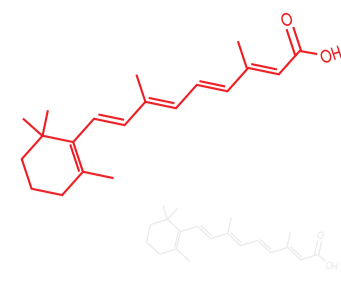


Retinoids

Retinoids are a class of molecules derived from vitamin A or having structural and/or functional similarities to vitamin A. The first medicinal use of vitamin A dates back to ancient Egypt where liver juices were used to treat endemic night blindness.²

Prescribed topical retinoids are divided into 6 classes: Tretinoin (alltrans retinoic acid), adapalene, tazarotene, trifarotene, alitretinoin, and bexarotene. The last 2 classes, alitretinoin and bexarotene, are topical and oral retinoids used in Kaposi's sarcoma and cutaneous T-cell lymphoma, although infrequently.³

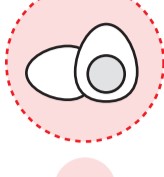
Cosmeceutical and over-the-counter retinoids undergo several conversions depending on their initial molecular structure from retinyl esters to retinol to the biologically active form retinoic acid.³



History

1909

Vitamin A identified as an essential factor in the viability of an embryo in an egg yolk²



1960s

Instability led to losing favor with dermatologists

1943

First dermatological use for acne vulgaris⁴

1969

Topical tretinoin proven effective for acne vulgaris⁶



1962
Therapeutic effectiveness of topical tretinoin established for keratinisation disorders ichthyosis, actinic keratoses and other hyperkeratotic conditions⁵

1984

Efficacy in the treatment of photoaging first demonstrated

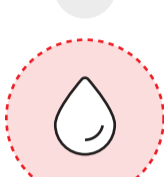
1982
FDA approved isotretinoin for severe nodulocystic acne²

1996

JOHNSON & JOHNSON first to launch pure stabilized retinol products in the US



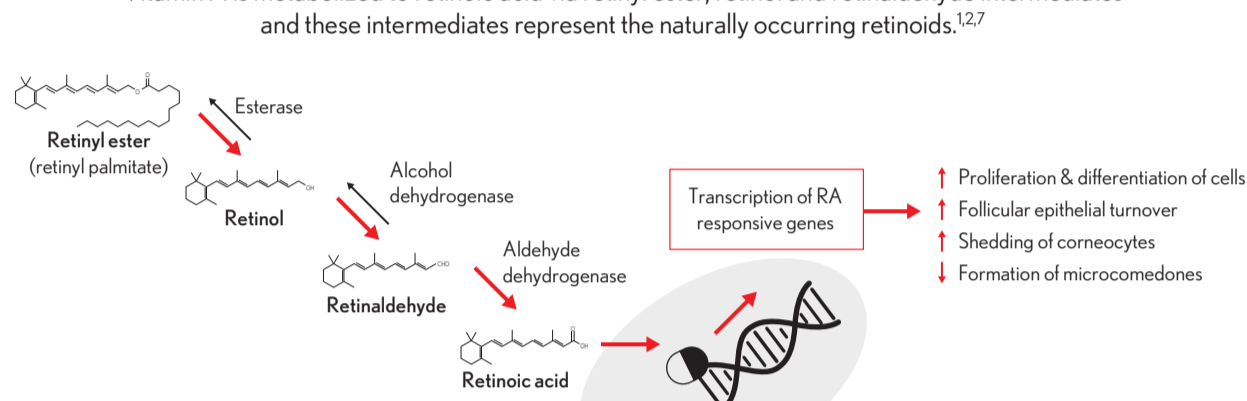
1990's
Skincare industry innovations in retinol stability led to a growth of interest in the molecule



TODAY
Stabilized retinol is paired with complementary ingredients to address acne, discoloration and aging.

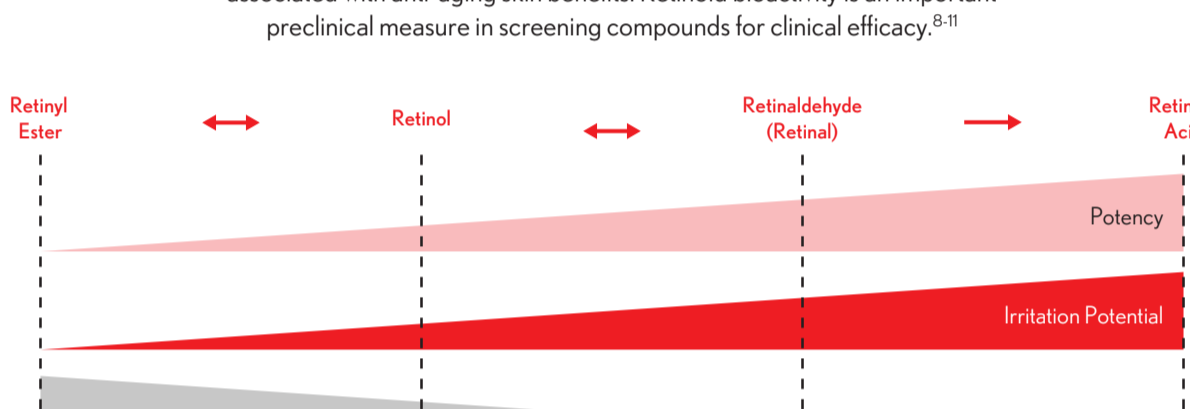
Vitamin A Metabolism and Action

Retinoids are vitamin A derivatives comprised of both natural and synthetic forms. Vitamin A is metabolized to retinoic acid via retinyl ester, retinol and retinaldehyde intermediates and these intermediates represent the naturally occurring retinoids.^{1,2,7}

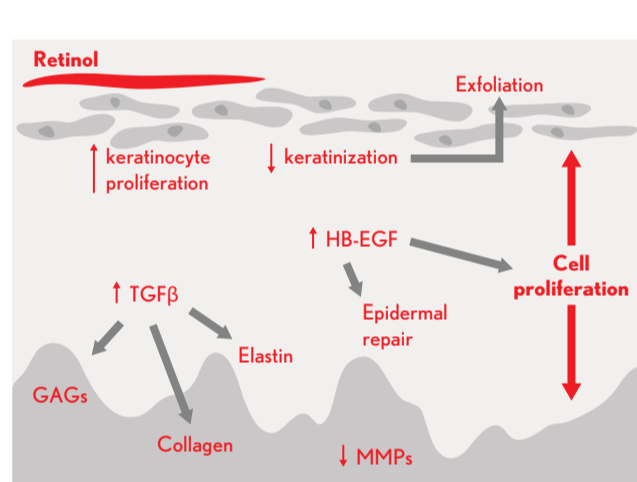


Relative Potency, Irritation Potential, and Stability

Retinyl esters, retinol and retinaldehyde are over the counter (OTC) cosmetic ingredient options in products available to consumers; however, they are naturally unstable. This presents formulation challenges in developing products for topical application. Additionally, retinoids in general may vary in the ability to activate genes associated with anti-aging skin benefits. Retinoid bioactivity is an important preclinical measure in screening compounds for clinical efficacy.⁸⁻¹¹



Johnson & Johnson Consumer Health has advanced the stabilization, efficacy, tolerance and aesthetics of retinol with more than 100 clinical studies on over 4,000 patients.¹²



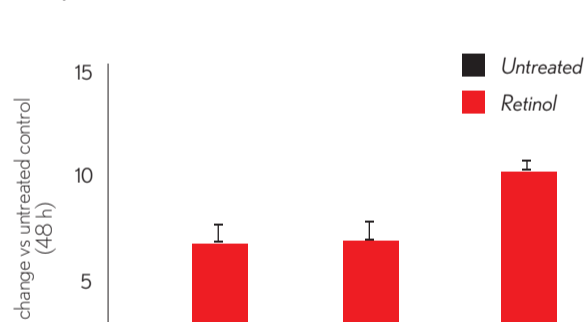
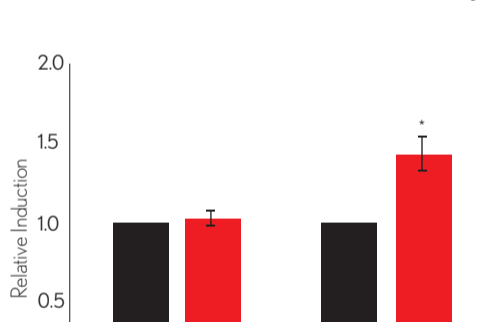
GAGs – Glycosaminoglycans; TGF-β – Transforming Growth Factor-β; HBEGF – Heparin-binding Epidermal Growth Factor; MMPs – Matrix metalloproteinases

Retinol: Mechanism of Action in OTC Skincare

Retinol exfoliates the skin, increases skin cell turnover, and stimulates collagen synthesis. It is considered the gold standard for its anti-aging and skin clearing benefits.

Retinol influences the proliferation and differentiation of cells. Their biological effects are mediated and regulated by cytosolic binding proteins and nuclear hormone receptors.³

Retinol Activates Glycosaminoglycan and Hyaluronic Acid Expression



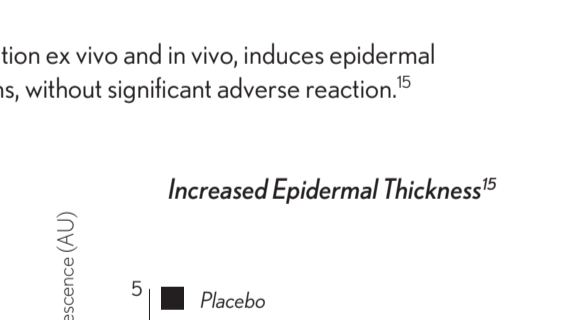
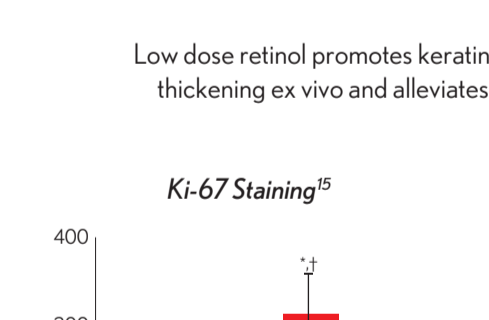
Adapted from Wen-Hwa Li, et al. Stabilized-RetinolL-stimulated human hyaluronan synthase mRNA in human skin explants in vitro. Graph shows increase in gene expression by retinoic acid binding proteins CRABP2, Hb-EGF, and HAS3.

Through significant induction of glycosaminoglycan, which is known to retain substantial water, and increased collagen production, topical retinol improves fine wrinkles associated with natural aging.¹³

Retinol increases skin expression of Hyaluronic Acid, a significant contributing factor responsible for wrinkle formation and skin moisture, which decrease during aging. Taken together with the activity to increase collagen, elastin, and cell proliferation, studies show retinol provides multi-functional activity for photodamaged skin.¹⁴

Retinol Activates Cell Proliferation

Low dose retinol promotes keratinocyte proliferation ex vivo and in vivo, induces epidermal thickening ex vivo and alleviates skin aging signs, without significant adverse reaction.¹⁵



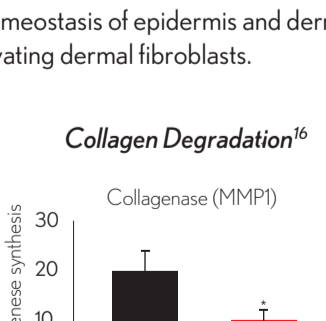
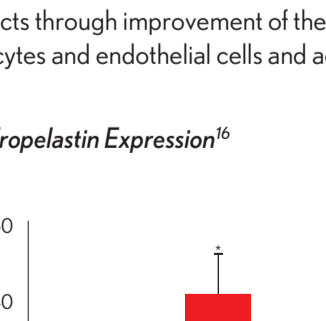
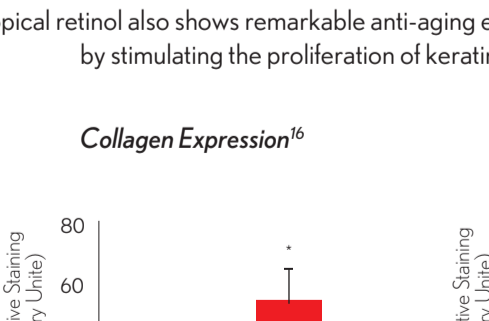
Retinol-induced increase in the number of epidermal proliferating cells in human skin explants.

Retinol-induced increase in epidermal cell proliferation measured in vivo.

Retinol Induces Collagen and Tropoelastin Synthesis and Decreases Enzymatic Degradation of Collagen¹⁶

Topical retinol improves fine wrinkles associated with natural aging through significant induction of glycosaminoglycan, which is known to retain substantial water, and increased collagen production.

Topical retinol also shows remarkable anti-aging effects through improvement of the homeostasis of epidermis and dermis by stimulating the proliferation of keratinocytes and endothelial cells and activating dermal fibroblasts.



REFERENCES
1. Khalil S, Bardawil T, Stephan C, et al. Retinoids: a journey from the molecular structures and mechanisms of action to clinical uses in dermatology and adverse effects. *J Dermatolog Treat.* 2017;28(8):684-696.
2. Mukherjee S, Date A, Patravale V, Korting HC, Roeder A, Weindl G. Retinoids in the treatment of skin aging: an overview of clinical efficacy and safety. *Clin Interv Aging.* 2006;1(4):327-348. doi:10.2147/cia.2006.1.4.327
3. Motamed M, Chahade A, Sanghera R, Green P. A Clinician's Guide to Topical Retinoids. *Journal of Cutaneous Medicine and Surgery.* July 2021. doi:10.1177/12034754211035091
4. Straumfjord J, V. "Vitamin A Its Effect on Acne," *Northwest Med.* 42:219-255, August, 1943.
5. Stüttgen G. Historical perspectives of tretinoin. *J Am Acad Dermatol.* 1986 Oct;15(4 Pt 2):735-40. doi:10.1016/s0190-9622(86)70228-4. PMID: 3534016.
6. Klugman AM. The growing importance of topical retinoids in clinical dermatology: a retrospective and prospective analysis. *J Am Acad Dermatol.* 1998 Aug;39(2 Pt 3):52-7. doi:10.1016/s0190-9622(98)70437-2. PMID: 9703116.
7. LH Gans & EH Klugman (2000) Re-emergence of topical retinol in dermatology. *Journal of Dermatological Treatment.* 11:1, 47-52, DOI: 10.1080/0954663005017685
8. Nohynek GJ, Meuling WJ, Vaes WH, Lawrence RS, Shapiro S, Schulte S, Stelling W, Bausch J, Gerber E, Sasa H, Nau H. Repeated topical treatment, in contrast to single oral doses, with Vitamin A-containing preparations does not affect plasma concentrations of retinol, retinyl esters or retinoic acids in female subjects of child-bearing age. *Toxicol Lett.* 2006 May 5;163(1):65-76. doi:10.1016/j.toxlet.2005.09.029. Epub 2005 Oct 21. PMID: 16243460.
9. Lupo MP. Antioxidants and vitamins in cosmetics. *Clin Dermatol.* 2001 Jul; Aug;19(4):467-73. doi:10.1016/s0738-081x(01)00188-2. PMID: 11535390.
10. Erling, T. Skin Treatment with Two Different Galenical Formulations of Retinyl Palmitate in Humans. *J Appl Cosmetol.* 1993;11:71-76.
11. Fluhr JW, Vienne MP, Lauze C, Dupuy P, Gehring W, Gloor M. Tolerance profile of retinol, retinaldehyde and retinoic acid under maximal and long-term clinical conditions. *Dermatology.* 1999;199 Suppl 1:57-60. doi:10.1159/000051381. PMID: 10473963.
12. Data on file.
13. Kati R, Kwak HSR, Schumacher WE, et al. Improvement of Naturally Aged Skin With Vitamin A (Retinol). *Arch Dermatol.* 2007;143(5):606-612. doi:10.1001/archderm.143.5.606
14. Li, Wen-hwa; Wong, Heng-kuan; Serrano, José; Randhawa, Manpreet; Kaur, Simarna; et al. Archives of Dermatological Research; Heidelberg Vol. 309, Iss. 4, (May 2017): 275-283. DOI:10.1007/s00403-017-1723-6
15. Bellemère G, Stamatés G, N, Brubère Y, Bertin C, Issachar N, Oddos T. Antiaging Action of Retinol: From Molecular to Clinical. *Skin Pharmacol Physiol* 2009;22:200-209. doi:10.1159/000231525
16. Shao Y, He T, Fisher GJ, Voorhees JJ, Quan T. Molecular basis of retinol anti-ageing properties in naturally aged human skin in vivo. *Int J Cosmet Sci.* 2017 Feb;39(1):56-65. doi:10.1111/ics.12348. Epub 2016 Jul 4. PMID: 27261203; PMCID: PMC5136519.