

Retinoids and their use in cosmetics

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Although already veterans among the cosmetic active agents they are the number one active agents among the cosmeceuticals: retinoids. This naturally occurring substance class is omnipresent in our daily skin care, our medical drugs and our daily nutrition.

Retinoids belong to the terpene family which is commonly found in the flora and fauna. Terpenes occur in aromatic substances and spice plants, cellular structuring substances, hormones and vitamins. Their basic unit is isoprene which has 5 carbon atoms (C). Monoterpenes consist of two isoprene units and consist of 10 C atoms. Diterpenes have 20, triterpenes 30 and tetraterpenes 40 C atoms. Chemical functionalization results in alcohols, aldehydes, ketones, ethers and acids.

Supporting the metabolism

Vitamin A (retinol) is a diterpene alcohol (C₂₀H₃₀O) occurring in cod liver oil, innards and egg yolk; it has broad influence on the human metabolism. Vitamin A is used in regenerating skin care products because of its stimulating effect on cell formation and collagen synthesis. As almost all the retinoids, vitamin A is sensitive to oxygen – hence vitamin A containing cosmetic preparations should not be applied during the day and in blazing sun. Oxidation into vitamin A acid, the main active agent also happens in the epidermis; in this case however the oxidation is targeted for. Vitamin A acid has been banned in skin care preparations for years, but is licensed as tretinoin (INN) in dermatological applications.

Careful! Risk of irritations ...

Vitamin A has an irritation threshold. In other words: With higher concentrations and combinations with penetration supporting nanodispersions typical vitamin A acid effects such as irritations may be observed. Since the number of vitamin A receptors increases with the duration of the treatment, it is recommended to start with small dosages and then gradually augment the dose. Adverse reactions can hence be avoided.

Since vitamins are consumed during their bodily functions, a continuous supply is required. This applies for the organism as a whole but also for the skin. Topical applications are advantageous to the oral systemic intake in so far

as the dosage is minimal referred to the whole body however comparably high in terms of the local application.

There is a whole range of vitamin A variants. Retinyl Acetate (INCI), Retinyl Palmitate (INCI) and Retinyl Propionate (INCI) are vitamin A esters that can easily be processed in the oily phase of skin care preparations or nanodispersions. After their passage through the skin barrier, the esters are enzymatically cleaved and release the vitamin right there where it is needed. Retinal is the technical term for vitamin A oxidised into an aldehyde. It occurs in the eyes and is vital for the visual function. In the skin, retinal is oxidised into vitamin A acid (retinoic acid) similar to retinol.

3-Dedhydroretinol occurs in the liver of cold water fish and is referred to as vitamin A₂.

This is where colour comes in

Beta-carotene (provitamin A) is a tetraterpene which is sensitive to oxygen; it is responsible for the typical colour of carrots and used as food dye (E 160a). As provitamin A it is enzymatically cleaved into two vitamin A molecules in the body. The carotenoid family consists of numerous fat-soluble tetraterpenes with colours varying from red via orange to yellow (e.g. tomatoes, bell peppers [alternatively called capsicums, sweet peppers], rose hips or oranges). They also are used as colouring additives in food and cosmetic products. E 160c is the code for the dark red capsanthin (bell pepper extract) which for instance is used as feed supplement in order to intensify the colour of egg yolk. Lycopene (E 160d) is a component of the red colour of tomatoes and rose hips. The oxygen containing xanthophylls such as for instance the orange-yellow luteine (E 161b) also are tetraterpenes with a colour range from yellow to violet.

Even the feed supplement astaxanthin (E 161j) and canthaxanthin (E 161g), both responsible for the colours of shellfish such as lobster or shrimps or the typical colour of salmon belong to the colourful carotenoids.

The coloration of carotenoids originates from the conjugated double bonds which also are

responsible for the antioxidant features. Assumed anti-carcinogenic and anti-aging effects could not be proved in the field. On the contrary, even carcinogenic effects could be observed under artificial conditions.

The consumption of carotenoids (carotene, lycopene) influences the skin complexion and an appropriate consumption in terms of quantity and duration can individually cause a light sun protection factor in the range of 2 to 3. In the skin care field, retinoids, mostly in the form of retinol esters, are frequently used in nano-disperse biodegradable form to prevent premature skin aging, accelerate the recovery in the case of cornification disorders and to treat problem skins. Examples are:

- **Mature skin:** The regenerative effects of vitamin A in combination with the antioxidant vitamins E and C can reduce wrinkle formation. Cell formation and collagen synthesis are stimulated.
- **Blemished skin and acne:** In these cases a combination of vitamin A with liposomal vitamin B₃ (INCI: Niacinamide) is recommended since vitamin B₃ also has recovering and anti-inflammatory effects on the cornification disorders at the exits of the sebaceous glands. The linoleic acid released by the phosphatidylcholine of the liposomes also inhibits inflammations and fluidizes the sebum.
- **Ichthyosis:** The fish skin disease as well is a form of hyperkeratosis and appears as a disordered scaling of corneocytes. In this case it is advisable to apply vitamin A in combination with lamellar creams (without emulsifiers).
- **Other hyperkeratoses and various types of scars:** Beneficial are the vitamins A, C and E – it is suggested to apply pure active agent concentrates at an early stage already. Appropriate peelings at regular time intervals may be helpful.
- **Rosacea** is characterized by erythemas caused by damaged superficial capillary vessels and disorders of the connective tissue. The synergy of vitamin A (recovery), antimicrobial azelaic acid (5-alpha reductase inhibitor) and anti-inflammatory boswellic acids (protease inhibitors) is beneficial in the cosmetic skin care.
- **Hyperpigmentations:** In the context of abrasive techniques such as mechanical, chemical peelings or microdermabrasion, vitamin A supports a fast cell replacement and accelerates

the skin whitening. Tyrosinase inhibitors such as liposomal ascorbyl phosphate (vitamin C phosphate), natural polyphenols or tranexamic acid have synergistic effects.

Risks and adverse effects...

With higher concentrations and in combination with penetration enhancing nanodispersions, vitamin A acid effects such as erythema and irritations can be observed. An oral overdose of vitamin A in pregnant women can cause adverse health effects to the unborn child. This should be considered in the nutrition scheme (liver, innards). The daily oral demand is about 2500 IU (1 IU = 0.75 mg); a daily oral intake of 10,000 IU is considered as safe. Cosmetic active agent concentrates can contain up to 6000 IU/ml. This sounds quite a lot, however needs to be put into perspective to the small amounts that are applied, to the substance losses during the passage through the skin barrier and the rather fast metabolization in the epidermis.

Systemically relevant concentrations are not yet known. A study could prove that the application of 0.3% retinol and 0.55% retinol palmitate (30,000 IU = 9 mg) once a day on a surface of 3000 cm² of skin (back, thighs) over a period of 21 days has no measurable effect on the plasma level. The German Federal Institute for Risk Assessment (BfR – Bundesinstitut für Risikobewertung) has no objections against its application twice a day (0.3% facial cream, 0.05% body lotion). Nevertheless, the Federal Institute for Risk Assessment mentioned in statement 005/2014, issued on 31st January 2014: The BfR recommends restricting the vitamin A concentration in cosmetic preparations to the facial and hand care. Vitamin A should not be used in lip and body care products.

Use in cosmeceuticals

Vitamin A esters are an elegant option for activating dermal growth factors. They generally are clearly superior to the growth factors with high molecular peptide structures used in cosmeceuticals which even in combination with penetration enhancing substances are not very effective due to their poor penetration.

Medical retinoids

In the medical field vitamin A acid (retinoic acid, tretinoin) is primarily prescribed against acne and hyperkeratoses. As for vitamin A, the teratogenic effects in the case of overdoses have to be considered. Isotretinoin (13-cis retinoic acid) distinguishes by the different cis-

position of the tretinoin acid group (trans-position). Indications basically are similar.

Other pure synthetic compounds such as acitretin (INN), adapalene (INN) and tazarotene (INN) also belong to the medical retinoids prescribed to treat cornification disorders (acne, psoriasis). They are structurally different from the natural retinoids because of their aromatic ring systems.

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