by wade cheng & shirley depetris

Vitamin A Complex

The topical application of vitamins is popular in the cosmetic industry—and there's a reason for this. Orally ingested vitamins aren't always transported to the skin in sufficient quantities due to poor absorption, improper function of the metabolic system or aging. It is estimated that only 20–40% of orally ingested vitamin E, an antioxidant, is absorbed in the body, and it is not known how much actually reaches the skin.

This points to the need for topical application of vitamins that provide the skin and hair with local vitamin concentrations higher than those attained by oral ingestion. Use of vitamins on the skin has been suggested to help prevent, retard or arrest certain degenerative changes associated with the aging process—dry, scaly skin; the formation of wrinkles; and undesirable hyperpigmentation. In addition, the naturalness of vitamins has promoted their use in creams and lotions to maintain soft, smooth skin by replenishing moisture. While antioxidants, including vitamin C, are used often, the synergistic approach of vitamin A complex deserves attention as well.

Basics of vitamin A

Since vitamin A and its derivatives all are beneficial to healthy skin, it is wise to look into vitamin A complex. Before doing so, however, consider vitamin A itself, also called retinol. It is a yellow, fat-soluble compound found in egg yolk, butter, carrots and other vegetables, and is an essential nutrient that helps develop and maintain normal skin, in addition to other tissues and bones. The human body cannot synthesize vitamin A. It must obtain this vitamin from direct food intake or by converting carotenoids such as beta-carotene, the orange pigment that gives a carrot its color. This is why beta-carotene often is referred to as pro-vitamin A.

The human body stores vitamin A to a much greater extent than water-soluble vitamins such as vitamin C and some types of vitamin B. More than 90% of the body's vitamin A is stored in the liver. A United States Pharmaceutical Grade (USP) unit of vitamin A is defined as 0.3 microgram of vitamin A. (One microgram is equal to 0.000001 gram or 10^{-6} gram.) One gram of pure vitamin A contains 3.33 million I.U. (International Units).

The ancient Egyptians used vitamin A to treat night blindness and other eye disorders. But vitamin A does far more than just benefit vision. Skin abnormalities, some resembling cancerous changes, were among the first of many symptoms of vitamin A deficiency to be noticed in humans.

Vitamin A often is referred to as a normalizer because it is essential not only for normal differentiation of epidermal cells, but also for the growth and maintenance of bones, teeth, glands, nails and hair.[1]

Vitamin A derivatives

Vitamin A has quite a few derivatives, or chemical variations, technically known as retinoids.

There is no magic in biochemistry and dermatology. The skin's reaction to retinoic acid is determined by its chemical structure. The chemical and molecular structure of common retinoids such as vitamin A (retinol), vitamin A_2 (retinol$_2$), vitamin A aldehyde (retinal), vitamin A acid (retinoic acid), vitamin A acetate (retinyl acetate), vitamin A propionate (retinyl propionate) and vitamin A palmitate (retinyl palmitate)

Wade Cheng, PhD, is vice president and director of research and development for Rejuvi Laboratory in San Francisco. Before joining the company, he was a senior research chemist at Smithkline Beckman Corporation, the California Public Health Department and Biorad Laboratories. He has a bachelor's degree in chemistry and chemical engineering, a master's degree in analytical chemistry and a doctorate in biochemistry. Cheng also has more than 20 published works in a variety of scientific journals.

Shirley DePetris is director of sales and training at Rejuvi Laboratory in San Francisco. A licensed esthetician trained in France, New York and California, she has more than 15 years of experience in the industry. Before joining Rejuvi, DePetris was the national trainer for a French cosmetic company and had been a promotion expert for several divisions of the Revlon Corporation. She is a skilled public speaker, lecturer and esthetic instructor.

Chemical Properties of Retinoids

Retinoid Name (Alternate Name)	Chemical Formula	Molecular Weight	Chemical Stability
Vitamin A (Retinol)	$C_{19}H_{29}COH$	286.44	Very oxidative
Vitamin A_2 (Retinol$_2$)	$C_{19}H_{27}COH$	284.42	Very oxidative
Vitamin A aldehyde (Retinal)	$C_{19}H_{27}CHO$	284.42	Oxidative
Vitamin A acid (Retinoid acid)	$C_{19}H_{27}COOH$	300.42	Less oxidative
Vitamin A acetate (Retinyl acetate)	$C_{19}H_{29}COOCCH_3$	328.50	Stable
Vitamin A propionate (Retinyl propionate)	$C_{19}H_{29}COOCC_2H_5$	342.52	Stable
Vitamin A palmitate (Retinyl palmitate)	$C_{19}H_{29}COOCC_{15}H_{31}$	524.88	Most stable

are listed in **Chemical Properties of Retinoids.**

The differences between the retinoids' cis- and trans-isomers, which have the same molecular structure but varied geo-metrical arrangements, will not be discussed because they are complicated and beyond the scope of this article.

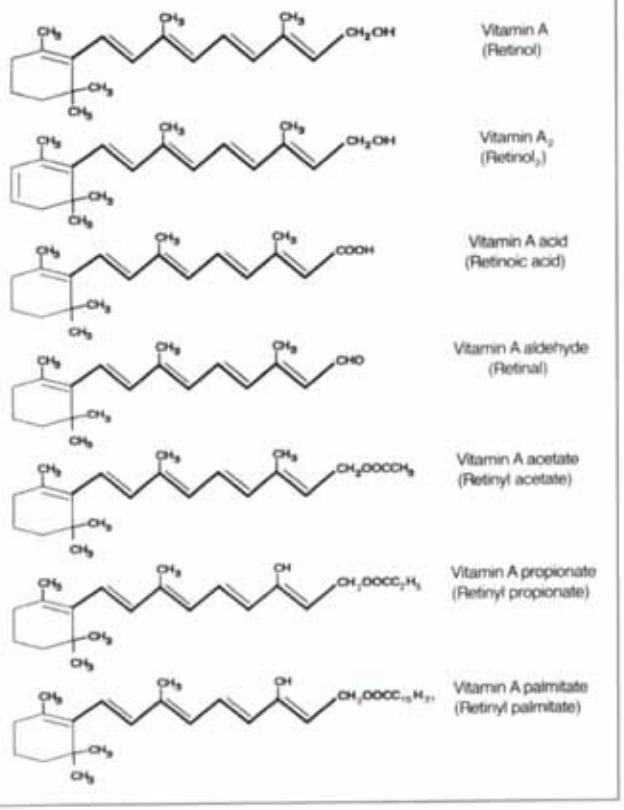
In looking at the **Chemical Properties of Retinoids,** it is obvious that all of these retinoids have the basic retinol structure with some variation at the right terminal except retinol$_2$. In **Chemical and Molecular Structure of Retinoids.**, it is evident that there is no difference between retinol and retinol$_2$, except an extra dark vertical line in the left aromatic ring structure of retinol$_2$. This double vertical line denotes a double bond, which might provide more antioxidation potential. In a chemical structure, a single line is called a single bond. Due to the retinol moiety—the one of two approximately equal retinol portions of the retinoid molecules—all retinoids show the distinct yellow color and are oil-soluble, or lipophilic, a physical property that allows them to be well-absorbed into the skin.

Chemical classes

In chemistry, retinol with an hydroxyl group (–OH, where O is oxygen and H is hydrogen) at the right terminal is classified as an alcohol. Alcoholic beverages contain ethyl alcohol. The cosmetic ingredient cetyl alcohol has a much longer carbon chain attached to the –OH, and is used as a thickening agent in cosmetic products. Retinal, with the aldehyde group (–CHO, where C is carbon, H is hydrogen and O is oxygen) is chemically related to formaldehyde and acetaladehyde. Retinoic acid with its carboxyl group (–COOH) is classified as an organic acid. Acids can be reacted with bases to form salts or esters. For example, lactic acid neutralized with sodium hydroxide produces the salt sodium lactate. Retinyl acetate, retinyl propionate and retinyl palmitate (with –OOCR) are classified as esters, products generated after an acid is neutralized with an organic base. R is the organic group. Examples include CH_3 (for retinyl acetate), CH_2CH_3 (for retinyl propionate and $CH_{15}CH_{31}$ (for retinyl palmitate), respectively.

These different chemical classes of vitamin A show slightly different chemical properties. The alcohol form is

Chemical and Molecular Structure of Retinoids



very sensitive to oxidation when exposed to air—turning more yellow—but is stable in an oil solution. The aldehyde and acid forms are slightly less sensitive to air oxidation. The ester form is most stable to oxidation. The ease of oxidation can be expressed by this hierarchical list:

Retinol>Retinal>Retinoic acid>Retinyl esters

On the basis of the this order, retinol is the most powerful antioxidant and retinyl esters are the least powerful antioxidants. Vitamin A palmitate is the most popular one used in the cosmetic industry due to its low price and high stability. It is easy to store and does not quickly change color. Its molecular weights, chemical formula and properties are summarized in **Chemical Properties of Retinoids**. Retinol is a natural substance. All other retinoids are industrially synthesized materials.

Retinoids and the skin

Regarding biochemical activity as it relates to the skin, retinoic acid is most aggressive, followed by retinal, then retinol. Retinyl esters are least aggressive. This order can be expressed by:

Retinoic acid>>Retinal>Retinol>Retinyl esters

Due to the similarity in chemical structure, the retinol moiety, all retinoids retain similar biological properties on skin.

In the past ten years, the vitamin A family has received additional publicity due to the studies conducted with

topical retinoic acid, which has demonstrated an ability to reverse many effects of skin photoaging. What exactly is retinoic acid doing in the skin? Using sensitive helium-neon laser-Doppler devices, researchers have been found that retinoic acid stimulates new growth of tiny blood vessels, which may help the regeneration of damaged skin cells.[2] Retinoic acid could speed up the production of collagen and elastin as well. There also is evidence that retinoic acid inhibits the production of the pigment granules, called melanosomes, within the melanocytes.[3] The side effects of retinoic acid, such as skin redness, swelling, stinging, dryness, itching and sensitivity to sunlight, are well known among skin care professionals. Recently, Renova*, a 0.05% retinoic acid cream, has been approved with substantial cautions by the Food and Drug Administration (FDA) as a topical anti-aging prescription drug.

Retinol is an important regulator of epidermal cell growth. Epidermal development in part is regulated by retinol and retinol can modulate total collagen synthesis just like retinoic acid.[4] Laboratory studies also reveal that cells return to a more normal stage, or normalize, if retinol is mixed with a cell that shows signs of becoming cancerous. Retinol's ability to normalize pre-cancerous squamous cells and pre-cancerous basal cells probably is caused by its effect on the deoxyribonucleic acid genetic material within them.[2] Skin absorbs retinol well and maintains its softness and plumpness because of it. Retinol improves the skin's water barrier properties, rendering it useful in treating seasonal or environmental problems such as dryness, heat or pollution. The Hamburg Clinic of Experimental Dermatology in Germany conducted a test on men and women between 22 and 43, and discovered that a low concentration of retinol (0.034%) could reduce the number and depth of wrinkles.[5]

A radioactive tracking method has proven that retinol can be absorbed readily by the skin, much like vitamin E.[6] Vitamin A is mobilized from the liver and delivered to tissues in the form of retinol bound with a specific protein.[7] This probably is why retinol can be absorbed efficiently by the skin. It has been demonstrated that the skin is able to oxidize retinol to retinoic acid through nonspecific esterase enzyme activity.[4]

Retinyl palmitate has been shown to have a significant biological effect on the skin as well. After application of 0.1–5% w/w** vitamin A palmitate on the skin for 14 days, there was a maximum 32% increase of protein per unit of skin surface area and a maximum 128% increase of collagen per unit of skin area when compared to a blank (0%) vitamin A vehicle.[8] In an in vivo use test—an on-site or real condition study—incorporating a special analytical method using a non-invasive test method, retinyl palmitate exhibited a 14.4% improvement in skin elasticity, and a 22.66% improvement rate after two and four weeks, respectively, as compared to the placebo.[9] A significant increase in skin thickness was observed as well. Since retinyl palmitate is the largest retinyl ester, having the highest molecular weight of the retinoids, it might have poor skin penetration.[3]

Retinyl propionate is reported to address skin changes taking place from natural or innate aging.[10] Retinyl acetate has the smallest molecular weight among all retinyl A esters. Retinyl acetate, therefore, most likely penetrates the skin better than retinyl propionate and retinyl palmitate. Due to gentle biochemical activity, retinol, retinal and retinyl esters do not have the harsh side effects of retinoic acid, even at concentrations of up to 10%.

Two-way reactions

In chemistry, most retinoids can be derived from retinol. (See **Retinoid Routes**.)

According to the chemical equilibrium theory, there are always two-way reactions. This is similar to two-way traffic. For instance, the triglyceride fats can be hydrolyzed to free fatty acids and glycerol. In turn, free fatty acids and glycerol can be combined to form triglycerides. Which direction is more favorable? It depends on the conditions, such as relative concentrations, temperature and the enzymes present.

For example, during physical exercise the concentration of fatty acids that supply energy decreases due to body consumption, so the hydrolysis of triglycerides becomes more favorable. In contrast, if the activity of lipase, a triglyceride enzyme, increases, the triglyceride hydrolysis is favored and more decomposition occurs. Most of the anti-fat products on the market intend to stimulate the lipase activity of lipase to achieve fat hydrolysis.

In **Retinoid Routes**, retinol or retinoic acid could be converted to retinyl ester by esterification. Conversely, the retinyl esters could be converted back to retinol or retinoic acid by hydrolysis as well. A large proportion of retinyl esters would facilitate hydrolysis to produce retinol or retinoic acid. Therefore, including a significant concentration of retinyl esters is a clever way to keep retinol stable.

Vitamin A complex

A mixture of retinoids has been designed appropriately to achieve a synergistic effect of the vitamin A family on the skin.[11] This mixture, called vitamin A complex, uses a low concentration of retinol stabilized with much greater concentrations of different retinyl esters. Vitamin A complex should be incorporated into an appropriate oil base in a stable emulsion, either a cream or lotion.

The vitamin A complex takes advantage of the diverse anti-aging effects of all retinoids, while excluding the possible harsh side-effect of retinoic acid.[11] The normalizing effect of the vitamin A complex is certainly a plus for helping prevent of skin cancer.

In addition, vitamin A complex is quite stable compared to retinol and achieves significantly better skin penetration than the popular retinyl palmitate. Many users, including those with sensitive skin, experienced some favorable results after using vitamin A complex for five to seven weeks.[12]

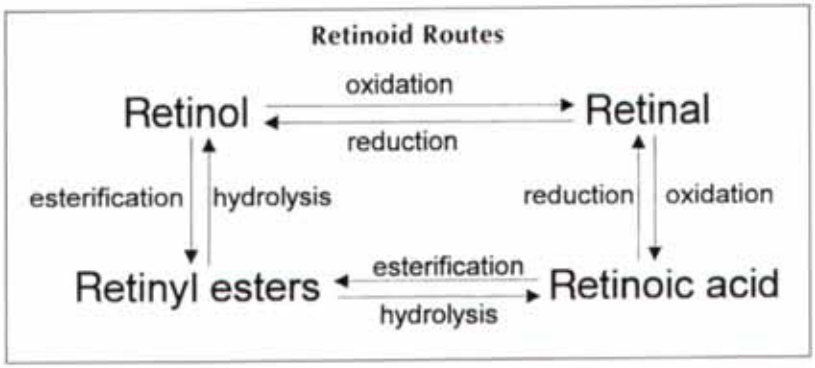
Since all retinoids are oil-soluble, the vitamin A complex is lipophilic and can take care of lipophilic sites on the skin. Thus, vitamin A complex is an excellent complement

*Renova is a registered trademark of Ortho-McNeil Pharmaceutical, Raritan, NJ.

**Weight by weight. For example, 0.1% means 0.1 gram in 100 gram total weight.

to alpha hydroxy acid (AHA) treatments, which are water-soluble and treat hydrophilic sites on the skin more effectively. Extensive application has shown that AHA treatments can achieve considerably better results after preconditioning skin with vitamin A complex every night for two to three weeks. Vitamin A complex may be an excellent replacement for the preconditioning usually done with retinoic acid before a chemical peel.

The use of Vitamin A complex is an innovative approach in skin care technology. It harnesses the advantages of natural vitamin A and several of its derivatives to provide powerful anti-aging skin benefits. The skin absorbs vitamin A complex better than the most stable derivative alone, and the complex is both safe for the skin and possesses a fairly stable shelf life. ■



References

1. D Djerassi, The role of the corrective vitamins A, B5 and C in new high performance Cosmetics, *Drug & Cosmetic Industry*, 60–62 (June 1997)
2. R Weiss, Wrestling with wrinkles, *Science News*, 134, 200–202 (1988)
3. D Blumenthal, Bold New Skin Treatments, *The New York Times Magazine*, 17–40 (April 16, 1989)
4. B Idson, Vitamins in cosmetics, *Drug & Cosmetic Industry*, 36-39 (May 1990)
5. The Ointment, *Vogue*, 266–267 (November 1988)
6. KH Merrell, Skin Rx, *Allure*, 124 (November 1994)
7. A Bendich, L Langseth, Safety of vitamin A, *Amer J Clin Nutr*, 49, 358–371 (1989)
8. DF Counts, F Skreko, J McBee, AG Wich, The effect of retinyl palmitate on skin composition and morphometry, *J Soc Cosmet Chem*, 39, 235–240 (July/August 1988)
9. CG Fthenakis, In vivo assessment of skin elasticity using ballistometry, *J Soc Cosmet Chem*, 42, 211–222 (1991)
10. S Lord, Veni Vidi Vici Vitamins, *Vogue*, 87 (January 1994)
11. J Hopkins, New anti-wrinkle gel screens harsh sunlight, *The Amer Chiropractor*, 87 (March 1989)
12. J. Hopkins, Rejuvi "a" An Aging Skin's Rejuvenator, *Whole Life Times*, 27 (October 1989)

Notes

Notes