

An overview about Therapeutic uses, clinical efficacy, safety and classes of Retinoids and its efficacy for Treatment of skin aging

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Abstract—Skin aging has both underlying and extraneous factors. the outermost organ of the human body, the skin suffers from environmental damage to agents such as air pollution and cigarette smoking, the resulting skin aging is called extraneous aging, which is also known as photoaging or the exposure to sunlight via UV radiation. Retinoid refers to the synthetic and natural analogues of vitamin A. Retinoids are a class of compounds derived from vitamin A or showing structural and/or functional similarities to vitamin A. Retinoids as dermatological agents that are widely applied in cosmetics and effective against acne, psoriasis, skin aging, and other skin conditions. Their susceptibility to degradation is a limiting factor for their widespread use, In other words; retinoid concentration in cosmetics is restricted, and one particular form—retinoic acid, is banned due to safety reasons. These include retinol, retinal, tretinoin (retinoic acid), isotretinoin, and alitretinoin, etretinate, adapalene, bexarotene, tazarotene, and Trifarotene. The aim of this review is to introduce the different uses of different types of retinoid in cosmetic and dermatological treatments

Keywords— Retinoids, skin, photoaging, vitamin A

I. INTRODUCTION

Skin aging has both underlying and extraneous factors [1]. underlying aging occurs not only on the skin, but also on all tissues[2]. At the same time, as the outermost organ of the human body, the skin suffers from environmental damage to agents such as air pollution and cigarette smoking, the resulting skin aging is called extraneous aging, which is also known as photoaging or the exposure to sunlight via UV radiation [3]. Skin that only undergoes underlying aging is

usually present in hidden areas about sunlight, and photoaging can be thought of as a superposition of chronological skin aging by UV radiation. Both underlying and extraneous aging can lead to a decrease in the structural integrity of the skin and loss of physiological function [4]. Reactive oxygen species (ROS) induce and accelerate the aging process including skin aging, although the presence of small amounts of ROS has been proved to play a beneficial role in maintaining the health of the body or cells, such as activating cyclooxygenase and lipoxygenase, regulating inflammatory process and so on [5]. ROS is continuously produced as a byproduct of the mitochondrial aerobic metabolism electron transport chain and considered to be the main cause of underlying aging in addition to hereditary factors. Similarly, the occurrence of photoaging is also associated with the production of ROS. As the most dangerous component of the sun, UV can cause an increase in ROS, damage the structure and function of cells, and mediate inflammatory responses [6]. ROS activate a myriad of signaling pathways that result in reduced collagen production, synthesis and activation of matrix metalloproteinases (MMPs) responsible for degrading connective tissue, secretion of senescence-associated secretory phenotype (SASP) which ultimately promote aging of skin [7].

Retinoid refers to the synthetic and natural analogues of vitamin A. Retinoids are a class of compounds derived from vitamin A or showing structural and/or functional similarities to vitamin A [8-9].

The body obtains vitamin A from two sources: preformed vitamin A (retinol and retinal in the form of retinyl esters), and



provitamin A carotenoids (beta carotene, alpha carotene, beta cryptoxanthin). Preformed vitamin A is found in cod liver oil, butter, eggs, animal products, and fortified grains. Provitamin A carotenoids are found in highly pigmented vegetables such as carrots, squash, yams, and green leafy vegetables. Once in the body, retinol is ultimately converted into retinoic acid and its isoforms, collectively known as retinoids [10-11].

Retinoids as dermatological agents that are widely applied in cosmetics and effective against acne, psoriasis, skin aging, and other skin conditions. Their susceptibility to degradation is a limiting factor for their widespread use, In other words; retinoid concentration in cosmetics is restricted, and one particular form—retinoic acid, is banned due to safety reasons [12-13].

Retinoids are molecules that can bind to and activate the appropriate nuclear receptors and to induce transcription of relevant genes either directly or after metabolic transformation [12].

These include retinol, retinal, tretinoin (retinoic acid), isotretinoin, and alitretinoin, etretinate, adapalene, bexarotene, tazarotene, and Trifarotene [14-15], [16].

The aim of this review is to introduce the different uses of different types of retinoid in cosmetic and dermatological treatments.

II. PROCESS OF SKIN AGING

A. Underlying aging

Underlying aging regulated by inherited factors affects all sections of the skin. underlying aging has obvious characteristics, such as thinning, dryness, fine wrinkles, insufficient sweating, and increased sensitivity to temperature. The thinning of the epidermis leads to a decrease in skin barrier function, in part due to a decrease in the proliferation and renewal ability of keratinocytes and a reduction in the number of epidermal stem cells [17-18].

During the underlying aging process, the number of dermal fibroblasts reduced, and the synthesis ability of collagen and elastin in ECM is decreased, especially for type I and III collagen, which is thought to cause the thinning of dermis, the increase of wrinkles and the loss of elasticity, making the skin fragile. The production of sebum decreases with age, especially in postmenopausal women, In addition, chronic itching is very common in aging skin, suggesting that the loss of age-related Merkel cells causes the sense of touch to turn to itching [19].

In recent years, the mechanisms underlying environmentally-induced skin aging have been intensively studied. One concept emerging from this research explains extrinsic skin aging as the result of primary processes that are initiated at the level of the dermis, where, as a consequence of environmental damage, macromolecular damage accumulates causing resident cells to become senescent [20].

In this regard, the dermis is particularly susceptible because it represents a postmitotic tissue consisting of fibroblasts and relying on adaptation and damage repair for homeostasis [21].

This process is caused by:
A- Air pollution: Air pollution-induced health effects are relevant for skin pigmentation and related skin aging traits as well as for skin wrinkle formation. Current knowledge is

consistent with the concept that pigmentation-associated skin aging traits (e.g., lentigines) are primarily related to the exposure to diesel exhaust particles [22-23]. Also gases such as nitrogen dioxide (NO₂) [24] and ground-level ozone can lead to air pollution [25].

B-Photoaging:

Major arguments include epidemiological evidence that chronic exposure to sunlight is associated with clinical hallmarks of skin aging [26].

That regular use of sunscreens is effective in reducing the histopathological and clinical signs of skin aging [27].

Animal studies that demonstrate the generation of skin wrinkles in chronically UV-irradiated mouse models [28].

C- Cigarette smoke is another exposomal factor that contributes to extrinsic skin aging [29]. The major skin-aging effect of cigarette smoke is skin wrinkling, particularly around the mouth, the upper lid, and eyes [30]. The accumulation of collagen breakdown products is a hallmark of aging skin and results in a decrease in mechanical tension that leads to wrinkles. Age-related differences in the amount and structure of proteoglycans that bind to collagen also determine the mechanical properties of the skin [31].

III. TYPES OF RETINOIDS

First generation retinoids are natural and have the closest structure and function to vitamin A. These include retinol, retinal, tretinoin (retinoic acid), isotretinoin, and alitretinoin. While naturally occurring, their use as therapeutic agents are associated with the most toxic effects compared to newer generations, which have been modified to increase their tolerability [14].

Second generation retinoids are synthetic (man-made) and have similar chemical structure to first generation retinoids. These include etretinate and its metabolite acitretin. These activate all types of retinoic acid receptors but bind poorly to them and are more easily eliminated from the body than first generation retinoids, making them more tolerable [14-15].

Third generation retinoids are structurally designed to bind more specifically and effectively with certain retinoic acid receptors (such as retinoid X receptors) and include adapalene, bexarotene, and tazarotene. By targeting specific types of retinoic acid receptors, these have useful clinical applications in cutaneous T-cell lymphoma and psoriasis, among other dermatologic conditions [14-15].

Fourth generation retinoid called Trifarotene was designed to be even more potent and selective for particular kinds of retinoic acid receptors, which makes it more effective with decreased skin irritation and a more tolerable safety profile overall compared to previous generations [7-8].

IV. THERAPEUTIC USES

They are used in pharmacotherapy of diseases such as acne and rosacea, psoriasis, cancer, inflammation of hair follicles with bacterial aetiology, pyoderma, lupus erythematosus and ichthyosis [32-33]

V. MECHANISM OF ACTION

Retinoids are involved in the process of embryogenesis during development of the nervous system, liver, heart, kidneys, intestine, eyes and limbs [34]. Retinoids as a molecule that binds to and activates retinoic acid receptors through direct ligand-receptor binding, thereby eliciting transcription of retinoic acid responsive genes. Retinoids influence the proliferation and differentiation of cells. Their biological effects are mediated and regulated by cytosolic binding proteins and nuclear hormone receptors [35].

In The aging process : Vitamin A and its derivatives, particularly retinol, are substances slowing the aging process most effectively. Fat soluble retinol penetrates the stratum corneum and it slightly penetrates into the dermis. When retinol reaches a keratinocyte, it enters its interior and binds to an appropriate receptor [35-36]. Retinol stimulates the cellular activity of keratinocytes, fibroblasts, melanocytes and Langerhans cells. Retinol, by interacting with receptors inside keratinocytes, promotes their proliferation, strengthens the epidermal protective function, reduces transepidermal water loss, protects collagen against degradation and inhibits the activity of metalloproteinases which are responsible for degradation of the extracellular matrix. Moreover, it enhances remodeling of reticular fibers and stimulates angiogenesis.

In the papillary layer of the dermis: Irritant properties of vitamin A and its derivatives as well as their instability are factors that limit their application in cosmetic and pharmaceutical products [37].

In acne: Retinoid normalize abnormal desquamation by increasing follicular epithelial turnover and accelerating the shedding of corneocytes, leading to the expulsion of mature comedones and the suppression of microcomedone formation [38], Sebum suppression, P. acnes reduction—secondary to decrease in sebum and Anti-inflammatory [39].

In psoriasis: Vitamin A and its derivatives undergoes hydrolysis in the tissues for examole; Tazarotene undergoes hydrolysis in the tissues to tazarotenic acid, which then binds to the retinoic acid receptors. This receptor-ligand interaction results in the regulation and expression of retinoid-responsive genes, including those involved in cell proliferation and inflammation, a hallmark feature in psoriasis, a condition characterized by increased epidermal proliferation and inflammation [40-41] Acitretin mechanism of action has not been fully elucidated; however, it is known to have antiproliferative, anti-inflammatory, and anti-angiogenic effects. low-dose therapy of Acitretin continues to play a significant role in the management of resistant psoriasis and other keratinizing disorders [42-43].

VI. RETINOIDS CLASSES:

a-Tretinoin Retin-A® also known as all-trans retinoic acid (ATRA) have been shown to reverse photoaging. Tretinoin 0.05% cream was approved for the treatment of photodamaged skin in the mid 1990s and has been shown to improve fine wrinkles via increased collagen production [44-45].

Some previous studies published that 0.1% topical tretinoin reduced the effects of photo-ageing maximally after 10 months, with no further improvements if treatment was continued until 22 months. It decreases the number and activity of melanocytes, and possibly induced angiogenesis, also it activate epidermal hyperplasia, compaction of the stratum corneum and the deposition of ultrastructurally visible collagen fibrils in the papillary dermis [46].

Tretinoin happens to be the retinoid that is investigated firstly implicated in the treatment of photoaging. Studies involving tretinoin treatment for more than 6 months. The ability of long-term (more than 6 months) tretinoin treatment to maintain improvement in photoaging was first evaluated by [47] in a 22-month study, All the subjects used 0.1% tretinoin for the first 4 months. Thereafter, It was observed that the improvement of wrinkling continued up to the 10th month and was maintained thereafter. The stratum corneum and epidermal thickness returned to the normal during the course of treatment. In another trial, [48] studied the effect of 0.05% tretinoin emollient cream applied daily for 12 months. Tretinoin treatment showed significant improvement in the clinical signs of photoaging. However, the major degree of changes occurred after 6 months and later on they tended to remain stable as observed in the earlier study. Extension of the study for 6 more months with either weekly or thrice weekly application showed further improvement in overall signs of photoaging .

b- Retinol Aquasol A® also called vitamin A1, Vitamin A alcohol or all-trans retinol is present in many cosmetics and cosmeceuticals at concentrations of 0.08% or less. Although retinol has lower potency than tretinoin, it can improve photodamage and stimulate collagen production without the irritation associated with retinoic acid [49].

Vitamin A alcohol belong to the family of endogenous natural retinoids and is a precursor for synthesis of endogenous retinal and retinoic acid. Previous studies showed that application of all-trans-retinol on normal human skin induces epidermal thickening and keratinocyte proliferation, as does retinoic acid. it was observed that retinol is 20 times less potent than tretinoin and it requires further conversion to retinoic acid (in vivo) to demonstrate its action [50-51]. first conducted a controlled clinical trial with retinol formulation. They observed that retinol formulation resulted in significant improvement in fine wrinkles after 12 weeks of treatment. Subsequently, other researchers studied the effect of topical application of 1% retinol in 53 individuals (80 years or above) with aged skin [52]. Thus, it can be concluded that retinol should be effective in the treatment of aging and photoaging. However, the vehicle used for retinol delivery would play a crucial role in eliciting its efficacy, as retinol is extremely unstable and easily gets degraded to biologically inactive forms on exposure to light and air .

c- tazarotene Tazorac® is a novel acetylenic retinoid known to be effective in the topical treatment of mild to moderate plaque psoriasis, acne vulgaris and photoaging.. Tazarotene is a prodrug, rapidly metabolized to its active metabolite tazarotenic acid. they are effective in monotherapy, clinical studies with a focus on novel combination treatments and a comparison of different agents for these skin disorders are accumulating . The concomitant use of tazarotene with a mid-potency or high-potency corticosteroid enhances the efficacy in psoriatic plaques and reduces the risk of steroid-induced skin atrophy. Combining phototherapy with adjunctive tazarotene accelerates the clinical response and reduces the cumulative UVB or PUVA exposure load. Tazarotene applied once daily is superior to adapalene monotherapy in acne vulgaris and is efficacious in the treatment of photodamage. Novel therapeutic regimens such as short-contact therapy have been developed for both acne and psoriasis in order to diminish the major adverse events like pruritus, burning, local skin irritation and erythema [53-54].

Due to its rigid polyaromatic structure, it does not undergo any isomerization or conformational change in the skin. Tazarotenic acid modulates the expression of retinoid-responsive genes, including those that regulate cell proliferation, cell differentiation, and inflammation, corresponding to its binding capacities to various RAR receptors. Tazarotene also down-regulates the abnormal expression of keratinocytes, epidermal growth factor receptor, and hyperproliferative keratins [55-56].

d- Adapalene (Differin®)

Adapalene is considered to be a third-generation synthetic retinoid which contains a naphthoic acid backbone. is a retinoid agent indicated for the topical treatment of acne vulgaris. Adapalene has a rapid onset of action and a particularly favourable tolerability profile compared with other retinoids. Adapalene is thought to modulate keratinisation, differentiation and inflammation of follicular epithelial cells. This results in a reduction in microcomedones, the precursors of acne lesions [57]. Absorption of 0.1% adapalene gel through human skin is low, There are no known interactions with other drugs and, because of the low absorption through the skin, interaction with systemic drugs is unlikely [58]. The most commonly reported adverse events in both adapalene and comparator recipients were erythema, dry skin, pruritus, desquamation and stinging/burning sensations [59]. Unlike retinoic acid, adapalene shows selectivity for the nuclear retinoic acid receptor (RAR β/γ). It targets abnormal desquamation of the skin, modulates cellular differentiation, and possesses anti-inflammatory properties [60]. Moreover, due to its receptor selectivity, it causes less skin irritation. Adapalene is successfully being used for the treatment of acne. However, not much has been done to investigate its potential in aging/photoaging. So far only one study has been carried out to determine the potential of adapalene in photoaging [61].

7- Examples of formulation of retinoid and other

1-The cosmeceutical emollient **4% hydroquinone/0.3% retinol** cream more effectively diminished the collective signs of photodamage than 0.05% tretinoin emollient cream in terms of dyspigmentation, fine wrinkles, and tactile roughness in 16 weeks [62].

2- The topical combination of (0.1% AHA-RC, 2% salicylic acid, and 10.4% l-lactic acid), with broad-spectrum SPF 50+ sunscreen as needed, over an 8-week period produced acne improvement after 4 weeks with continuing cumulative improvement at 8 weeks. AHA-RC represents a new molecule combining several mechanisms of action to achieve acne improvement [63].

3- The combination of 5% SAP and 0.2% retinol treatment was the most effective in reducing inflammatory lesions. The synergistic effect of these two active ingredients results in the potent remedy of acne vulgaris [64].

4- Combined therapy with both topical tretinoin and erythromycin is more effective than either alone. During the first weeks of treatment of acne, tretinoin leads to temporary deterioration of the disease, which can mostly be avoided by the anti-inflammatory effect of erythromycin simultaneously applied [65].

5- The combination regimen that alternates between tazarotene and a high-potency topical corticosteroid treatment each day, significantly increased the treatment success rate, In addition, there was a trend towards a lower incidence of treatment-related adverse events [66].

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