

# Highly effective – Cosmeceuticals

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When can we or should we speak of cosmeceuticals or to put it another way, cosmetic ingredients with pharmaceutical effects? Cosmetologists and lawyers assiduously discuss the matter. Read more on the respective criteria and on the substances and applications that act as the model for cosmeceuticals.

**C**reating new terms is part of the cosmetics and skin care business since new terms stir up curiosity and encourage testing. If these terms are borrowed from medicine or pharmacy you can be sure that the public becomes interested in the new product. Dermatocosmetics, dermaceuticals, skinceuticals and finally also cosmeceuticals were created in this way. If on top of that, a "Dr." garnishes the brand name to refer to a medical or scientific background excellent sales figures are almost guaranteed. However, the term cosmeceuticals neither appears in the European Cosmetic Directive nor in the stringent regulations of the American FDA. Nevertheless, it makes sense to define the term if a certain level of quality should be associated with it.

## Transdermal applications

Pharmaceuticals, hence topically applied pharmaceuticals intervene in the physiology of the skin and the subjacent tissue or even have systemic effects – keyword: transdermal applications. They are used for the treatment of the skin and if applicable also for the prevention of diseases. The aim either is to restore physiological functions or to modify them in order to relieve the implications of a disease such as pain, inflammations etc. Often enzymes or growth factors of the body are stimulated, replaced or inhibited in the process. For a long time, it has been assumed that cosmetics do not (or shall not) produce such effects. Although a successful treatment of dry skin through lipids with the related effects of a tightening of the skin (on first sight) intervenes in the physics of the horny layer it will not interfere in the physiology of the living epidermis. That is why the cosmetic legislation explicitly excludes the healing and relief of diseases and all public relation in this context is illegal on principle.

Nevertheless, it is not a new discovery that cosmetics can have more than just physical effects. To instance again the treatment of dry skin: If instead of a neutral oil (INCI: Caprylic/Capric Triglyceride) a vegetable oil

such as evening primrose oil (INCI: Oenothera Biennis Oil) is used, the neurodermatitis patient suffering from a delta-6-desaturase deficit will not only see a skin tightening effect but also experience a substantial modification or in other words improvement of the symptoms of his disease. At least since the studies of Albert M. Kligman on "water dermatology" as he called it and on corneotherapy in the late nineties, it has become known that even plain cosmetic moisturizers may have clinical effects. In order to avoid legal problems, terms such as "supports the prevention of..." have been coined already at an early stage. As a matter of fact, this phrase cannot be criticized since an individually adapted skin care is beneficial for almost every medical indication. If this specific skin care is administered in medical centres or clinics we speak of "advanced corneotherapy" today.

## Cosmeceuticals – the criteria

Though, when can we or should we speak of a cosmetic ingredient with pharmaceutical effect alias cosmeceutical? This is a major point of discussions between cosmetologists and lawyers although there is consensus on the following criteria:

- The ingredient should not be listed among the banned substances in the European Cosmetic Directive.
- Systemic effects have to be excluded. Example: Hormones are banned in cosmetics. Phytohormones (isoflavonoids) are permitted, they have low, however localized estrogen effects.
- The active agent needs to be capable of penetrating into the skin barrier and then permeating into the epidermis as his destination. For this purpose it can be combined with penetration enhancing substances (carriers). Example: Phosphatidylcholine "transports" lipophilic as well as hydrophilic substances.
- The destination (cell, tissue, blood vessel, enzyme, receptor etc.) and the

triggered, intervened or inhibited biochemical process there should be proven in vitro and in vivo.

- The externally visible and advertised effect has to be clinically evident, statistically proven, reproducible and significant. This kind of reasoning however is difficult to accomplish in the case of an advertised antiaging effect. That is why not just any new radical scavenger can be counted among cosmeceuticals.
- The product safety of the substance with regard to its toxic profile according to the requirements of the EU Cosmetic Directive has to be documented in the safety report.
- The ingredient also can be a pharmaceutical active agent that improves and stabilizes the condition of the skin and eliminates skin disorders. Examples: D-panthenol (in the case of erythema), azelaic acid (utilized in liposomal form in the case of bad skin, up to 1 %), tranexamic acid (skin whitening), clotrimazol (dandruff). The pharmaceutical claims such as skin healing, acne treatment, inhibition of fibrinolysis and antimycotic effects are not allowed for sales promotion purposes even if they are evident with the use in cosmetic formulations.

If the above-mentioned criteria are strictly interpreted, many highly praised and modern cosmeceuticals would just fall through the cracks – either as a single substance or in a preparation combined with other substances. Frequently the originally proven effect is assumed to be effective in much lower doses without ever having verified it. In other words: Not every package that is labelled as a cosmeceutical contains cosmeceuticals. It should also be mentioned that there are preparations which fully comply with the criteria for cosmeceuticals however are not advertised as such.

### Basic conditions

Substances such as the mentioned evening primrose oil often are not used at 100% but included in a matrix of emulsions, membrane creams, liposomes, nanodispersions or non-aqueous formulations. In this context the diluting matrix not necessarily reduces the efficacy as already mentioned above but may even enhance it due to an improved availability. It is crucial to choose the adequate galenic formulation though.

Since they are not used on the skin surface but destined to be effective in the deeper layers of

the skin, cosmeceuticals should be free of counterproductive additives. Consequently perfumes and allergenic preservatives do not fit the concept. In order to avoid a washout of active agents and skin components, non-degradable emulsifiers are a taboo in the case of barrier disorders. With cornification disorders as for instance acne, paraffin oils and comedogenic hydrocarbons do not correspond with the cosmeceutical principle. While lipids should be avoided in the formulations in the case of perioral dermatitis minor doses are allowed with rosacea.

To come straight to the point: The matrix should guarantee an excellent availability, correspond with the physiology of the skin, be free of unnecessary additives and avoid adverse effects. Basically it can be said that these are the same, albeit often also disregarded claims as for topical pharmaceuticals, a fact that has contributed to the *raison d'être* of cosmeceuticals. Conclusion: Cosmetic products have fewer restrictions regarding the selection of their matrix components but are in no way inferior to pharmaceuticals.

### Application

- **Antimicrobial substances** (acne, rosacea, perioral dermatitis): azelaic acid (5-alpha-reductase inhibitor), salicylic acid, clotrimazol, rosmarinic acid, betulinic acid
- **Antioxidants (anti-aging):** oligomeric proanthocyanidins (OPC), vitamin C- and vitamin E-esters (after enzymatic cleavage), glutathione, coenzyme Q<sub>10</sub> (after reduction in the skin), other polyphenols
- **Stimulation of growth factors (anti-aging, regeneration):** retinoids, vitamins, echinacea
- **Chemical peelings:** fruit acids in high concentrations with low pH, salicylic acid
- **Localized hormonal effects incl. influence on hair growth:** isoflavonoids and other polyphenols, prostaglandin-analogues (eyelashes)
- **Stimulation of the collagen formation (anti-aging):** peptides, vitamin C esters
- **Wrinkle reduction:** peptides, spilanthol and capsaicinoids (influence on nerves), hyaluronic acid (hydrogen bridge bonds), 2-dimethylaminoethanol (DMAE, metabolite of phosphatidylcholine), retinoids (regeneration)
- **5-lipoxygenase inhibitors (neurodermatitis, acne):** 3-acetyl-11-keto- $\beta$ -boscwellic acid, nordihydroguajaretic acid,

- hyperforin (St. John's wort extract), omega-3 fatty acids
- Stimulation of lipolysis and microcirculation: caffeine, green tea, centella asiatica, isoflavonoids
- Tyrosinase inhibitors (hyperpigmentation): vitamin C phosphate, tranexamic acid, specific vegetable extracts, arbutin, antioxidative polyphenols
- Inflammation inhibitors: gamma- and alpha linolenic acid, D-panthenol, 3-acetyl-11-keto- $\beta$ -boswellic acid, aloe vera,  $\alpha$ -bisabolol, rosmarinic acid
- Trace elements: copper peptides (collagen formation), liposomal zinc salts (anti-inflammatory), manganese salts (vitiligo)
- Tightening and vessel stabilizing substances (rosacea, couperosis, eye and décolleté preparations): saponins of kigelia, butcher's broom, horse chestnut and horsetail, tranexamic acid
- Growth factors and messenger substances (anti-aging): different peptides
- AGE inhibitors (AGE = Advanced Glycation Endproducts): kinetin (N-furfuryladenine), alpha-lipoic acid, resveratrol, curcumin
- Barrier active substances (barrier disorders): ceramides, linoleic acid, phosphatidylcholine
- Active agents against cornification disorders (e.g. acne): retinoids, phosphatidylcholine
- Moisturizers: amino acids and urea in combination with penetration enhancing substances
- Anti-itching substances: urea, allantoin, long-chained fatty acid amides

Studying the technical literature it becomes clear that many of the substances listed will not comply with the above-mentioned criteria, which is frequently due to the fact that specific data concerning biochemistry, penetration and also clinical studies are missing.

Often classic substances with long-term practical experience are concerned. One of the most analyzed substances is nicotinic acid amide (vitamin B<sub>3</sub>, niacinamide). By contrast, there are only few reliable data on hyaluronic acid; only a minor low molecular fraction will penetrate of the polysaccharide. Both improved skin hydration and wrinkle reduction are based on superficial effects – also in the case of liposomal combination products.

Vegetable stem cell extracts are omitted in the list since only concrete substances in relevant dosage are of importance and not their origin.

On the other hand, vegetable cell cultures can be an excellent method to biotechnologically produce complex cosmeceuticals. An example here is the anti-inflammatory and antimicrobial rosmarinic acid.

In the case of the vitamins A, C and E the esters are predominant (acetates, palmitates, stearates, phosphates etc.). They represent the inactive transport forms which are enzymatically cleft after passing the stratum corneum. In this case, already low concentrations are sufficient in order to meet the criteria for cosmeceuticals while even high concentrations of their free compounds as for instance 10-15% ascorbic acid are not enough to comply with the requirements. This also applies when they are combined with strong chelating agents such as EDTA which besides their heavy metal eliminating activity also inactivate physiological trace elements in the skin and are rather persistent with respect to biodegradability.

An interesting fact is the multifunctionality of some compound classes. Thus many polyphenols (flavonoids, isoflavonoids, resveratrol, proanthocyanidins, epigallocatechin gallate [EGCG] etc.) frequently show a combination of antioxidative, antimicrobial and tyrosinase inhibiting effects if effective penetration enhancing substances in the formulation guarantee a sufficient penetration of the partly very complex structures.

### Medical Skincare

In connection with cosmeceuticals also terms such as "medical cosmetics", "cosmedics" or "medicosmetics" are circulating. While in Germany they have to comply with the Cosmetic Directive, in the US and in different countries of South East Asia particular products such as sun protection products fall within the definition of "medical skincare". These products are submitted to a separate, complex and costly registration process. The authorities in charge also routinely control the content of UV filters. The close monitoring results from the fact that skin damages cannot be excluded if dosages are undercut and the consumers rely on the package labels.

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