Update on cosmeceuticals

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Summary
As youth and perception of beauty are considered to be of great importance, an increasing number of new cosmeceuticals have been developed in recent years. This article will briefly present the problems of distinguishing cosmetics, cosmeceuticals or drugs and describe important new developments in raw materials, carrier systems and ingredients from the dermatological point of view. Especially active ingredients against skin-aging, here in particular antioxidants and cell regulators, are reviewed. Important parameters for the quality of cosmetics and cosmeceuticals are evidence-based in-vivo and in-vitro efficacy as well as scientifically proven wanted and unwanted effects.

Introduction
The word cosmetic comes from Greek from the adjective “kosmétikos” or the verb “kosméo” and can be translated as “to straighten up” or “to decorate”. Over long time periods and cultural epochs up to today’s modern society cosmetics have been understood as procedures and products for beauty care that serve the preservation and restoration or improvement of the beauty of the human body. Even though ideals of beauty are in continual flux, the wish for preservation of and representation of youth has remained constant. Particularly in today’s Western civilization overflowing with the media, youth has become a cult, almost a standard of quality. Studies have proven that individuals with an attractive appearance have distinct social advantages in comparison to people who are subjectively perceived as less attractive. The skin is of great significance in the judgment of attractiveness. After all it is the medium that reflects beauty and youthfulness directly and is continually open to public view. At the same time, skin is the organ that displays signs of aging most visibly. With increasing average life expectancy the wish for an attractive appearance exists often into older age. Dermatocosmetic products against skin aging are – in addition to minimally invasive procedures – gaining in significance.

In current evidence-based dermatocosmetics, the traditional term of cosmetics has been expanded and is thus defined as cosmetics based on scientific and technological research.

Quality features
Even though the legal definition of a cosmetic product is uniformly regulated in German, the differentiation between cosmetic products (§ 2 Abs. 5 German Food
and Feed Code; Lebensmittel- und Futtermittelgesetzbuch, LFGB), medical products (§ 3 German Medical Devices Act; Medizinproduktegesetz, MPG) and drugs (§ 2 German Drug Law; Arzneimittelgesetz, AMG) can be highly difficult depending on purpose and mechanism of action. For example, cosmetic products can indeed serve as protection from pathological lesions and/or medical products can be expressly employed to prevent, treat or alleviate diseases [1]. The borders are increasingly becoming indistinct and the list of products on the borderline of the respective product groups is long. The term “cosmeceuticals” introduced by Kligman in the USA in the 1980s combines the English terms “cosmetics” and “pharmaceuticals” and is used for products that have a positive effect on the skin, but not a medical-therapeutic effect, thus attempting to close this gap. To date, however, the term is controversial, at least in Germany; at present, cosmeceuticals do not have a legal foundation.

The attention that the cosmetic and pharmaceutical industry pays to the development of pharmacologically active cosmetics and to cosmetically oriented medications currently leads to increasing medical importance of dermatosmetic products. Especially the immense abundance of cosmetic products against skin aging demands a critical evaluation of the promised effects. Dermatocosmetics whose quality is established should possess adequate scientifically documented proof of in vivo and in vitro efficacy and scientifically founded wanted and unwanted effects. According to the guideline “Dermatocosmetics against Skin Aging” of the Society for Dermopharmacy (GD) anti-aging agents are classified into three different categories according to scientific data. The first category includes agents with proven efficacy in vivo. The second category includes agents with proven efficacy in vitro, while the third category includes agents lacking evidence for efficacy in the scientific literature.

**Bases and vehicle components**

Efficacy, tolerability and properties of use of dermatocosmetics are determined not only by the individual active agents, but also by the vehicle employed. It is established that a well-formulated base adapted to the state of the skin can have numerous positive effects on the skin (e.g. hydration, stabilization of the epidermal barrier).

Further, a differentiated galenic preparation has great significance, as the effects of many dermatocosmetic active agents depend highly on the overall formulation. While, for example, petrolatum allows for only moderate penetration of vitamin E into the skin, a micro- or nanoemulsion can improve effectiveness distinctly. The overall formulation with interaction between vehicle, active ingredient and skin influences the effects of the preparation as well as the liberation of the active ingredient. Important basic and auxiliary ingredients of dermatocosmetics are summarized in Table 1.

**Emulsions**

Among skin care products emulsions play an important role. In lipophilic emulsions a water phase is dispersed in a lipid phase (“oil”) – a water-in-oil (W/O) emulsion. These emulsions leave a greasy film on the skin and are often cosmetically inacceptable. In hydrophilic emulsions the lipid phase (“oil”) is dispersed in a water phase – an oil-in-water (O/W) emulsion. Quantitatively they have the greatest significance on the commercial market of dermatocosmetic skin care products.

**Emulsifiers**

The micelle-forming emulsifiers (tensides) used to stabilize emulsions always consist of a hydrophilic and a lipophilic component. As they can potentially irritate and dry the skin and disturb epidermal barrier function, what are termed polymer and solid emulsifiers are being increasingly employed as alternatives to classical emulsifiers. Examples of less irritating emulsifiers are lipoproteins, sugar tensides or phospholipids.

**DMS (Derma Membrane Structure)**

DMS multilayer creams are lamellar preparations that are comparable to physiologic skin lipids with respect to structure (lipid double membrane) and ingredients. These novel galenic formulations are not based on the conventional W/O or O/W principle, but with their lamellar structure imitate the lipids of the intercellular substance of the stratum corneum and thus are intended to improve the skin barrier.

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Nanodisperse carrier systems (e.g. liposomes) are increasingly gaining in significance as vehicle and transport system for cosmetic active ingredients, as they can increase penetration of active ingredients that are difficult to bring into the skin.

Moisturizers that both protect from dryness and smooth a rough skin surface and fine dryness wrinkles contain, in addition to emollients, occlusive agents and moisture-retaining substances.

Based on their mechanisms of action dermatocosmetic active ingredients can be classified into two large categories:
- **Antioxidants** (e.g. vitamins) can via reduction of the concentration of free radicals lower the concentration of matrix metalloproteinase and thus counteract collagen degradation,
- **Cell regulators** (e.g. peptides) can directly influence the metabolism of fibroblasts and increase their synthesis performance.

### Active ingredients in cosmeceuticals against skin aging

Due to the enormous number of active ingredients presently employed in dermatocosmetics, only a selection of active substances, whose efficacy in the prevention and repair of signs of skin aging has been proven in scientific in vivo studies, can be described in an exemplary fashion within the framework of this article. Both intrinsically as well as extrinsically aged skin exhibit loss of elasticity and wrinkles; extrinsically prematurely aged skin is also characterized by pigmentation irregularities (hyper-/hypopigmentation) and solar/ senile lentigines, whose therapy will not be discussed in the following. In order to facilitate the depiction of the clinical use of active agents in the everyday dermatological routine, the selected active agents are classified into two large categories based on mechanisms of action:
- **Antioxidants** such as vitamins, coenzymes and botanicals (plant materials), that via reduction of the concentration of free radicals lower the concentration of matrix metalloproteinase and thus counteract collagen degradation,
- **Cell regulators** such as retinol, peptides and growth factors that directly influence the metabolism of fibroblasts and increase their synthesis performance.
Antioxidants (Table 3)
Antioxidants are a heterogeneous group of agents that have the goal of reducing the concentration of free radicals in the skin and that are significantly reduced during aging and by numerous extrinsic factors (e.g. UV radiation and smoking). Based on the theory of promotion of aging by free radicals an attempt is made with the help of diverse dermatocosmetic products to supply the skin with antioxidants from the outside. As some of the most commonly employed antioxidants are vitamins, at present vitamin C (L-ascorbic acid) and vitamin B3 (niacinamide) stand in the center of dermatocosmetic strategies to treat premature skin aging [2, 3]. Besides vitamin E (α-tocopherol), that is equally often used in dermatocosmetic products, the antioxidants coenzyme Q10, melatonin and various botanicals such as flavonoids like green tea polyphenols or pycnogenol can act in a photoprotective manner and counteract skin aging in topical use.

Vitamin C (L-ascorbic acid)
The water-soluble, heat-labile molecule L-ascorbic acid (vitamin C) is a hexuronic acid that can irreversibly be destroyed by oxidation. In addition to its antioxidative effects in the skin and reduction of the concentration of free radicals, vitamin C also provides preservative properties for the skin care product itself. There is very good and evidence-based documentation in the international literature for the anti-aging

Table 2: Moisturizers in cosmeceuticals.

<table>
<thead>
<tr>
<th>Type</th>
<th>Examples</th>
<th>In vivo effect</th>
</tr>
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<tbody>
<tr>
<td>Emollients</td>
<td>Lanolin, mineral oil, Petrolatum</td>
<td>Increased corneocyte cohesion</td>
</tr>
<tr>
<td>Occlusive agents</td>
<td>Paraffin, soy bean oil, propylene glycol, squalene, lanolin</td>
<td>Reduced transepidermal water loss (TEWL)</td>
</tr>
<tr>
<td>Moisture-retaining substances</td>
<td>Glycerol, urea, hyaluronic acid</td>
<td>Increased stratum corneum hydration</td>
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Table 3: Antioxidants and skin aging.

<table>
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<td>Vitamin C</td>
<td>RCT</td>
<td>• Clinical signs of skin aging</td>
<td>Significant</td>
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<tr>
<td>Niacinamide</td>
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<td>C4</td>
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<td></td>
<td></td>
<td>• Biophysical measurements</td>
<td>improvements</td>
<td></td>
</tr>
<tr>
<td>Vitamin E (α-tocopherol)</td>
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<td>• UV-induced skin damage</td>
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<tr>
<td>α-lipoic acid</td>
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<td>Coenzyme Q10 (ubiquinone)</td>
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<td>B3b C4</td>
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<td>Green tea polyphenols</td>
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<td>Elmets et al.</td>
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Vitamin C preparations in concentrations of up to 15% offer clinically well-documented anti-aging efficacy.

Vitamin E, a lipophilic antioxidant, is today found in concentrations of 2–20% in countless skin care products, as it with very good tolerability has both positive effects on the skin and can also protect lipids of the skin care product from oxidation. According to Hakozaki et al. and Draelos et al., possible mechanisms of action include the reduction of lipids of the skin care product from oxidation and the reduction of lipid peroxidation. In a double-blind, placebo-controlled study, Beitner demonstrated distinct antioxidative effects and a significant improvement of skin elasticity and fine wrinkles. Mayer et al. were able to detect a skin smoothening effect in a clinical study on 20 women after a 4-week treatment with vitamin E. In a double-blind, randomized and vehicle-controlled study, the vitamin E emulsion displayed a higher antioxidative capacity and was better able to prevent UV-induced erythema and inflammatory skin damage. Vitamin E is a fat-soluble, heat-stable molecule that belongs to the lipophilic antioxidants and is found today in concentrations of 2–20% in countless skin care products, as it with very good tolerability has both positive effects on the skin and can also protect lipids of the skin care product from oxidation.

Niacinamide (vitamin B3)

Niacinamide is a substance contained in all human cells. Nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) serve as antioxidants in a number of enzymatic reactions. The reduced forms NADH and NADPH act as redox coenzymes. Niacinamide regulates cellular metabolism and cell renewal and due to its cosmetic advantages has been used in recent years increasingly often in concentrations of up to 5% as an anti-aging agent in cosmeceuticals. Newer double-blind, vehicle-controlled studies were able to demonstrate that a three-month topical treatment with 5% niacinamide cream significantly reduces signs of skin aging such as hyperpigmentation, skin redness, senile lentigines, yellow discoloration and large pores. Further, niacinamide with very good tolerability leads to a significant improvement of skin elasticity and fine wrinkles. By activation of serine palmitoyl transferase and increased synthesis of free fatty acids, cholesterol and ceramides in topical use, it reduces transepidermal water loss and stabilizes the epidermal barrier and is also suitable as an anti-aging agent even in hypersensitive skin. According to Hako and Draelos et al., possible mechanisms of action beyond antioxidative effects include increased collagen synthesis shown in vitro in fibroblast cultures as well as normalization of glycosaminoglycan synthesis.

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Inui et al. were able to demonstrate a significant improvement of mitochondrial functions in the skin after only seven days of twice daily application of 0.01 % coenzyme Q10, and after five months of twice daily application of 1 % coenzyme Q10 clinically a reduction of wrinkles was verified.

Green tea polyphenols
Polyphenolic epicatechins found in green tea extract are naturally occurring antioxidants used in numerous cosmetics and whose photoprotective effect was verified in an in vitro study by Elmets et al. Their effects on the cellular stress system appear very complex: both direct effects on signal transduction as well as alteration in connection with the prevailing antioxidative status of the cell were shown. Thus Elmets et al. demonstrated in an in vivo study that topical application of green tea polyphenols before UV exposure leads clinically to an increase of MED as well as to the formation of significantly less "sunburn cells", a reduced decline in cutaneous Langerhans cells as well as reduced DNA damage.

Plant materials (botanicals)
In addition to polyphenols from green tea, a variety of plant constituents termed secondary plant materials can have positive effects on the skin. For example, the isoflavons from soy or red clover as well as some flavonoids are attributed a phytoestrogen effect via specific interaction with the estrogen receptors. The group of antioxidative flavonoids includes flavanols, flavanones, anthocyanidines, and flavones. A further anti-aging substance is the plant antioxidant pycnogenol, a standardized extract of proanthocyanidines won from the bark of the French sea pine (Pinus pinaster, ssp. atlantica). Oligomeric procyanidins (OPC) belong to the flavonoids and are among the most effective antioxidants. It has thus been established that pycnogenol is a much more active antioxidant than coenzyme Q10, α-lipoic acid and grape seed extract. Emblica is a standardized extract won from the plant Phyllantus emblica -lipoic acid and grape seed extract. Emblica is supposed to reduce free radicals and inhibit metal-induced oxidation by forming chelate complexes with iron and copper. This chelation prevents the formation of damaging hydroxyl radicals. Polyphenols which are found e.g. also in pomegranate can counteract extrinsic skin aging. Particularly the bark extract of pomegranate reduces the UV-dependent expression of matrix metalloproteinase 1 (MMP 1) distinctly and increase collagen production. Further plant extracts used as anti-aging substances include isoflavones from soy or red clover, pycnogenol, emblica, silymarin, ectoin, Focus vesiculosus extracts, white grape seed extracts containing polyphenols, Cimicifuga racemosa extracts or maritime plant extracts like those from algae or microalgae.

Cell regulators (Table 4)
While antioxidants reduce the concentration of free radicals in the skin and thus counteract collagen degradation, the cell regulators such as vitamin A acid derivatives and retinol, but also polypeptides and plant growth factors directly influence dermal metabolism and stimulate the synthesis of collagen or elastic fibers as well as extracellular matrix.

Retinol (vitamin A) and its derivatives (Figure 1)
Vitamin A is the generic term for a series of natural and synthetic compounds with a similar chemical structure but in part differing biological activities. This group of agents consists of various substances or derivatives such as fat-soluble vitamin A (retinol), aldehyde-retinal (retinaldehyde) and vitamin A acid (retinoic acid/retinoin). The most commonly used substance in modern anti-aging preparations is at present retinol, which in comparison to retinoin (drug requiring prescription) is less irritating to the skin and generally better tolerable in topical use [6, 7]. In a maximal concentration of up to 0.3 % retinol is today considered as the "gold standard" of cosmetic anti-aging agents. The synthetic retinoic acid (tretinoin), which requires a prescription, is a non-aromatic retinoid of the first generation and is not licensed for use in cosmetic products in Germany. In the USA this agent is licensed for up to a 0.05 % tretinoin cream for the treatment of signs of skin aging. Vitamin A derivatives belong to the anti-aging substances whose clinical efficacy has been well-studied scientifically and been proven. Topical therapy with vitamin A derivatives has several mechanisms: both direct effects on signal transduction as well as alteration in connection with the prevailing antioxidative status of the cell were shown. Thus Elmets et al. demonstrated in an in vivo study that topical application of green tea polyphenols before UV exposure leads clinically to an increase of MED as well as to the formation of significantly less "sunburn cells", a reduced decline in cutaneous Langerhans cells as well as reduced DNA damage.

Green tea phenols, natural antioxidants used in numerous cosmetics exhibit in addition to photoprotective effects complex effects on the cellular stress system.

In addition to polyphenols from green tea or pomegranate, a variety of plant constituents termed secondary plant materials, can have positive effects on the skin. Further plant extracts used as anti-aging substances include isoflavones from soy or red clover, pycnogenol, emblica, silymarin, ectoin, Focus vesiculosus extracts, white grape seed extracts containing polyphenols, Cimicifuga racemosa extracts or maritime plant extracts like those from algae or microalgae.

In a maximal concentration of up to 0.3 % retinol is today considered as the "gold standard" of cosmetic anti-aging agents.

In comparison to tretinoin, a drug requiring prescription that may not be used in cosmetics, retinol and retinaldehyde are less irritating to the skin and are generally better tolerable in topical use.
can be used both for prevention as well as on already photodamaged skin. Varani et al. showed, for example, that retinol has positive effects not only on extrinsic but also intrinsic skin agents and has similar effects as retinoic acid [7]. In concentrations of 0.1 % tretinoin can markedly reduce typical signs of UV-induced premature skin aging such as wrinkles, loss of elasticity of the skin, pigmentation irregularities, keratoses etc. [8], which was confirmed by Bhawan in placebo-controlled studies and clinically even with the help of histological examinations. Scientifically well-documented are the positive effects on collagen metabolism. Studies on topical use, for example, demonstrated that retinol and vitamin A acid (retinoic acid) can induce collagen synthesis. In addition to induction of collagen biosynthesis vitamin A derivatives can also reduce the expression of collagen-degrading enzymes such as matrix metalloproteinase 1 (collagenase 1). Just as for tretinoin and retinol, Boisnik et al. were able to show a stimulation of collagen synthesis for retinaldehyde, too. Collagenase activity declined and in part damaged collagen fibers were reconstituted with a restructuring of the connective tissue. In a randomized, double-blind, vehicle-controlled in vivo study on 90 subjects Creidi et al. applied 0.5 % retinaldehyde daily with good tolerability over 44 weeks. Optical profilometry of the wrinkles at the lateral corner of the eye revealed a significant reduction of wrinkle depth and skin surface roughness.

Table 4: Cell regulators and skin aging.

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<tr>
<th>Agents / authors</th>
<th>Design</th>
<th>Primary target criteria</th>
<th>Results</th>
<th>Evidence level</th>
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<tr>
<td>Retinol</td>
<td>RCT</td>
<td>• Clinical signs of skin aging • Histopathology • PCR (GAGs, procollagen)</td>
<td>Significant improvements</td>
<td>B2b</td>
</tr>
<tr>
<td>Retinaldehyde</td>
<td>RCT</td>
<td>• Biophysical measurements • Clinical signs of skin aging</td>
<td>Significant improvements</td>
<td>B2b</td>
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<tr>
<td>Signal peptides (Pal-KTTKS)</td>
<td>Reviews</td>
<td>• Clinical signs of skin aging • Biophysical measurements</td>
<td></td>
<td>B2b</td>
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<tr>
<td></td>
<td>RCT</td>
<td>• Clinical signs of skin aging • Biophysical measurements</td>
<td>Significant improvements</td>
<td>C4</td>
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<tr>
<td>Transport peptides (copper tripeptide)</td>
<td>RCT</td>
<td>• Clinical signs of skin aging • Biophysical measurements</td>
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<td>Carnosine</td>
<td>Reviews</td>
<td></td>
<td></td>
<td>B2b</td>
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![Figure 1](image1.png)

Figure 1: Skin surface morphology before (a) and after (b) four month of topical treatment containing retinol (smoother skin surface).
Polypeptides (Table 5)

Polypeptides or oligopeptides are composed of amino acids that are linked by protein bonds. Through advances in technology it became possible to produce peptide sequences that imitate the body’s own molecules such as collagen or elastin and thus attain the capability of influencing bodily processes such as collagen synthesis or transmission at the neuromuscular synapse. Therefore peptides are used in cosmeceuticals with the goal of improvement of skin aging features, be they due to increased mimical activity or increased collagen degradation [9]. Here, three groups of peptides are differentiated and summarized in Table 5.

**Table 5: Peptides in cosmeceuticals.**

<table>
<thead>
<tr>
<th>Type</th>
<th>In vitro mechanisms of action</th>
<th>In vivo effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Signal peptides</strong></td>
<td>Activation of fibroblasts by specific peptide sequences</td>
<td>Increased collagen and elevated glycoaminoglycan synthesis</td>
</tr>
<tr>
<td>e. g. Pal-KTTKS, Pal-KT</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Transport peptides</strong></td>
<td>Via inward transport of trace elements (e. g. copper) enzyme activation of collagen synthesis</td>
<td>Increased collagen neosynthesis</td>
</tr>
<tr>
<td>e. g. copper tripeptide</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Neurotransmitter-inhibiting peptides</strong></td>
<td>Interference with neurotransmitter release</td>
<td>Reduced muscle activity</td>
</tr>
</tbody>
</table>

Signal and transport peptides

In various in vivo studies with double-blind, vehicle-controlled and randomized design it was shown that palmitoyl pentapeptide-3 (Pal-KTTKS), a signal peptide, with good tolerability already after 12 weeks of daily application led to a stimulation of connective tissue metabolism with induction of type I and III collagen. Clinically this was seen in form of increased collagen content of the dermis that could be detected histopathologically in form of increased skin thickness and density measured by 20 MHz sonography as well as in a reduction of skin surface roughness and an increase in skin smoothness (Figure 2). In a further study Lintner et al. compared the clinical efficacy of a topical preparation containing palmitoyl pentapeptide with the efficacy of a preparation containing retinol. The effects on collagen metabolism did not differ significantly; the tolerability of application of the pentapeptide was markedly improved. Studies by Leyden et al. and Sigler et al. have shown the transport peptide copper tripeptide significantly penetrates the epidermal barrier and can also have positive clinical effects on prematurely aged skin. With good tolerability improved elasticity, reduced wrinkles and sonographically increased skin thickness and density were observed (Figure 3).

Other peptides

Carnosine, a dipeptide consisting of the amino acids β-alanine and histidine, has both antioxidative as well as anti-glycation properties. This peptide occurring naturally in the body is found in higher concentration especially in human muscle and brain tissue and declines in the body with increasing age. It reduces endogenous glycation in tissue and is purported to counteract oxidative stress and the synthesis of proinflammatory cytokines as well as cutaneous sclerosis.

Acetyl hexapeptide-8 (Argireline®), a hexapeptide containing six amino acids, inhibits the release of neurotransmitters in muscle cells which weakens muscle contraction, relaxes the muscle and thus reduces mimical wrinkles. In an initial uncontrolled study on 10 healthy women Blanes-Mira et al. demonstrated that application of an O/W emulsion containing 10 % Argireline® reduced wrinkle depth by 30 % after 30 days.

Growth factors

Madecassoside, a growth factor won from the plant Centella asiatica, beyond well-documented effects on wound healing is supposed also to support the synthesis of type I collagen fibers and protect collagen fibers from enzymatic degradation. Thus, through advances in technology it became possible to produce polypeptides that imitate the body’s own molecules such as collagen or elastin and thus attain the capability of influencing bodily processes such as collagen synthesis or transmission at the neuromuscular synapse.

The signal peptide Pal-KTTKS can with good tolerability lead to a stimulation of connective tissue metabolism with induction of type I and III collagen. The transport peptide copper tripeptide can significantly penetrate the epidermal barrier and also have positive clinical effects on prematurely aged skin. The hexapeptide Argireline® inhibits the release of neurotransmitters in muscle cells, which weakens muscle contraction, relaxes the muscles and thus reduces mimical wrinkles.
in various studies on subjects with extrinsically aged skin the clinical efficacy of a topically applied facial cream containing 0.1 % madecassoside and 5 % vitamin C was examined. Krüger et al. proved that with very good tolerability already after three months a significantly reduced TEWL and a significant increase of skin smoothness, dermal thickness and density occur. After six months Haftek et al. documented significant improvement of skin elasticity, the clinical score as well as self-evaluation of the subjects (among others, wrinkle depth, skin roughness and hydration) [4].

Madecassoside, a growth factor won from the plant *Centella asiatica*, beyond well-documented effects on wound healing is supposed also to support the synthesis of type I collagen fibers and protect collagen fibers from enzymatic degradation.

**Figure 2:** Corner of the eye before (a) and after (b) twelve weeks of topical treatment containing palmitoyl pentapeptide, greyscale visioscans (c, d) and color images (e, f) of calculated 3D models taken at baseline and after twelve weeks of topical treatment containing palmitoyl pentapeptide.

**Figure 3:** 20 MHz sonography before (a) and after (b) eight weeks of topical treatment containing copper tripeptide.
Clinical use
In order to facilitate the use of above-mentioned agents in everyday dermatological routine, beyond categorization of the agents according to mechanisms of action (antioxidants, cell regulators) the classification of patients into different skin aging stages can be helpful (Figure 4). To aid screening according to the individual skin aging stage, the Hamburg skin Aging Score was developed, which can be filled out within minutes during the patient dialog and can help developing a targeted individual treatment plan for each patient (Figure 5). Depending on skin aging stage and particular degree of specific clinical signs of skin aging, individual treatment concepts that have both a preventive and reparative character can be developed (Figure 6). Thus, the sole use of antioxidants is recommended for skin aging stage I and II, while cell regulators in combination with antioxidant, but also as monotherapy, are particularly suitable for skin aging stage III and IV as well as peri- and postmenopausally.

Combination possibilities
According to recent studies, especially the combination of antioxidants and cell regulators significantly reduces signs of skin aging and improve the regenerative capacity of the skin [4, 10]. Combinations of different antioxidants or the combination of growth factors and vitamin C also appear sensible. A randomized, double-blind study on 20 women with photodamaged skin showed that a six-month application of a topical preparation containing 5 % vitamin C and 0.1 % madecassoside can lead to a significant improvement of the clinical score (among others, deep and fine wrinkles, skin roughness and hydration), which could be confirmed histologically and by measurements of skin elasticity [4]. In a recent vehicle-controlled, randomized in vivo study on 196 subjects the clinical efficacy of a cosmeceutical containing niacinamide/peptide/retinyl propionate with a 0.02 % tretinoin preparation (Renova™) approved for the treatment of actinically damaged skin. Use of the preparation containing Pal-KTTKS and 5 % niacinamide demonstrated a significant reduction of wrinkles already after four weeks; a comparable result in the treatment with tretinoin was achieved only after 24 weeks. In addition, the tretinoin preparation was tolerated significantly less well [10].

Conclusions
In recent years the number of cosmetic agents to improve various signs of skin aging has increased considerably and has resulted in a broad range of cosmetic products against skin aging. Particularly in the targeted recommendation of specific agents and

Within the framework of a targeted recommendation of agents or also combination of agents in a dermatologic consultation the present data as well as the individual skin aging stage, the skin state of the patient and possible past minimally invasive procedures should be taken into consideration.
A frequent problem in the confirmation or comparison of efficacy of cosmeceutical products is still a lack of controlled, evidence-based studies. Even though the number of published studies on cosmeceutical products is rising almost exponentially, there are only a small number of controlled in vivo studies on a sufficient number of test persons.

Within the framework of a targeted recommendation of agents or also combination of agents in a dermatologic consultation, the present data as well as the individual skin aging stage (Figure 4, 5), the skin state of the patient and possible past minimally invasive procedures should be taken into consideration. For optimal prevention of light-induced signs of skin aging additionally daily consistent UVA and UVB protection is indispensable in every skin aging stage.

Conflicts of interest
None.

Figure 5: Hamburg Skin Aging Score.
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References


Fragen zur Zertifizierung durch die DDA

1. Welche In-vivo-Wirkung weisen Emollienzien auf?
   a) verminderter transepidermaler Wasserverlust (TEWL)
   b) erhöhte Korneozytenkohäsion
   c) erhöhte Kollagenneosynthese
   d) verminderte Konzentration freier Radikale
   e) erhöhte Hydratation des Stratum corneum

2. Die Effekte vieler dermatokosmetischer Wirkstoffe hängen stark von der Gesamtformulierung ab. Wie kann beispielsweise die Penetration von Vitamin E in die Haut deutlich verbessert werden?
   a) durch mizellenbildende Emulgatoren
   b) durch Vaseline
   c) mittels Mikro- oder Nanoemulsionen
   d) durch Silikonöle
   e) mittels Derma-Membran-Struktur (DMS)

3. Auf welches Hautalterungsstadium weisen folgende klinische Zeichen der Hautalterung hin: Mimikfalten, Lentigines solares, erste Teleangiektasien, wenig ausgeprägte Falten und geringer Elastizitätsverlust?
   a) keine Hautalterung
   b) Hautalterungsstadium I
   c) Hautalterungsstadium II
   d) Hautalterungsstadium III
   e) Hautalterungsstadium IV

4. Was versteht man unter Madecassoside?
   a) ein standardisierter Extrakt, der aus der Rinde der französischen Seckiefer (Pinus pinaster, ssp. atlantica) gewonnen wird
   b) ein Dipeptid, bestehend aus den Aminosäuren β-Alanin und Histidin
   c) ein Neurotransmitter-inhibierendes Peptid
   d) eine natürliche Feuchtthaitssubstanz
   e) ein aus der Pflanze Centella asiatica gewonnener Wachstumsfaktor

5. Was bedeutet die Abkürzung DMS?
   a) Derma-Membran-Struktur
   b) Dermostrategie
   c) Dermal-Moisturizing-System
   d) Definition of Medical Subjects
   e) Double Measurement Strategy

6. Was ist den dermatokosmetischen Wirkstoffen Niacinamid, Koenzym Q10, Pycnogenol, α-Liponsäure und α-Tocopherol gemein?
   a) Sie weisen eine signifikant schlechtere Verträglichkeit als Vitamin C auf.
   b) Sie haben eine ähnliche chemische Struktur.
   c) Sie greifen in den dermalen Stoffwechsel ein und stimulieren die Synthese kollagener oder elastischer Fasern.
   d) Sie sind Antioxidanzien, die die Konzentration freier Radikale in der Haut vermindern und so dem Kollagenabbau entgegen wirken.
   e) Sie sind körpereigene, in allen menschlichen Zellen enthaltene Stoffe.

7. Welche In-vivo-Wirkung weisen Signalpeptide (z.B. Pal-KTTKS) auf?
   a) Unterstützung der natürlichen Abwehrmechanismen der Haut
   b) Aktivierung der Protein- und Kollagensynthesseinduktion
   c) Aktivierung der Protein- und Kollagensynthesseinduktion
   d) Aktivierung von Fibroblasten durch spezifische Peptidsequenzen
   e) Enzym-Aktivierung der Kollagenneosynthese

8. In welche zwei großen Kategorien können dermatokosmetische Wirkstoffe basierend auf ihren Wirkmechanismen eingeteilt werden?
   a) Feuchthaltefaktoren und Photorégulatoren
   b) Emulsionen und Emulgatoren
   c) Antioxidanzien und Zellregulatoren
   d) Neurotransmitter und Wachstumsfaktoren
   e) hydrophile und hydrophobe Vehikelbestandteile

9. Welche In-vitro-Wirkmechanismen weisen Signalpeptide (z.B. Pal-KTTKS) auf?
   a) Unterstützung der natürlichen Abwehrmechanismen der Haut
   b) Aktivierung der Protein- und Kollagensynthesseinduktion
   c) Neurotransmitterfreisetzung
   d) Aktivierung von Fibroblasten durch spezifische Peptidsequenzen
   e) Enzym-Aktivierung der Kollagenneosynthese

10. Welcher der folgenden dermatokosmetischen Wirkstoff gilt heute als „Goldstandard“ der kosmetischen Anti-Aging-Wirkstoffe?
    a) Retinaldehyd
    b) Koenzym Q10
    c) Retinol
    d) Pal-KTTKS
    e) Niacinamid