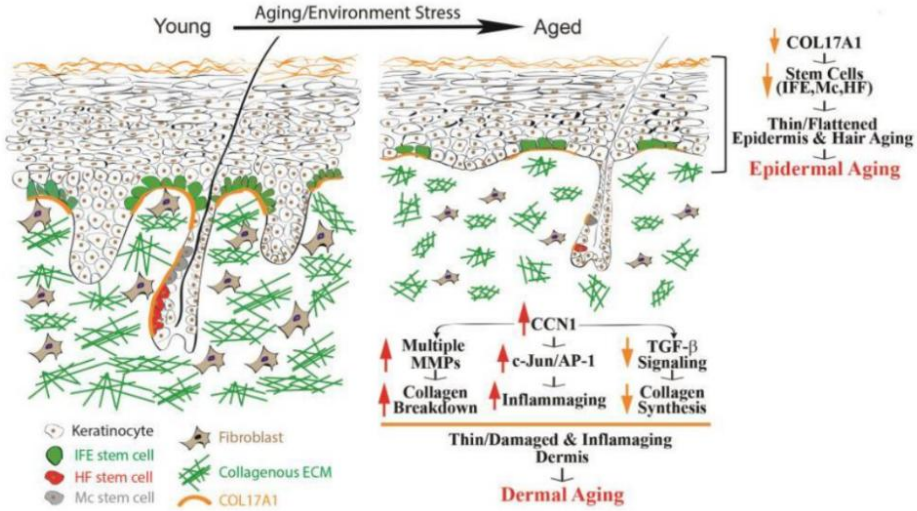


PHOTO1: Quan, T. Human skin aging and the anti-aging properties of retinol. Biomolecules 2023 , 13 , 1614. https://doi.org/10.3390/biom13111614

EPIDERMAL AGING

In the context of epidermal aging, important morphological changes are observed, such as the thinning of the epidermis (mainly the spinous layer responsible for cellular cohesion) and the flattening of the epidermal ridges, in addition to molecular changes related to the loss of the COL17A1 protein, which compromise the adhesion and functionality of basal cells.

This thinning is due to the decrease in the proliferative activity of keratinocytes and the reduction in the number of cells in the basal layer.

This change compromises the integrity of the skin barrier, increasing susceptibility to external agents, irritation, infections, dryness and mechanical trauma. In parallel, the flattening of the epidermal ridges occurs, reducing the contact surface between the epidermis and the dermis. In young skin, these ridges facilitate metabolic exchanges and provide greater mechanical resistance to the skin. With this

flattening, there is a reduction in oxygenation and nutrition from the dermis to the epidermis, being one of the factors responsible for the decrease in cell turnover.

With aging, its reduction results in less adhesion between the skin layers and contributes to the fragility and loss of skin elasticity (FISCHER et al., 2022; KIM et al., 2018).

Figura 3: Espécimes de pele dos grupos jovem (A) e idoso (B) corados por H&E, x100. No-tem-se o achatamento pro-gressivo da junção epider-mo-dérmica com o envel-hecimento e a redução da acidofilia na derme média (asterisco), refletindo a redução da densidade de fibras colágenas.

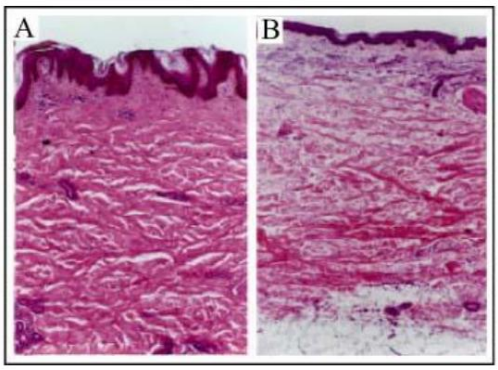


***Figure 3:** Skin specimens from the young (A) and eld-erly (B) groups, stained with H&E, x100. Note the progres-sive flattening of the dermoepidermal interface with aging and the re-duction of the acidophil-ia in the middle dermis (asterisk), reflecting the reduction in the den-sity of the collagen fibers.*

PHOTO 2: Study of age-related changes in human skin using histomorphometry and autofluorescence methods. Journal of Clinical, Laboratory and Therapeutic Research. An. Bras. Dermatol. 78 (4). Aug 2003 doi.org/10.1590/S0365-05962003000400004

DERMA AGING

Dermal aging is a multifactorial process characterized by structural and functional changes in the dermis, with emphasis on the progressive degradation of the extracellular matrix, especially collagen fibers. This process is mediated mainly by matrix metalloproteinases (MMPs), with MMP-1 – also known as collagenase-1 – being primarily responsible for the cleavage of type I collagen, which constitutes the majority of the dermal matrix (FISHER ET AL., 1996).

With intrinsic and extrinsic aging, especially due to chronic exposure to ultraviolet radiation (photoaging), there is a significant increase in the expression of MMPs by dermal fibroblasts.

This increase leads to the fragmentation of viable and organized collagen fibers, which compromises the mechanical and functional integrity of the ECM. Fragmentation of the extracellular matrix reduces cell adhesion, hindering cell communication between fibroblasts and the matrix, promoting a senescent cell phenotype with a pro-inflammatory profile and further decreasing the production of new collagen (QUAN ET AL., 2004).

In addition, dermal aging is associated with a dysfunction in the transforming growth factor beta (TGF-β) signaling pathway, one of the main regulators of collagen synthesis. Under physiological conditions, TGF-β acts through the activation of TβRII and TβRI receptors, which activate the SMAD signaling cascade, promoting the transcription of genes responsible for the production of collagen and other structural proteins of the dermal matrix (QUAN ET AL., 2013).

However, with advancing age, there is a decrease in the expression of TGF-β receptors, as well as an inhibition of the SMAD pathway, which results in a lower transcription of type I and III collagen. This deficiency in signaling contributes to the reduction of the thickness of the dermis, loss of elasticity and decrease in the mechanical resistance of the skin.

Therefore, dermal aging is characterized by a negative feedback loop: increased degradation of the matrix by MMPs, associated with reduced collagen synthesis due to dysfunction of the TGF-β pathway, compromises the structure and function of the skin, making it thinner, less elastic and more susceptible to external damage.

RETINOIDS X EPIGENETICS

Retinoids are compounds derived from vitamin A and play a fundamental role in regulating cell proliferation and differentiation in the epidermis. These compounds exert their action mainly through the modulation of gene expression in cells of the epidermis and dermis, directly affecting physiological processes.

They comprise a class of compounds that include retinol, retinaldehyde, retinoic acid and its esters. The biologically active form is retinoic acid, which binds to specific nuclear receptors called RAR (retinoic acid receptors) and RXR (retinoid X receptors), regulating the transcription of genes involved in cell proliferation and differentiation (KANG et al., 2001).

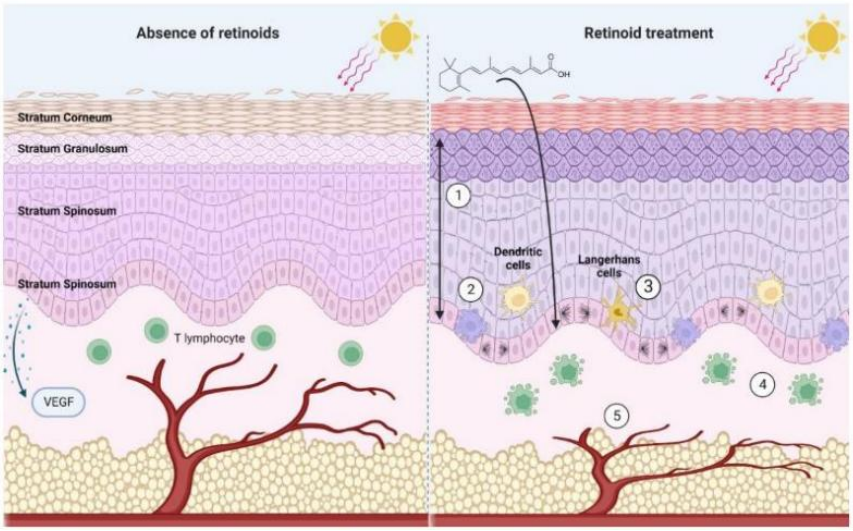


PHOTO 3: Ramchatesingh, B.; Martínez Villarreal, A.; Arcuri, D.; Lagacé, F.; Setah, S.A.; Touma, F.; Al-Badarin, F.; Litvinov, I.V. The Use of Retinoids for the Prevention and Treatment of Skin Cancers: An Updated Review. Int. J. Mol. Sci. 2022, 23, 12622. https://doi.org/10.3390/ijms232012622

In the absence of retinoids, UV radiation reduces the presence of Langerhans cells and dendritic cells in the skin. At the same time, UV radiation induces the activation of keratinocytes, particularly in the basal layer, leading to increased production of pro-angiogenic factors, including VEGF (vascular endothelial growth factor). This factor stimulates the formation of new blood vessels in the superficial dermis, a process known as angiogenesis, which is related to chronic inflammation (DETMAR, 2000).

In the presence of retinoids:
1. Increased proliferation of basal cells results in thickening of the stratum spinosum and stratum granulosum, and thinning of the stratum corneum, with a cumulative increase in epidermal thickness.
2. Increased basal cell apoptosis.
3. Protection of dendritic and Langerhans cells against UV-induced depletion.
4. Induction of apoptosis in T lymphocytes.
5. Inhibition of VEGF release in response to UV radiation, reducing angiogenesis.

RETINALDEHYDE
Retinal is an oxidized form of retinol and acts as an intermediary in the metabolic conversion to retinoic acid – the biologically active form. According to Sorg et al. (1999), Retinal presents an ideal balance between clinical efficacy and low irritability, being a promising alternative to classic retinoids such as retinoic acid.

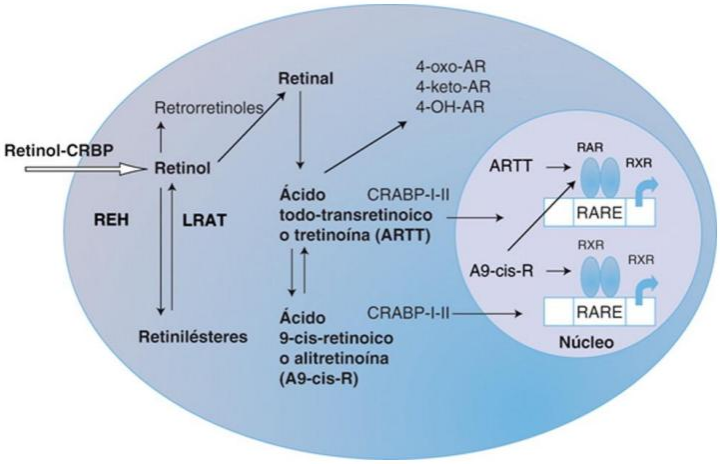


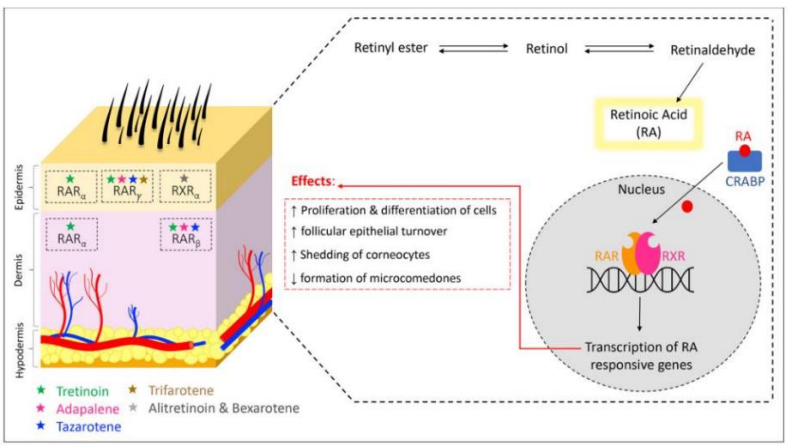
PHOTO 4: P. BERBIS, Retinoides, EMC - Dermatología,Volume 43, Issue 3,2009,Pages 1-18,ISSN 1761-2896,https://doi.org/10.1016/S1761-2896(09)70343-7.

Retinal is widely recognized as an effective route for administration to the skin, since it significantly limits systemic absorption, reducing the risk of relevant toxic adverse effects (Kang et al., 2005). It is not yet fully understood how retinal is internalized by keratinocytes, and this process remains under investigation. The biotransformation of retinal in epidermal cells appears to be related to both its chemical structure and the stage of cell differentiation, with metabolism being more active in the initial phases of keratinocyte maturation (Zasada & Budzisz, 2019).

MECHANISMS OF ACTION

Retinal conversion is mediated by the enzyme retinaldehyde dehydrogenase (RALDH), highly expressed in epidermal keratinocytes, where biotransformation occurs slowly and in a regulated manner. This enzymatic control prevents the abrupt accumulation of intracellular retinal, which explains the low irritability of retinal compared to tretinoin. Retinoic acid derived from retinal interacts with nuclear receptors known as RAR (Retinoic Acid Receptors) and RXR (Retinoid X Receptors) present in keratinocytes.

These receptors form heterodimers (functional complex) that bind to retinoic acid-responsive elements (RAREs) in DNA, transcriptionally regulating the expression of genes involved in the processes of differentiation, cell proliferation, epidermal thickening (granular and spinous layers) and the integrity of the skin barrier. This epigenetic modulation induces the renewal of the stratum corneum and restores the organization of the epidermal layers. (BERARDESCA et al., 2007).



I. Biological pathway of natural retinoids and target sites of synthetic retinoids.

PHOTO 5: Retinoic acid and retinoid receptors: potential chemopreventive and therapeutic role in cervical cancer, Abu, Jafaru et al. The Lancet Oncology, Volume 6, Issue 9, 712 - 720

In fibroblasts, retinal-induced retinoic acid also activates RAR/RXR receptors, promoting the expression of genes responsible for the synthesis of collagen types I and III, and consequent remodeling of the extracellular matrix (ECM).

In addition to directly activating genes linked to cell differentiation and epidermal renewal, retinoids also modulate gene expression through indirect pathways. A well-established example in the literature is their ability to suppress the activity of the transcription factor AP-1, known to stimulate the production of collagenases and other enzymes involved in the degradation of the dermal matrix.

The inhibition of this factor, promoted by retinoids, contributes to the reduction of collagen degradation and preservation of the dermal structure, which justifies their use in strategies for preventing and treating skin aging (Fisher et al., 1996). This anabolic effect contributes to increased dermal firmness and improved density of the dermoepidermal junction, which are essential in combating structural skin aging (VARANI et al., 2000).

Furthermore, scientific evidence, such as that presented by Saurat et al. (1994), demonstrates that topical use of retinaldehyde is effective in inducing epidermal thickness, promoting relevant clinical benefits, such as improved skin texture, reduction of fine lines and strengthening of the skin barrier function.

These effects are also noticeable in sensitive individuals, in whom retinaldehyde has a more favorable tolerance profile than retinoic acid. Studies have shown that retinal has an indirect effect on inflammatory mediators, suggesting an immunomodulatory potential. This property may be especially useful in the treatment of dermatological conditions characterized by persistent subclinical inflammation, such as acne and rosacea.

COMPARISON BETWEEN RETINOIDS

1. Retinol x Retinal
While retinol requires two enzymatic conversions to become retinoic acid, retinal requires only one. Fluhr et al. (1999) state that the enzymatic limitation of retinol compromises its clinical efficacy, making retinal more potent and efficient.

2. Retinal x Retinoic Acid
Retinoic acid acts directly on nuclear receptors, but with a high incidence of adverse reactions such as erythema and desquamation. In a clinical trial conducted by Creidi et al. (1998), it was observed that retinal has comparable efficacy to retinoic acid in the treatment of photoaging, with less irritability.

CLINICAL APPLICATIONS
1. Photoaging
Diridollou et al. (1999) reported that topical use of retinal promotes increased epidermal thickness and improved collagen density, promoting elasticity and reducing fine wrinkles.

2. Hyperpigmentation
Euvrard et al. (2001) showed that retinal modulates melanocyte activity and improves the appearance of hyperpigmented spots, such as melasma and solar lentigines, with good tolerance.

3. Acne vulgaris
Saint-Léger et al. (1995) observed that retinal has antibacterial action against Cutibacterium acnes and reduces follicular obstruction, being effective in controlling inflammatory and comedonal acne. Vahlquist (2001) reinforces its role in normalizing keratinization.

ANTI-AGING THERAPEUTIC STRATEGY
Topical therapy with retinoids should be initiated gradually, with concentration and frequency adapted to individual tolerance. Nighttime home care use is recommended, due to the photosensitivity of the compound, associated with the daily use of broad-spectrum sunscreen. Strategies such as "alternate-day application" and the "retinoid sandwich" method (hydration before and after the retinoid) are useful to minimize adverse effects such as erythema, flaking and burning (DAHICHE et al., 2022).

SAFETY AND TOLERABILITY

The great advantage of retinaL lies in its safety profile. Fluhr et al. (1999) demonstrated that the compound does not cause skin barrier dysfunction or marked photosensitivity, even with prolonged use. Vienne et al. (1999) also observed the absence of relevant irritant reactions in long-term treatments.

FINAL CONSIDERATIONS

In view of the molecular mechanisms already established, retinaldehyde (retinal) stands out as a retinoid with high therapeutic performance and remarkable skin tolerance. Its gradual and enzymatically controlled conversion into retinoic acid avoids the irritative peaks common to other retinoids, allowing efficient, yet modulated, activation of cellular pathways involved in epidermal renewal and dermal matrix remodeling.

More recently, it has been observed that the effects of retinal go beyond the simple regulation of cell proliferation: its action also appears to influence epigenetic mechanisms, interfering in gene expression without altering the DNA sequence. Through the modulation of histones and the methylation of gene promoters, retinal can contribute to the functional reprogramming of keratinocytes and fibroblasts, restoring intercellular communication and the balance of the skin microenvironment.

This type of action represents a significant advance, as it allows for more stable and sustainable cellular responses, even after treatment is discontinued. The combined action on keratinocytes and fibroblasts favors not only the integrity of the epidermal barrier, but also increases firmness and improves skin texture — essential factors in protocols aimed at rejuvenation. Combined with its safety profile, this retinoid has been gaining ground in dermatology and aesthetic practices as a versatile tool, especially indicated for patients seeking progressive, long-lasting results with minimal irritation.

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