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Comparative Analysis of Retinoid Generations in the Management of Skin Photoaging

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Abstract. *Retinoids constitute the most thoroughly researched group of topical agents in dermatological anti-aging treatments due to their significant effects on epidermal cell proliferation, differentiation, and dermal extracellular matrix remodeling. This review comprehensively evaluates the pharmacological classification, mechanisms of action, clinical efficacy, safety profiles, and formulation-related issues of natural and synthetic retinoids used in the management of skin aging. Tretinoin, a first-generation retinoid, is still considered the gold standard, particularly in the improvement of photo-aged skin, thanks to strong clinical evidence; however, its use is often limited due to dose-dependent irritation. Although metabolic precursors such as retinol and retinaldehyde offer higher tolerability, their clinical success largely depends on enzymatic conversion capacity and formulation stability. Retinyl esters, frequently used in cosmetic products, show limited and variable clinical results and also raise additional concerns regarding photodegradation and potential pro-oxidant effects. While second-generation retinoids are not currently widely preferred in topical anti-aging applications, third-generation retinoids such as adapalene and tazarotene demonstrate similar efficacy to tretinoin but offer more selective receptor interaction and, in some cases, faster clinical responses. Although fourth-generation retinoids such as tripharotene and seletinoid G have shown promising results in preclinical studies, clinical data on their effects on photoaging are still insufficient. One of the key factors determining the effectiveness of retinoids is formulation technology; stability problems and limitations in skin penetration significantly affect treatment outcomes. While newly developed nanoformulation systems have the potential to increase efficacy and reduce irritation, clinical evidence in this area is still limited. Consequently, while tretinoin remains the reference standard, new generation retinoids and advanced delivery systems may offer more advantageous therapeutic profiles. However, more extensive controlled clinical trials are needed to clarify the long-term efficacy, safety, and comparative superiority of these agents.*

Keywords: *retinoids, skin aging, photoaging, topical anti-aging therapy, nanoformulations*

Introduction

Skin aging is the result of complex molecular and cellular changes caused by internal and external factors, manifesting with noticeable clinical findings such as wrinkle formation, thinning of the dermal layer, and loss of elasticity. These changes lead to progressive degeneration of the skin structure and a decrease in the functional components of the skin over time (Shin et al., 2019; Zhang & Duan, 2018).

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While chronological aging is considered part of the natural biological process, photoaging, caused by ultraviolet (UV) radiation, is considered the main external factor accelerating skin aging through the excessive production of reactive oxygen species (Ganguly et al., 2022).

In recent years, anti-aging dermatological applications have received intense scientific and clinical attention due to comprehensive approaches aimed at restoring skin structure, improving skin texture, and enhancing aesthetic appearance. Among these treatment options, topical retinoids are among the most researched and clinically proven agents. Current photoaging prevention and treatment strategies are mostly based on regular photoprotection, sunscreen use, and the combined application of topical preparations containing retinoids and antioxidants (Zasada & Budzisz, 2019).

Retinoids are a broad group of natural and synthetic compounds that show structural similarity to retinol (vitamin A). The anti-aging effects of topical retinoids are explained by various biological mechanisms such as increasing keratinocyte proliferation, supporting collagen synthesis, strengthening epidermal barrier function, reducing transepidermal water loss, suppressing collagen degradation, and inhibiting matrix metalloproteinase activity (Zasada & Budzisz, 2019).

The biological effects of retinoids occur via nuclear retinoic acid receptors (RAR-α, RAR-β, RAR-γ) and retinoid X receptors (RXR-α, RXR-β, RXR-γ) (Shin et al., 2019). Based on their molecular structure and receptor binding properties, retinoids are generally classified into four different generations, and this classification is summarized in Table 1.

Table 1
Classification of Retinoids According to Generation and Representative Compounds

Retinoid Generation	Structural Characteristics	Representative Compounds	Key Features
First-Generation Retinoids	Naturally occurring retinoids and closely related non-aromatic derivatives with flexible molecular structures	Tretinoin (all-trans-retinoic acid); Isotretinoin (13-cis-retinoic acid); Alitretinoin (9-cis-retinoic acid); Retinol (all-trans-retinol, vitamin A); Retinal (retinaldehyde); Retinyl palmitate; Retinyl propionate; Retinyl acetate; Retinyl retinoate; Retinyl N-formyl aspartamate	Exhibit broad receptor activity and are widely used in dermatological and cosmetic formulations
Second-Generation Retinoids	Monoaromatic retinoids produced through structural modification of the cyclic end group	Etretinate; Acitretin; Motretinate	Characterized by enhanced chemical stability and improved pharmacokinetic properties
Third-Generation Retinoids	Polyaromatic retinoids with greater receptor selectivity and reduced adverse effects	Tazarotene; Adapalene; Bexarotene	Designed to increase therapeutic specificity while minimizing irritation and systemic toxicity
Fourth-Generation Retinoids	Selective receptor-targeting retinoids developed using advanced molecular engineering approaches	Trifarotene; Seletinoid G	Demonstrate highly selective receptor affinity and improved tolerability profiles in topical therapy

Following topical application, retinyl esters are converted to retinol via enzymatic hydrolysis, and then retinol is converted to the biologically active metabolite retinoic acid (tretinoin) through a two-step oxidation process via retinaldehyde by dehydrogenase enzymes (Riahi et al., 2016).

Considering the metabolic conversion steps, the biological efficacy of first-generation retinoids increases gradually from retinyl esters to retinoic acid: retinyl esters << retinol < retinaldehyde < retinoic acid. Conversely, the tolerability profile progresses in the opposite direction; the highest tolerance is observed with retinyl esters, and the lowest with retinoic acid: retinyl esters > retinol = retinaldehyde >> retinoic acid.

Therefore, topical preparations containing retinol, retinaldehyde, and retinyl ester require metabolic conversion within the skin to form the active form, tretinoin. In contrast, some retinoids can exhibit biological activity directly in their applied form without requiring additional biochemical conversion.

Tretinoin, alitretinoin, adapalene, tazarotene, bexarotene, and tripharotene are included in approved topical pharmaceutical formulations used in the treatment of various dermatological diseases such as acne and psoriasis. Among these agents, tretinoin and tazarotene are the main retinoids approved for the adjunctive treatment of photo-aged skin.

In contrast, commercial cosmetic and cosmeceutical products mostly use retinol, retinaldehyde, and retinyl esters. The concept of cosmeceuticals defines cosmetic products containing biologically active ingredients intended to exert pharmacological effects on skin structure and function, forming an intermediate category between traditional cosmetics and prescription topical drugs. However, unlike pharmaceutical products, cosmeceuticals generally undergo more limited pre-marketing evaluations in terms of safety and clinical efficacy (Tetali et al., 2020).

Since retinoids in cosmeceutical products need to be converted to tretinoin in the skin to become biologically active, the effectiveness of these products remains a subject of scientific debate when compared to formulations containing directly active tretinoin (Resende et al., 2022).

Although retinoids are among the important anti-aging and depigmenting agents widely used in modern cosmetic formulations, they present various formulation challenges due to limited skin penetration, chemical stability problems, and irritation potential related to their physicochemical properties. Adverse effects associated with topical retinoid use are mostly dose-dependent and manifest as "retinoid dermatitis," characterized by erythema, dryness, desquamation, and irritation at the application site (Szymański et al., 2020).

One of the significant safety concerns regarding retinoid use is their potential teratogenic effects. Although the teratogenicity of oral retinoids has been clearly established, evidence regarding retinoid-induced embryopathy after topical use is largely based on limited case reports. However, despite the lack of definitive evidence of harm, the current clinical approach is cautious, and the use of topical retinoids during pregnancy is generally not recommended due to insufficient safety data.

The mechanisms of retinoid-induced side effects at the molecular level have not yet been fully elucidated. In clinical practice, it is recommended to prefer low-concentration preparations and to discontinue treatment if skin intolerance develops. Furthermore, it has been reported that first-generation retinoids with non-selective receptor activity cause skin reactions more frequently than later-generation retinoids (Williams et al., 2020).

Tretinoin (all-trans-retinoic acid) is considered one of the most reliable topical retinoids for anti-aging, thanks to its potent therapeutic effect and extensive clinical study support. It is one of the most thoroughly researched retinoids in the field of dermatology. Topical formulations typically range from 0.01% to 0.1%, with the most commonly preferred concentrations being 0.025%, 0.05%, and 0.1%. These prescription preparations are widely used in the treatment of acne vulgaris, facial photoaging, and hyperpigmentation. Clinical studies have shown that tretinoin provides significant benefit in reducing signs of sun-induced skin aging (Darlenski et al., 2010).

In a two-year placebo-controlled study involving 204 individuals with moderate to severe facial photodamage, a moisturizing cream containing 0.05% tretinoin applied daily was found to be effective and safe with long-term use. Although a 0.05% concentration is often preferred in clinical practice, the appropriate dose and duration of treatment should be adjusted according to the patient's skin tolerance and the desired clinical outcome. General assessments report that 0.025% preparations offer more balanced results in terms of efficacy and tolerability (Darlenski et al., 2010).

The clinical success of tretinoin is directly related to the concentration used. Comparative studies show that lower doses provide significant clinical and histological improvement, albeit at a milder level, while also reducing the risk of side effects. Therefore, treatment is usually started with low doses, and the dose is gradually increased according to skin tolerance. Furthermore, its use in conjunction with moisturizing products is recommended to reduce irritation and support the skin barrier (Buchanan & Gilman, 2016).

In recent years, various nanoformulation technologies have been developed for tretinoin, such as liposomes, nanoemulsions, and lipid-based nanocarrier systems. While the majority of research focuses on controlled drug release and in vitro permeability, some studies have also evaluated irritation in rat and rabbit models (Liu et al., 2021). The findings indicate that these systems provide better stability compared to classical formulations, aid in more controlled drug release, and can reduce skin irritation (Pinto et al., 2019).

The main goal in developing nanoformulation-based tretinoin delivery systems is to increase product stability, improve safety profile, and enhance patient compliance (Lima et al., 2021). However, despite positive research results, there is currently no commercially available nanoformulated tretinoin product.

Isotretinoin, a cis-isomer of retinoic acid, is a retinoid used particularly in acne treatment in systemic capsule form and is associated with various side effects, primarily mucocutaneous dryness (Abdelmaksoud et al., 2020). Current studies show that topical isotretinoin application in skin with signs of aging due to sun damage; Studies show that it can significantly improve fine wrinkles, pigmentation irregularities, and skin texture.

Topical isotretinoin, despite its positive clinical effects, has some limitations in terms of use due to its potential to cause skin irritation and its low physicochemical stability. Although various nanoformulation approaches have been developed to mitigate these problems, the majority of current studies focus on acne treatment rather than photoaging (Gupta et al., 2020).

Alitretinoin, on the other hand, is a pan-agonist retinoid that can bind to all retinoic acid receptors and retinoid X receptors. A 0.1% topical alitretinoin gel has received approval for use in the treatment of cutaneous Kaposi's sarcoma. However, data on its effects on photoaged skin are quite limited and supported only by a 16-week open-label pilot study with 20 participants (Cheng et al., 2008). Although some improvement in skin parameters was observed in the study, the high rate of reported side effects limits the use of this agent in anti-aging treatments.

Retinol is a versatile retinoid that shows positive effects on photoaged skin. Hyaluronic acid contributes to improved skin structure by increasing collagen and elastin synthesis, as well as supporting epidermal proliferation and cellular differentiation (Li et al., 2017; Romana-Souza et al., 2019).

Among retinoids used in cosmetic products, retinol is one of the most thoroughly studied compounds in randomized, double-blind, and carrier-controlled trials. Clinical trials involving whole-face and

split-face designs have evaluated different concentrations ranging from 0.075% to 0.5%, but results have varied (Spierings, 2021).

The main factors that complicate the interpretation of these studies include differences in study designs, the variability in retinol concentrations used, and potential conflicts of interest in industry-sponsored research. Therefore, it is still uncertain to what extent the reported positive results reflect the true clinical efficacy of retinol-containing products.

To better assess the efficacy of retinol, direct comparisons with tretinoin have been made in many studies. The findings showed no statistically significant difference between retinol and tretinoin-based formulations in terms of the evaluated clinical parameters (Table 2).

In a more recent 12-week randomized, double-blind, controlled study, three different retinol serums were compared with equivalent tretinoin cream concentrations. The study employed a dose escalation protocol where application frequency and concentration were gradually increased to improve tolerability, and the use of moisturizers was also encouraged (Babcock et al., 2015). Overall, the results indicated that retinol-containing formulations showed similar, and even superior, clinical performance in some parameters compared to tretinoin-based products.

Table 2
Comparative Clinical Studies of Topical Retinoids in Facial Anti-Aging Treatment (Tretinoin vs. Other Retinoids)

Retinoid	Study design	Duration	Subjects	Comparison	Evaluated parameters	Main outcomes	References
Retinol	Randomized, double-blind, split-face study	12 weeks	65	Retinol 0.25%, 0.5%, 1.0% vs tretinoin 0.025%, 0.05%, 0.1%	Photodamage, fine/coarse wrinkles, skin tone, pigmentation, roughness	Significant improvement from baseline in all parameters; no significant differences between groups	(Babcock, 2015)
Retinol	Randomized, parallel, double-blind, whole-face controlled study	3 months	120	Retinol 0.2% + tetrahydrojasmonic acid 2% vs tretinoin 0.025%	Wrinkles, pores, pigmentation, global photodamage, 3D skin profiling	Both treatments improved skin parameters; no significant differences observed	(Bouloc, 2015)
Retinol derivatives	Double-blind, parallel-arm, whole-face study	24 weeks	24	Retinol (1%) + retinyl acetate (0.05%) + retinyl palmitate (0.05%) vs tretinoin 0.02%	Wrinkles, pigmentation, global photodamage (Griffiths scale)	Comparable efficacy; no significant differences	(Chien, 2022)
Retinaldehyde	Randomized, double-blind, vehicle-controlled study	44 weeks	125	Retinaldehyde 0.05% vs tretinoin 0.05% vs vehicle	Wrinkle depth, skin roughness (optical profilometry)	Both active treatments significantly improved skin; no differences between groups	(Kwon, 2018)
Retinaldehyde (nanoformulation)	Randomized, double-blind, split-face study	12 weeks	30	Retinaldehyde hydrogel (0.025%) vs tretinoin 0.025%	Wrinkles, fine lines, texture parameters (surface, entropy, contrast, etc.)	Nano-retinaldehyde showed superior anti-aging effects	(Pisetpackdeekul, 2016)

Adapalene	Multicenter, randomized, investigator-blinded study	24 weeks	128	Adapalene 0.3% gel vs tretinoin 0.05% cream	Global photodamage, wrinkles, pigmentation, actinic keratoses	Significant improvement in both groups; no significant differences	(Bagatin, 2018)
Tazarotene	Randomized, multicenter, vehicle-controlled study	24 weeks	349	Tazarotene 0.01–0.1% vs tretinoin 0.05% vs vehicle	Multiple photodamage signs (wrinkles, pigmentation, roughness, elastosis)	Both agents effective; 0.05% tazarotene ≈ tretinoin; 0.1% most effective	(Kang, 2001)
Tazarotene	Multicenter, double-blind, randomized study	24 weeks	173	Tazarotene 0.1% vs tretinoin 0.05%	Wrinkles, pigmentation, elastosis, actinic damage	Faster and stronger improvement with tazarotene 0.1%	(Liu, 2020)

In a separate 12-week clinical trial conducted on 41 healthy female volunteers, a formulation containing 0.1% retinol was shown to reduce the severity of facial wrinkles using imaging-based analysis methods. However, the absence of a control group in the study limits the scientific strength of the results obtained (Kong et al., 2016).

Retinol is frequently formulated with different bioactive components to enhance therapeutic efficacy and achieve potential synergistic effects. Bouloc et al. (2015) compared a commercial preparation containing 0.2% retinol and 2% tetrahydrojasmonic acid with a 0.025% tretinoin cream. The study results showed that both treatments demonstrated similar levels of efficacy, while the retinol-based formulation was reported to be better tolerated and more positively evaluated by users (see Table 2).

Nevertheless, clinical data supporting the efficacy of retinol still have some methodological limitations. In particular, small sample sizes, short follow-up periods, and the lack of carrier-controlled studies reduce the reliability of the current findings. This is important because the carrier systems themselves can improve skin appearance and thus affect the actual efficacy results (Spierings, 2021). However, the number of properly designed carrier-controlled studies in this area is quite limited.

One of the most significant problems with retinol is its low stability. Retinol is a highly sensitive compound that can easily degrade under the influence of light, oxygen, high temperatures, and trace metals. A recent evaluation of 12 commercial products containing retinoids revealed significant stability losses under both long-term and accelerated storage conditions, and showed degradation in most of the products studied. Under ideal production conditions — use of inert atmospheres, appropriate packaging such as aluminum tubes, and storage below 20 °C — retinol stability generally lasts less than six months. However, since these controlled conditions are often not achievable in daily use, questions arise regarding the consistency of results on the clinical effects of retinol. Furthermore, it is emphasized that each product should be evaluated individually, as the stability of retinoids largely depends on the formulation used (Temova Rakuša et al., 2021).

Quality control studies have also revealed significant discrepancies in retinol-containing cosmetic products on the market. In 35 products examined by researchers, serious discrepancies were found between the amount of retinoid stated on the label and the actual content; some products contained concentrations below therapeutic efficacy, while others contained concentrations above the recommended limits. Moreover, many cosmetic products do not explicitly state the amount of active ingredients. This situation highlights the need for stricter regulatory controls and improved quality control processes in retinol-containing cosmetics (Temova Rakuša et al., 2021).

To reduce retinol stability problems, intensive research is being conducted on nanotechnology-based carrier systems. In this context, various retinol-loaded nanoformulations have been developed. For example, solid lipid nanoparticles containing 0.5% retinol have been prepared using ultrasonication and integrated into gel systems. In vitro cytotoxicity and permeability analyses, as well as in vivo irritation tests performed on rats, have shown that these systems offer safe use and suitable application characteristics. The results support the idea that nanoformulations may be a promising approach for topical retinol applications (Boskabadi et al., 2021).

Despite these positive preclinical results, sufficiently robust and well-planned clinical trials evaluating the anti-aging effects of retinol-containing nanoformulations are still lacking.

Retinaldehyde

Retinaldehyde is a natural precursor form of retinoic acid and is considered one of the compounds with the best balance of efficacy and tolerability among retinoids used in cosmetic dermatology. Its conversion to retinoic acid depends on the state of cellular differentiation and occurs more efficiently, especially in mature keratinocytes.

Its low irritation potential is associated with the limited metabolic capacity of epidermal cells. After topical application, retinaldehyde does not bind directly to receptors; while the majority is converted to retinyl ester derivatives, only a small fraction is oxidized to retinoic acid, exhibiting biological activity. This controlled metabolism provides a significant advantage as it limits the irritation mechanism resulting from excessive receptor activation of retinoids, defined as "receptor overload." Thus, retinaldehyde, as a more stable precursor, reduces the risk of irritation.

In general, formulations containing 0.05% retinaldehyde are among the effective and well-tolerated options in anti-aging applications. Furthermore, the absence of a significant increase in systemic retinoid levels, even with long-term or higher doses, supports minimal systemic absorption (Kwon et al., 2018).

However, a significant disadvantage of retinaldehyde is its high sensitivity to both light and oxidation, meaning it has poor chemical stability (Pisetpackdeekul et al., 2016). Therefore, nanotechnology-based carrier systems have been developed to improve stability and ensure controlled release.

In vitro and in vivo studies show that proretinal nanoparticle systems can provide more effective and sustained release of retinaldehyde while maintaining a suitable safety profile (Limcharoen et al., 2020). However, despite these promising data, comprehensive clinical trials are still needed to definitively establish the efficacy and safety of retinaldehyde in different formulation systems.

Retinyl Palmitate

Retinyl palmitate (RP) is one of the most common retinyl esters naturally found in human skin. Due to its high thermal stability, it is preferred over retinol in many anti-aging cosmetic products. However, RP is more susceptible to photodegradation compared to retinol.

Under certain conditions, particularly when exposed to UV radiation, RP can exhibit pro-oxidant effects through processes such as photodegradation products, reactive oxygen species, and lipid peroxidation. Furthermore, some experimental studies suggest that topical products containing RP may enhance UV-related photocarcinogenesis (Farooq et al., 2018). However, the long-term clinical significance of these findings is not yet clear.

Based on current toxicological and regulatory data, RP is generally considered safe at recommended cosmetic concentrations. In terms of biological activity, 0.6% RP is estimated to have approximately half the efficacy of 0.25% retinol.

Despite its widespread use, there are not enough clinical studies conducted under standard conditions to evaluate the anti-aging effects of RP. Only one study comparing two commercially available RP-containing products exists in the literature, but the RP concentrations are not explicitly specified (Farooq et al., 2018). This indicates that existing studies are methodologically inadequate and lack standardization.

Despite this, RP continues to be widely used in cosmetic products. Current research focuses on improving stability and bioavailability through nanotechnology-based systems, microencapsulation approaches (Bradley et al., 2015), and combination formulations created with biopolymers such as pectin (Nandy et al., 2020; AlZahabi et al., 2019).

In general, nanoformulated RP systems show better stability, increased skin penetration, and reduced irritation potential. However, much of this data is based on preclinical studies, and a sufficient number of well-designed clinical trials are not available.

In conclusion, currently, there is no strong clinical evidence confirming the anti-aging efficacy of retinyl palmitate in either classical or advanced carrier systems. Despite its widespread use in cosmetics, RP is among the compounds whose anti-aging efficacy has not been sufficiently clinically proven.

Retinyl propionate is a retinyl ester derivative reported to exhibit higher retinoid activity in both in vitro and ex vivo settings compared to retinol and retinyl palmitate (Bjerke et al., 2021). Some research suggests that combination of this compound with other active substances may enhance anti-aging effects (Lam et al., 2021). However, there are currently no published studies examining the use of retinyl propionate in nanotechnology-based carrier systems. Given its potential biological activity, more comprehensive clinical and formulation research is needed to clarify its clinical value.

Retinyl acetate is another retinoid derivative widely used in cosmetic anti-aging products. Nevertheless, no clinical studies have yet evaluated its topical anti-aging efficacy alone. Although its potential cocarcinogenic effects in terms of photocarcinogenesis have been investigated, the current data are inconsistent, and its mechanistic effects are not fully elucidated. Retinyl retinoate is a hybrid retinoid structure obtained as a result of a condensation reaction between retinol and retinoic acid. This structure aims to increase light stability and reduce photodegradation. Compared to first-generation retinoid derivatives, it has been reported to have higher chemical stability and lower irritation potential, and can also support hyaluronan synthesis (Kim et al., 2010). Clinical data suggest that it may be effective in reducing fine wrinkles; however, due to the small sample size and methodological limitations of current studies, the results are not conclusive. Retinyl N-formyl aspartamate is a synthetic retinoid derivative that exhibits higher photostability and lower irritation potential compared to retinol. In a 24-week randomized, controlled, single-blind study with 24 participants, its topical use was reported to be well tolerated and resulted in significant improvement in clinical parameters compared to the carrier group (Lee et al., 2006). However, the small sample size limits the generalizability of the results. Overall, clinical evidence strongly supporting the anti-aging efficacy of retinyl esters such as retinyl palmitate, retinyl propionate, retinyl retinoate, and retinyl acetate is insufficient. Despite their widespread use in cosmetic products, high-quality studies confirming their therapeutic efficacy are still lacking.

Second-generation retinoids are not currently actively used in topical anti-aging treatments due to the development of more effective and better-tolerated alternatives (Motamedi et al., 2022). Therefore, their current clinical importance is quite limited.

Tazaroten
Tazaroten is a prodrug that is rapidly converted in the body to its active form, tazarotenic acid. It selectively exerts an agonist effect on retinoic acid receptors RAR-β and RAR-γ, while having no significant affinity for RXR receptors.

In clinical practice, tazaroten; Tazarotene is a prescription agent used in the treatment of acne and psoriasis at concentrations of 0.045%, 0.05%, and 0.1%. The 0.1% form is also approved as an adjunct in the treatment of fine wrinkles, pigmentation disorders, and lentigo associated with photoaging. Its efficacy and safety in sun-damaged skin are well-documented, and side effects are generally mild to moderate (Ogden et al., 2008).

Comparative studies with tretinoin have reported that tazarotene shows similar efficacy, but may cause a more frequent temporary burning sensation in the initial stages of treatment (Kang et al., 2001; Lowe et al., 2004). However, this effect is mostly short-lived.

In general, tazarotene offers comparable efficacy and tolerability profiles to tretinoin in the treatment of photoaging. Although theoretically it could be better tolerated due to its receptor selectivity, tretinoin is more widely used in clinical practice due to its longer history and cost advantage. Recent research on tazarotene has focused particularly on nanotechnology-based carrier systems and new dermatological applications (Liu et al., 2020).

Adapalene
Adapalene is a synthetic retinoid that selectively acts on retinoic acid receptors RAR-β and RAR-γ. Its 0.1% and 0.3% topical forms are used especially in acne treatment and are known for their good efficacy and tolerability profile. However, it also has off-label use in photoaging treatment (Rusu, 2020).

Bexarotene
Bexarotene is a retinoid that binds selectively to all subtypes of retinoid X receptors and has a complex mechanism of action. Clinically, it is approved in a 1% topical gel form for the treatment of stage IA and IB cutaneous T-cell lymphoma. To date, there are no clinical studies evaluating the use of bexarotene in anti-aging or photoaging treatment, and its potential in this area is limited. The study is still in the research phase (Schadt et al., 2013).

Trifarotene
Trifarotene is a fourth-generation retinoid and is currently an approved agent for acne treatment in a 0.005% topical cream form. Clinical studies are ongoing to evaluate its efficacy and safety profile in this indication (Blume-Peytavi et al., 2020).

Pharmacologically, trifarotene is a potent agonist showing high selectivity, particularly for RAR-γ, among retinoic acid receptors, and has more than 20 times greater affinity for RAR-γ compared to RAR-α and RAR-β. Preclinical studies have shown that it can exhibit both pigment-reducing and pigment-regulating effects in animal models (Aubert et al., 2018).

Due to the predominant retinoid receptor subtype in the dermis being RAR-γ, trifarotene is considered a promising candidate in the treatment of photoaging. Mechanistically, it is suggested that it may produce anti-aging effects by activating downstream signaling pathways similar to tretinoin (Cosio et al., 2021).

Preclinical data suggest that trifarotene may offer a more balanced efficacy-tolerability profile compared to previous generation retinoids. However, to date, no clinical studies have directly compared its efficacy and safety in terms of anti-aging use. Therefore, its role in the anti-aging field

is not yet definitively established and requires further clinical validation. Also, as it is a new retinoid, it is expected that studies on different formulations will increase in the future.

Seletinoid G

Seletinoid G is a synthetic retinoid derivative that exhibits selective agonist effects on the RAR-γ receptor. This compound has been reported to regulate the expression of extracellular matrix proteins and matrix-degrading enzymes in a manner similar to tretinoin. Thanks to these properties, it is suggested that it may contribute to the remodeling of aged dermal connective tissue and the reduction of UV-induced collagen degradation.

Seletinoid G has been reported to have significantly lower irritation potential compared to tretinoin. However, the fact that these findings are based on a limited sample size and short exposure time limits the generalizability of the results. In vitro preclinical data suggest that this compound can improve skin barrier function by increasing keratinocyte migration and normalizing dermal collagen regulation; this points to potential anti-aging activity with fewer side effects (Lee et al., 2020).

However, no clinical studies evaluating the anti-aging efficacy of seletinoid G under real-life conditions have yet been conducted. Therefore, its therapeutic potential is currently theoretical and needs to be confirmed by comprehensive clinical research.

Discussion

Retinoids remain the most extensively researched group of topical agents in anti-aging dermatological treatments, thanks to their ability to control epidermal cell proliferation, differentiation processes, and dermal structural remodeling. All retinoid generations primarily act via nuclear retinoic acid receptors, modulating gene expression pathways that regulate collagen synthesis, extracellular matrix turnover, and epidermal balance. However, despite shared mechanisms of action, different retinoid compounds exhibit significant differences in efficacy, receptor selectivity, tolerability, and level of clinical evidence. Tretinoin, a first-generation retinoid, is considered the reference standard in anti-aging treatments. Numerous long-term clinical studies have demonstrated its effectiveness in reducing signs of photoaging, reducing wrinkle depth, and improving dermal structure. However, this strong efficacy is often limited by dose-dependent irritation and poor tolerance. This has increased the need for the development of better-tolerated alternative retinoids. Although precursor molecules such as retinol and retinaldehyde provide better tolerability due to their stepwise conversion to retinoic acid, their clinical effects largely depend on formulation stability and intradermal enzymatic conversion capacity, resulting in variability in outcomes. Retinyl esters, despite their widespread use in cosmetic products, stand out as the retinoid group with the weakest level of clinical evidence. While generally considered safe, their bioavailability is low due to requiring multiple metabolic conversion steps, making their clinical efficacy uncertain. Safety concerns such as photodegradation under UV exposure and potential pro-oxidant effects are also reported. While retinyl retinoate offers relatively more positive data among ester derivatives, current studies are limited in both scale and methodological quality. Second-generation retinoids are no longer used in current topical anti-aging treatments with the development of better-tolerated and more selective molecules. In contrast, third-generation retinoids, such as adapalene and tazarotene, bind more selectively to RAR-β and RAR-γ receptors, producing more targeted biological effects. Clinical studies have shown that these agents can provide anti-aging results comparable to tretinoin; in some cases, they offer a faster onset of action or better tolerability. Nevertheless, their clinical use is mostly limited to acne and psoriasis indications, and the lack of long-term studies in the anti-aging field is noteworthy. Although adapalene was initially developed for the treatment of acne, controlled studies have shown that it improves pigmentation and tissue changes associated with photoaging. Similarly, tazarotene has demonstrated strong clinical efficacy, showing results equivalent to or superior to tretinoin in some studies. Despite this, tretinoin remains the most commonly preferred agent in clinical practice due to

its long-standing clinical experience and established usage protocols. Fourth-generation retinoids, such as tripharotene and seletinoid G, are notable for their high selectivity, particularly to the RAR-γ receptor, which is dominant in the dermis. Preclinical data suggest that these molecules may offer a better efficacy-tolerability balance and more targeted dermal restructuring potential. However, current clinical evidence is quite limited. While data on tripharotene are largely based on acne studies, seletinoid G is only supported by short-term experimental research. Therefore, their role in photoaging treatment remains at the theoretical level. Formulation properties play a critical role in the clinical success of retinoids. Retinol and retinaldehyde, in particular, experience stability problems due to their sensitivity to light, oxygen, and heat. Differences in ingredients, lack of standardization, and labeling inconsistencies in cosmetic products also complicate the interpretation of clinical results. While nanotechnology-based carrier systems are promising in terms of increasing stability and skin penetration, much of the evidence in this area is still at the preclinical level. Overall, the literature shows a clear hierarchy of evidence among retinoids: tretinoin maintains its gold standard status with strong clinical validation, while newer generation retinoids offer potential for better tolerability and selectivity but lack long-term comparative data. Cosmetic retinoids, particularly retinyl esters, are used with limited scientific support due to insufficient clinical evidence. Therefore, future studies should focus on standardized, large-scale, and carrier-controlled clinical designs; and also on different retinoids.

Conclusion

Research generally shows that the clinical success of topical retinoids depends not only on the active ingredient but also on formulation characteristics such as the adjuvants used and the manufacturing technologies. A properly developed formulation can increase the stability of the active ingredient, improve skin penetration, and enhance tolerability. This allows for the achievement of a clinically viable tretinoin-like effect while reducing the occurrence of side effects.

Increased tolerability is critical, especially in terms of long-term aging and improvements, as it directly extends patient compliance and treatment. Therefore, modern formulation solutions such as controlled-release systems and nanotechnology carriers hold significant potential for both reducing irritation and optimizing therapeutic effect.

Nevertheless, despite positive studies on different retinoid classes and new delivery systems, current products have some significant limitations. The small distribution of studies, short follow-up periods, high heterogeneity among formulations, and the lack of sufficient carrier-controlled or direct comparative studies reduce the generalizability of results. This situation makes it difficult to reach definitive conclusions regarding the efficacy of retinoid anti-aging trials.

Therefore, more comprehensive, well-designed, and standardized clinical trials are needed to establish evidence. Future studies should place great emphasis on direct comparison of different generations of retinoids, long-term efficacy and safety maintenance, and clinical development of advanced manufacturing technologies in real-life conditions.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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