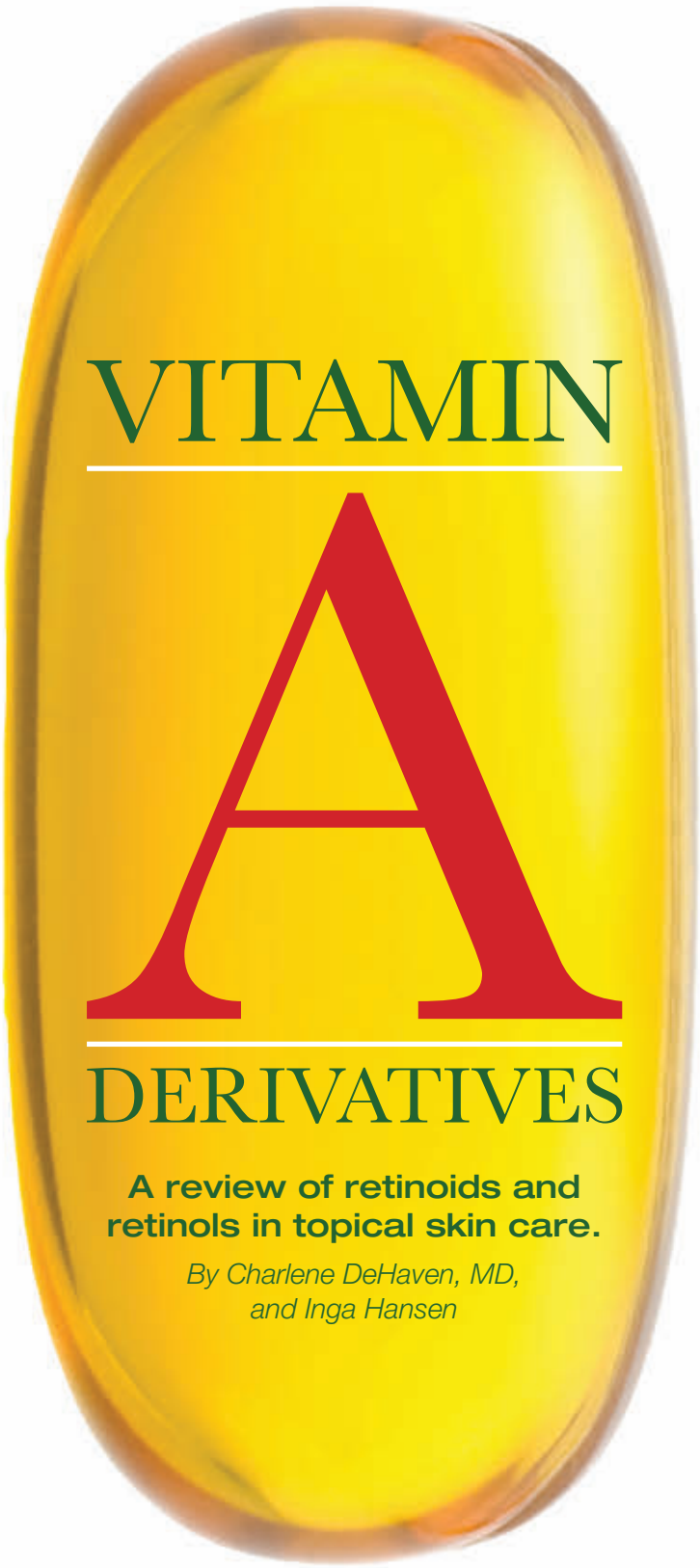


VITAMIN A DERIVATIVES

A review of retinoids and retinols in topical skin care.

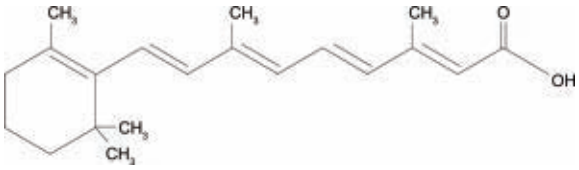
By Charlene DeHaven, MD, and Inga Hansen

It has been more than 50 years since Retin-A first gained approval for the treatment of acne. In the years since, topical derivatives of vitamin A have found wide applicability in aesthetics for indications including acne, photoaging and pigmentation concerns. This article will summarize the prescription and non-prescription vitamin A-derived actives currently used in aesthetic medicine and dermatology.

All-trans retinoic acid is the major biologically active form of vitamin A. The actions of vitamin A and its cellular metabolite, all-trans retinoic acid, in skin include:[1,2,3,4]

- Epithelial growth and differentiation
- Skin barrier functionality
- Collagen synthesis
- Wound healing, all stages
- Antioxidant activity
- Anti-inflammatory activity

The molecular structure for retinoic acid is:



Retinoic acid

ACTIONS, PREPARATIONS AND SIDE EFFECTS

All topical retinoids share common activations on many nuclear receptors, including RAR (retinoic acid receptor) and RXR (retinoid X receptor), thus accounting for their similarities in functionality and toxicity. They regulate epithelial cell growth and proliferation via receptor activities and intercellular communications. Topical retinoids have similar potential side effect profiles that are concentration and dose dependent.

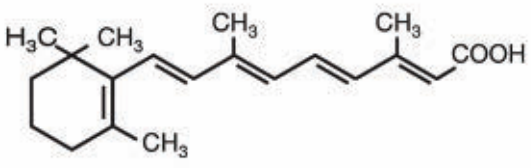
The 'retinoid reaction' is a description of the most frequent and common adverse reaction seen with these compounds. It is an irritative response with pruritus, burning, itching, peeling or flaking, and erythema. This reaction is related to the release of pro-inflammatory cytokines during the first weeks of use.

Photosensitization can occur at the beginning of therapy but fatigues after a few months. Sunscreen use and sun avoidance are advised at the initiation of use.

Topical retinoids are available in cream, gel, lotion and liquid forms.

Tretinoin (Retin A)

Tretinoin was initially used for acne treatment, but its use then expanded into anti-aging. It is one of the first-generation, non-aromatic vitamin A derivatives.



Tretinoin

Tretinoin exhibits several beneficial mechanisms in acne treatment.[5] It is comedolytic as it improves exfoliation in the pilosebaceous unit. It lessens cellular adhesion and prevents follicular plugging and also has an antimicrobial effect on P. acnes, which creates a more aerobic pilosebaceous environment that is less conducive to bacterial overgrowth. Both inhibitory and activating effects occur from tretinoin on the inflammatory cascade and phagocytic cellular events. The eventual result of these immunomodulatory events is to reduce the severity of lesions and the overall inflammation.

Anti-aging benefits are also seen with topical tretinoin.[6] An initial short-term study of four months using 0.1% tretinoin cream documented improvement of fine wrinkles, roughness and sallowness.[7] Many longer studies of six months and beyond showed continued improvement

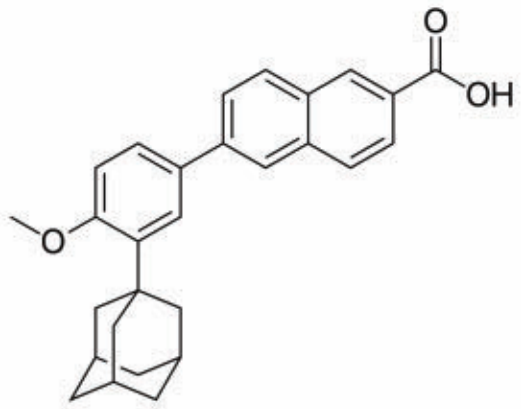
1 Fisher GJ, Voorhees JJ. Molecular mechanisms of retinoid actions in skin. FASEB J. 1996. 10: 1002-1013.
2 Kong R, Cui Y, Fisher GJ, Wang X, Chen Y, Schneider LM, Majmudar G. A comparative study of the effects of retinol and retinoic acid on histological, molecular, and clinical properties of human skin. J Cosmet Dermatol. 2016 Mar. 15(1): 49-57.
3 Zinder R, Cooley R, Vlad LG, Molnar JA. Vitamin A and wound healing. Nutr Clin Pract. 2019 Dec. 34(6): 839-849.
4 Palace VP, Khaper N, Qin Q, Singal PK. Antioxidant potentials of Vitamin A and carotenoids and their relevance to heart disease. Free Radic Biol Med. 1999 Mar. 26(5-6): 746-761.

5 Schmidt N, Gans EH. Tretinoin: a review of its anti-inflammatory properties in the treatment of acne. J Clin Aesthet Dermatol. 2011 Nov. 4(11): 22-29.
6 Mukherjee S, Date A, Patravale P, Korting HC, Roeder A, Weindl G. Retinoids in the treatment of skin aging: an overview of clinical efficacy and safety. Clin Interven Aging. 2006. 1(4): 327-348.
7 Weiss JS, Ellis CN, Headington JT, Tincoff T, Hamilton TA, Voorhees JJ. Topical tretinoin improves photoaged skin. A double-blind vehicle-controlled study. JAMA. 1988 Jan 22-29. 259(4): 527-532.

in parameters of photoaging.[8] Side effects of irritation, erythema or dermatitis often accompanied these higher concentrations between 0.05% and 0.1%. Interestingly, studies using a lower percentage of 0.02% showed equivalent photoaging benefits but less toxicity.

Adapalene (Differin)

Adapalene is a third-generation synthetic poly-aromatic retinoid, exhibiting extensive modifications to its parent compound, retinol.



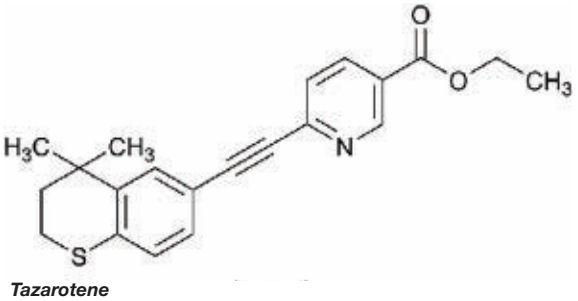
Adapalene

In comparison to tretinoin for acne, adapalene has generally been reported to have fewer side effects, comparable acne benefits and faster onset of action.[9] Adapalene is available over the counter in a 0.1% concentration. Topical adapalene gel has anti-aging benefits with wrinkle improvements, lightening of solar lentigines and improvements in actinic keratoses.[10]

Tazarotene (Tazorac, Avage, Fabior and ARAZLO)

Tazarotene is used primarily for acne and mild to moderate plaque psoriasis, although it also has anti-aging benefits.[11] For psoriasis, it is often combined with corticosteroids or phototherapy. Tazarotene is a third-generation, synthetic, poly-aromatic retinoid with major modifications of the retinol parent. Tazarotene is a pro-drug and is metabolized to the active metabolite, tazarotenic acid.

8 Mukherjee S, et. al. Ibid.
9 Piskin S, Uzunali E. A review of the use of adapalene for the treatment of acne vulgaris. Ther Clin Risk Mgmt. 2007. 3(4): 621-624.
10 Kang S, Goldfarb M, Weiss J, et al. Assessment of adapalene gel for the treatment of actinic keratoses and lentigines: a randomized trial. J Am Acad Dermatol. 2003. 49: 83-90.
11 Roeder A, Schaller M, Schafer-Korting M, Korting HC. Tazarotene: therapeutic strategies in the treatment of psoriasis, acne, and photoaging. Skin Pharmacol Physiol 2004. 17: 111-118.

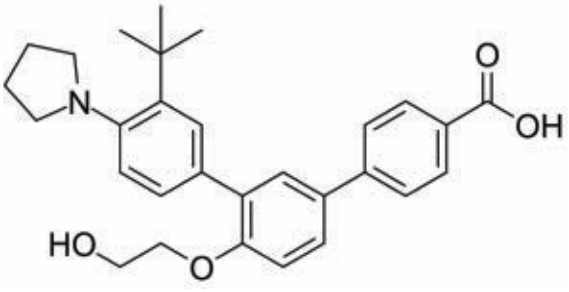


Tazarotene

Tazarotene, along with other retinoids, exhibits effects on cellular proliferation, differentiation and inflammation. Actions of tazarotene also include downregulation of keratinocyte abnormal expression, EGFR (epidermal growth factor receptor) and keratin hyperproliferation, that make it especially helpful for psoriasis. In general, it is better than adapalene for acne. Tazarotene shares with other retinoids the potential side effects of erythema, dermatitis, itching and burning.

Trifarotene (AKLIEF)

Trifarotene is a fourth-generation, selective retinoic acid receptor (RAR)-γ agonist, developed by Galderma and approved in 2019 for the treatment of acne.



Trifarotene

"Each retinoid works a little differently in that they have different affinities for the retinoid receptors, but they are more similar than different," says Emil Tanghetti, MD, of the Center for Dermatology and Laser Surgery in Sacramento, California.

He calls tazarotene, "the most robust retinoid in the class. Though it can be a little bit more irritating than tretinoin."

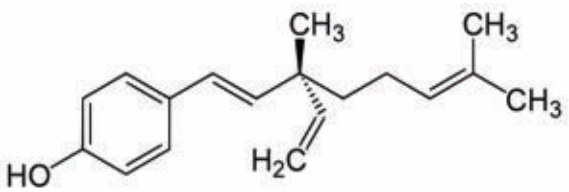
In 2008, Dr. Tanghetti and colleagues showed that when patients use a non-soap cleanser, apply a thin layer of moisturizer, wait for it to dry and then apply the tazarotene that it dramatically diminishes irritation. Building on this research, Ortho Dermatologics developed a vehicle

for its acne topical ARAZLO that features microsphere-encapsulated moisturizer. “When it hits the salt on the skin, the microspheres dissolve and the moisturizer and tazarotene mix, which makes the tazarotene molecule more efficacious with an incredible tolerability profile,” says Dr. Tanghetti.

Trifarotene, the newest prescription retinoid, is the active ingredient in Galderma’s AKLIEF (trifarotene) Cream, 0.005% for acne. “Trifarotene is more like tazarotene in terms of its chemical composition than tretinoin or adapalene,” says Dr. Tanghetti.

Retinols

The three over-the-counter vitamin A-derivatives most often used in anti-aging skin care are retinol, retinaldehyde and retinol esters. Retinol increases epidermal thickness and has anti-aging effects. However, when compared in topical preparations, it is associated with considerably fewer side effects of irritation, erythema and dermatitis compared to retinoic acid.[12] It is also less effective due to the conversion required. Once applied, enzymes in the skin convert retinaldehyde to retinoic acid. In the case of retinol, it is first converted to retinaldehyde and then retinoic acid. Retinol esters are converted first to retinol then retinaldehyde and then retinoic acid. With each step efficacy is reduced.



Bakuchiol

ALTERNATIVE COMPOUNDS

Bakuchiol, a meroterpene from the botanical *Psoralea corylifolia*, has been described as a potential alternative to topical retinoids for anti-aging.[13]

A study by Zoe Draelos, MD, compared topical 0.5% bakuchiol applied twice daily for 12 weeks with a topical 0.5% retinol applied daily and found their anti-aging effects of wrinkle and hyperpigmentation improvements were comparable, but bakuchiol was better tolerated, with patients exhibiting less facial scaling and discomfort.

“In terms of structure, bakuchiol is not similar to retinol but functionally or mechanically, there are a lot of similarities,” says Hemali Gunt, PhD, head of clinical and scientific affairs at Burt’s Bees, which has been spearheading recent research into bakuchiol as a natural alternative to retinoids. “If you look at how it works with the retinoic acid receptors and how it upregulates some of the key enzymes related to collagen upregulation, there are a lot of similarities between retinol and bakuchiol. And if we take it to the protein level, using techniques such as ELISA chemistry, bakuchiol and retinol have shown similar functionality in terms of upregulation of types 1 and 4 collagen and also stimulation of type 3 collagen in fibroblast models.”

In October, Hoth Therapeutics reported results from phase 1 studies of its investigational topical HT-003, a retinoic acid metabolism blocking agent (or RAMBA), designed to prolong the presence of retinoic acid in the skin.

The studies, led by Jonathan Zippin, MD, PhD, associate professor of dermatology at Weill Cornell Medicine and Hoth senior scientific advisor, showed that HT-003 significantly inhibited toll-like receptor 2 (TLR2). The hope is that HT-003 will provide the efficacy of prescription retinoids against acne without irritation and inflammation.

“We don’t have any phase 2 or phase 3 data to evaluate at this point, but I applaud them for doing retinoid research,” says Dr. Tanghetti. “There have not been many people doing much of that lately. As soon as they put a product together and start clinical trials, we should get some indication of what this active is really going to do.” ME

Charlene DeHaven, MD, is the clinical director of Innovative Skin Care in Burbank, California.

Inga Hansen is the managing editor of *MedEsthetics*.

12 Kang S, Duell EA, Fisher GJ, et. al. Application of retinol to human skin in vivo induces epidermal hyperplasia and cellular retinoid binding proteins characteristic of retinoic acid but without measurable retinoic acid levels or irritation. 1995. J Investig Dermatol. 105: 549-556.
13 Dhaliwal S, Rybak I, Ellis SR, Notay M, Trivedi M, Burney W, Vaughn AR, Nguyen M, Reiter P, Bosanac S, Yan H, Foolad M, Sivamani RK. Prospective, randomized, double-blind assessment of topical bakuchiol and retinol for facial photoageing. Br J Dermatol. 2019. 180: 289-296.