

Skin whitening agents from A to Z – a summary

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When you cut an apple and leave it uncovered, it will quickly turn brown. This brown colouring originates from the oxidation of the polyphenols of the apple with atmospheric oxygen assisted by the enzyme phenoloxidase. Lemon juice with its high content of antioxidant vitamin C can impede this reaction.

The tanning of the skin actually is a similar reaction and occurs as follows: The natural enzyme tyrosinase in the skin which is formed by the melanocytes of the basal layer is closely related to the vegetal phenoloxidase. While absorbing atmospheric oxygen, it transforms the phenolic amino acid tyrosine into blackish-brown eumelanin after passing through the intermediate stages of L-dopa, dopaquinone and indole-5,6-quinone. The reddish-yellow pheomelanin forms by reaction of dopaquinone and sulfurous cysteine via the intermediate stage of cysteinyl dopa. Varying ratios of eumelanin and pheomelanin together ("melanin") determine the skin colour. UV radiation intensifies the melanin formation. Melanosomes and melanocytes increase and the skin starts to tan.

Nevertheless, people have different attitudes towards tanned skin. The population in South East Asia generally prefers even and fair skin while people in our climes rather favour tanned skin although they try to get rid of pigmented spots that attract the attention due to the contrasting effect. Examples in this context are freckles, age marks respectively melasma (chloasma faciei) which is the generic term for hyperpigmentations.

Hyperpigmentations

There are various causes for hyperpigmentations. Besides the UV light induced activation of the tyrosinase that stimulates the pigment formation in order to protect the skin, also endogenous radicals occurring with local inflammatory processes or in medical drugs participate in the process. Photosensitizing substances contained in our nutrition, in vegetable extracts and teas as well as cosmetic products are further, relatively frequent triggers. On top of it, there are pigment naevi appearing in different colours and forms.

Besides the melanin triggered forms, there are pigmentations that contain deposits of endogenous metabolic products evoked by the oxidation of proteins and lipids (lipofuscin) as for instance the age marks.

Active agents

Undesired pigmentations and hyperpigmentations are treated with medical and cosmetic therapies. Besides equipment-based techniques such as laser and microdermabrasion, the following active agent groups are administered:

Active agents in the preventive depigmentation

- tyrosinase inhibitors
- antioxidants
- substances that reflect UV radiation or transform them into heat

Active agents to remove existing pigment spots

- melanin-degrading substances
- substances with regenerative effects
- peelings

Vitamin C

It is frequently difficult to distinguish between the individual effects. Liposomal vitamin C in the form of Ascorbyl Phosphate (INCI) acts not only as a tyrosinase inhibitor but also impedes the oxidation related consecutive steps; it even can reduce partially quinoid structures of eumelanin. This can be recognized by a light bleaching of the already formed melanin, particularly if an abrasive peeling or microdermabrasion has been implemented before the application. Apart from that, Ascorbyl Phosphate is used for preventive purposes. Free vitamin C is less appropriate due to its instability towards atmospheric oxygen and its low penetrability. This can easily be recognized during laser treatments which stimulate the tyrosinase activity. Liposomal ascorbyl phosphate completely suppresses the formation of melanin while free vitamin C reacts with a brownish colouring (application before and after the laser treatment). The chemically bound linoleic acid in the liposomes-forming phosphatidylcholine synergistically contributes to the bleaching process.

Polyphenols

Antioxidants only are partially beneficial since they are fast consumed by scavenging the oxidizing oxygen. This particularly applies for polyphenol compounds such as catechins, resorcinols, flavones, isoflavones and gallates respectively the extracts from green and black tea, coffee, pomegranates, soybeans and red clover. Hence they are not very often used for skin whitening purposes.

The readily oxidation of polyphenols can be observed after leaving a cup of hot black tea uncovered; it darkens and forms black rims. Stronger antioxidants such as the vitamin C of lemon juice suppress this reaction and the tea maintains its light colour.

Rucinol (4-butyl-benzene-1,3-diol) is a tyrosinase inhibitor of the resorcinol group and can be applied in topical pharmaceutical but also cosmetic preparations.

Azelaic acid

Competitive tyrosinase inhibitors such as azelaic acid only are effective in higher concentrations which only are reserved for topical pharmaceutical preparations. Nevertheless, the maximally licensed dosage for cosmetic products of up to one per cent also is effective if applied on a long-term base. Azelaic acid is a non-toxic dicarboxylic acid that naturally occurs in cereal crops and has antimicrobial effects on the acne and rosacea skin. In the case of troubled acne skin the contrast reducing effect is beneficial.

Hydroquinone & Co.

Cosmetic active agents generally take several weeks until their preventive effects become visible. Frequently vegetable extracts are used for preventive treatments. Their specific whitening components and mode of action sometimes still are unknown in detail. Examples are extracts from common mallow (*malva sylvestris*), peppermint (*mentha piperita*), cowslip (*primula veris*), lady's mantle (*alchemilla vulgaris*), common gypsyweed (*veronica officinalis*), balm (*melissa officinalis*), yarrow (*achillea millefolium*), or liquorice root (*glycyrrhiza glabra*, (active agent: glycyrrhizin). Some of the extracts contain arbutin (4-hydroxyphenyl- β -D-glucopyranoside), a glycosidic compound of hydroquinone with glucose that also is used in whiteners as a pure substance. In comparison with hydroquinone, arbutin is less sensitive to atmospheric oxygen which is an advantage though. Studies on the arbutin metabolism have shown that only minor amounts of the substance are cleaved into their individual

components¹. In spite of that, the Federal Institute for Risk Assessment in Germany (BfR) classifies the release of hydroquinone as unsafe². Hydroquinone only is licensed for hair dye products up to a maximum concentration of 0.3% with the respective labelling "contains hydroquinone"; yet it is no longer approved for cosmetic whitening products. By contrast, the substance still is contained in medical preparations. Hydroquinone impedes the tyrosinase and presumably contributes to the degradation of melanosomes and the destruction of melanocytes. Correspondingly, a preventive effect and the whitening of an already existing pigmentation can be observed.

Retinoids

In topical whitening pharmaceuticals hydroquinone is combined with other substances as for instance hydrocortisone and retinoids such as vitamin A acid. Vitamin A acid prompts intense cell formation activities and accelerates the degradation of pigments. A similar effect can be achieved with biodegradable cosmetic vitamin A nanoparticles which excel by their high bioavailability of vitamin A that is metabolized into vitamin A acid in the epidermis. Hydrocortisone in medical whitening preparations reduces the pigment formation of the melanocytes³.

Kojic acid

Similar to hydroquinone, kojic acid (5-hydroxy-2-hydroxymethyl-4H-pyran-4-one) is a highly effective reducing agent and inhibits the tyrosinase. Kojic acid has intense bleaching effects and is commonly used in Asia. In Europe, for a long time, the substance with its mutagenic effects on bacteria has been under suspicion of being carcinogenic. Until today the studies led on this topic could not substantiate the suspicion¹. In Switzerland, kojic acid is not licensed for cosmetic preparations.

Tranexamic acid

Also very commonly used in Asia is tranexamic acid; in Germany it is administered as antifibrinolytic medication (plasmin inhibitor). Since

¹ BfR: 73., 74. und 75. Sitzung der vorläufigen Kommission für kosmetische Mittel, Tagungsbericht vom 20. November 2008

² β -Arbutin in Hautaufhellungsmitteln ist gesundheitlich bedenklich; Stellungnahme Nr. 007/2013 des BfR vom 25. Februar 2013

³ Niedner R, Glukokortikosteroide in der Dermatologie, Deutsches Ärzteblatt 94 (44), A-2868-2872 (1996)

tranexamic acid also effectively inhibits the tyrosinase⁴, it has not only a bleaching effect on the pigmentation but also reduces the translucent reddish colouring of the blood vessels and hence leads to an even complexion. Liposomal dispersions are particularly effective in the case of melasma.

Dr. Hans Lautenschläger

Treatments and precautions

The effects of whitening agents are intensified by accompanying fruit acid therapies. AHA acids such as glycolic acid remove the superficial melanin-containing material. By stimulating the cell formation also the melanin containing cells are faster replaced. Salicylic acid and highly concentrated free vitamin C (ascorbic acid) also have keratolytic effects. The same applies for mechanical peelings with exfoliating wax particles or enzyme peelings.

When applying whitening formulations it is most important to use reflective and UV radiation absorbing sun protection preparations as an accompanying measure. Since the natural protection through melanin is missing, it is obvious that the skin is more sensitive to the impact of UV radiation. In this context also the accompanying use of CM-glucan as a cell protecting measure is suggested for the daily skin care.

Details on photosensitizing and phototoxic substances involving undesired pigmentations have only recently been discussed in the article "Schattenseiten - Erscheinungsformen von Lichtdermatosen", Kosmetik International 2013(5), 32-35, also published on our website as "Shady sides – on the manifestations of light dermatoses". It is essential to avoid these substances particularly if they are of cosmetic or pharmaceuticals-related origin.

Skin whitening also can appear as a side effect of using particular substances as for instance dibenzoyl peroxide, which is an active agent of pharmaceutical anti-acne creams and used for tooth bleaching or hair lightening purposes. Recent studies also assume that senile hair greying can be ascribed to the effects of endogenous hydrogen peroxide⁵.

⁴ Lee JH, Park JG, Lim SH, Kim JY, Ahn KY, Kim MY, Park YM, Localized intradermal microinjection of tranexamic acid for treatment of melasma in Asian patients: a preliminary clinical trial. *Dermatol Surg.* 2006 May ;32(5):626-31

⁵ Wood JM, Decker H, Hartmann H, Chavan B, Rokos H, Spencer JD, Hasse S, Thornton MJ, Shalhaf M, Paus R, Schallreuter KU, Senile hair graying: H₂O₂-mediated oxidative stress affects human hair color by blunting methio-

nine sulfoxide repair. In: *The FASEB Journal* 23 (7), 2065–2075 (2009)