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Innovation in cosmetics

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ABSTRACT

Cosmetics market is still rapidly growing with new ranges of cosmetics emerging. New ingredients are added to formulas in order to obtain innovative activity and higher external effects such as anti-aging, anti-inflammatory, antibacterial, regenerating, soothing, relaxing muscles, or simply moisturizing or cleaning. One of the biggest family of innovative ingredients used in cosmetics are peptides. Thanks to their chemical and physiochemical properties, they show various activities that may gain different applications. Compounds derived from natural sources such as milk, plants or marine organisms become especially popular. Their activity may not always stay strictly cosmetic, but also therapeutic as it is shown in cases of opioid peptides derived from milk or anticancer peptides from algae.

Keywords: Cosmetics, cosmeceuticals, peptides, milk peptides, marine peptides, opioids

1. INTRODUCTION

Cosmetics available on market often consist of wide range of biological or chemical additives that have some unique properties. Those can, as producers claim, stimulate growth of cells, counteract ageing processes, lift skin up, help avoid redness, act as bacteriostatics or even, in cases of cosmeceuticals or drugs in cosmetic form (ointments, creams etc.), have therapeutic properties. Target ingredients may include phytochemicals, vitamins, peptides, ceramides, enzymes and oils (Antonopoulou 2016; Lintner 2009). During last years cosmeceuticals have become important part of the OTC skin treatment sector, but still they are unclassified as the amount of active ingredients in them is too low to become a drug, and too high to act only as a traditional cosmetic (Draelos 2009).

One of recently most common compounds in cosmetics are bioactive peptides – groups of amino acids whose specific sequences enable biologically active properties that affect living organism functions. Added in small amounts peptides can have various activity e.g. moisturizing, antibacterial, regenerating or nutritious. Peptide activity is strictly connected to their amino acid sequence. Most of peptides demonstrating multifunctional properties consist of two to twenty amino acid residues and are activated after releasing from precursor complex through hydrolysis process (Mohanty 2016, Meisel 2000). Only in USA, in 2009, there were more than 25 different peptides used routinely in cosmetics (Zhang 2009).

Very popular are compounds derived from natural sources. Thanks to the commonness of their occurrence, peptides and proteins can come from both animals and plants. Most common plant sources are: soy, algae, macadamia, garden tulip, *Mirabilis jalapa*, amaranthus, bean, daffodil, shallot, barley, pumpkin (Nawrot 2014, Farrokhi 2008). In case of animal derived peptides they can be extracted from e.g. snake venom (Całkosiński 2010), hornet venom (Argiolas 1984), humblebee venom (Argiolas 1985) or simply from meat, milk and eggs.

Peptides derived from such natural sources are gaining on popularity thanks to their higher biocompatibility and lower potential to induce allergies. It is documented that peptides from human milk can possess antibacterial, antihypertensive and regenerative properties as well as stimulate immunological and digestive system, defend from infections and help faster recovery from disease (Lis 2013). Thanks to those properties they may become useful in products dedicated to children, pregnant women and other groups of higher risk.

Already there are milk preparations on market used in nutrition – most commonly they are used in milk replacers formulas for infants and small children. Apart from that they can be found in supplements for sportsmen and energetic drinks. Also such products as Calpis (fermented milk drink that, as producer claim, improves health, reduced tiredness and stress symptoms and regulate blood pressure), Evolus (drink for blood pressure regulation), PeptoPro (substrate used in energetics drinks) or BioZate (whey hydrolysate added to snacks as protein source) are available on market.

Milk products are also added to cosmetics. According to CosIng database they can occur under INCI names: *milk, hydrolyzed milk protein, hydrolyzed whey protein, milk extract, hydrolyzed milk, lac, lac extract, lac powder, lactis proteinum, lactis proteinum extract, lac ferment, lactoferricin, lactoferrin, milk protein, nonfat dry milk, whey, whey dry milk, yogurt*. Among available on market cosmetic preparations containing milk derivatives there are e.g. such products as cream from mare milk (MEDESOL-WERK-GMBH GERMANY) that is dedicated to sensitive skin with eczema and psoriasis. One of more interesting cosmetics ingredient is Milk Peptide Complex (CLR Chemisches Laboratorium Dr. Kurt Richter GmbH) that according to producer stimulates skin cells to production of extracellular matrix which gives effect of refining skin and its regeneration.

2. BIOACTIVE PEPTIDES

To become an effective active substance in cosmetics or cosmeceuticals a compound has to be able to cross the skin barrier. Until recently, a general rule functioned in the cosmetic environment that to obtain this, a compound has to possess following properties:

- Molecular weight less than 500 Da
- Aqueous solubility > 1 mg/ml
- Melting point < 200 °C
- Limited number of polar centers
- Log of partition coefficient octanol/water between 1 and 3

Nowadays we know that this paradigm is not always applicable, especially considering dry and aged skin. Apart from that, addition of some enhancers to cosmetic formula can also simplify penetration process. E.g. some peptides that cross the skin barrier has higher sizes – e.g. *Palmitoyl Tripeptide-3*: 578,8 Da, *Palmitoyl Tetrapeptide-3/7*: 694,9 Da, *Palmitoyl Oligopeptide*: 736,98 Da, *Palmitoyl Pentapeptide-3*: 802,05 Da, *Acetyl Hexapeptide-3*: 889,0 Da. Such situation is possible thanks to addition of fatty acid to the peptide chain that changes ability of the compound to penetrate stratum corneum barrier by increasing the lipophilic properties (Gorouhi 2009).

2. 1. Neuropeptides

An idea to use peptides as neuroinhibitors came from the fact of using botulinum toxin in esthetic medicine in order to avoid wrinkles. Many tests were conducted to produce an artificial chemical compound with the same activity, but the penetration through skin was not satisfactory. A new approach was reached with production of neuropeptides such as Argireline (Lipotec) - acetyl heksapeptide-8 or Syn-ake (Pentapharm) that thanks to their small sizes and high activity gave similar effects as botox. Raised threshold for minimal muscle activity enforces more signals and reduces frequency of muscle contraction which gives an effect of limited wrinkle amount (Fields 2009). Another example is pentapeptide-3 (Vialox, Cellular Skin, Rx) that mimics activity of tubocurarine by competitive antagonism to acetylcholine postsynaptic membrane receptors. Thus ion channels remain closed and cells are not depolarized and contraction of muscles does not occur (Lupo 2007).

2. 2. Signaling peptides

Chronologically, aged skin has lower amount of collagen and increased activity of proteolytic enzymes that digest produced collagen (Fields 2009). Peptides are able to initiate intercellular processes that stimulate collagen synthesis. Peptides with chains long enough can stimulate fibroblast growth in dermis. Signaling peptides are most usually fragments of collagen and elastin build up during protein biosynthesis. Delivering of such substances in form of a cosmetics to the site where synthesis occurs may become a signal to beginning production of new collagen molecules (e.g. type I and type III collagen) and fibronectin. Exogenously, this will be seen as improvement of skin appearance. Such properties has e.g. palmitoyl pentapeptide-3 (Sederma) and palmitoyl oligopeptide (Sederma), palmitoyl pentapeptide-4/3 (Matrixyl®, Sederma) or Acetyl tetrapeptide-9 and Acetyl tetrapeptide-11.

2. 3. Carrier peptides

Some peptides are able to stabilize and transport trace elements (like Cu and Mn) necessary in wound healing and many enzymatic processes. Copper takes part e.g. in neutralization of free radicals in skin by being a cofactor in antiradical systems conducted by superoxide dismutase and catalase. It also is important for lysyl oxidase that takes part in

production of collagen and elastin and for angiogenesis. Such carrier peptide is e.g. glycyl-L-histidyl-L-lysine that complexes with copper and facilitates its uptake by cells. The visual effects of its activity are seen as improvement of skin firmness and texture, fine lines and hyperpigmentation (Lupo 2009). Also, some studies showed that short arginine-rich intracellular delivery peptides simplify transport of some proteins into living cells (Hou 2007).

2. 4. Milk peptides

Mammalian milk is a natural nutrition for infants that comprises specific composition responsible for nutrient and stimulating properties important for proper growth of organisms. Depending on species, lactation stadium and nutritional habits as well as total body condition, its composition may vary.

Most common cow milk consists of, among others, 5% lactose, 4% fat, 3,2% proteins and 0,7% mineral elements such as potassium, magnesium and calcium (Darewicz 2015; Jäkälä 2010). In comparison, human milk consists of, among others, 7,2% lactose, 4,1% fat, 1,3% proteins, goat milk: 4,6% lactose, 4-4,5% fat, 3,2% proteins (Yedav 2016). Considering protein content, human milk has its lowest level – cow (3,5%), pig (5,5%), rabbit (14%) (Kostyra 2004).

Among casein proteins there are α -, β -, κ -caseins. Whey proteins consist mainly of β -lactoglobulin (48-58%), α -lactalbumin (13-19%), immunoglobulin (8-12%), plasma albumin (5-6%), lactoferrin (2%), lactoperoxidase (0,5%), glycomacropeptide (12-20%), lysozyme, cytokines and lactoferricin (Lis 2013). Whey proteins has highest energetic value thanks to higher amount of exogenous amino acids.

Colostrum, first milk produced after child delivery, is especially rich in nutritious substances, immunoglobulins, growth factors and antibacterial substances (Clare 2003). Proportion between casein and whey protein is 20:80 (in follow-on milk this proportion is 40:60, in mature milk 50:50) (Lönnerdal 2003). Apart from that, its specific composition enables to fulfill all the needs of newborn child in scope of nutrition, development stimulation, immunology and adaption to new environment. Peptides from human colostrum can also have positive impact on treatment of gastrointestinal disorders like inflammatory bowel disease, non-steroidal anti-inflammatory drug-induced gut injury and chemotherapy-induced mucositis (Playford 2001).

Human milk is known for many years as not only best nutrition for babies, but also for its other properties. Young mothers are advised by doctors and nurses that they can use their own milk to sooth sensitive skin of the baby, purulent eyes or cracked and bleeding nipples. Thanks to antiseptic and soothing properties it can be used for diaper rash, crusta lactea, atopic skin and itching or to improve immunity.

Studies conducted by Darewicz et al. showed that from 1 g of milk protein there can be extracted 24-65 mg of opioid peptides (Darewicz 2014). Opioid peptides derived from milk show different properties than other opiate peptides – they have other sequences at N-terminus. Traditional peptides usually have tyrosine at N-terminus (apart from opioids derived from α -casein) and an aromatic amino acid – Phe or Tyr – in position 3 or 4. This have enormous impact on activity of a peptide because of the bonding to opioid receptors (Meisel 2000). Ligand activity (in this case – opioid peptides) is based on its ability to bind to opioid receptor, and this depends on compound size, steric effects and electric properties.

β -casein consists of 209 amino acids and there are at least 12 different types depending on localization of certain amino acids (Raies ul Haq 2014). Under activity of enzymes in digestive system casein is digested into smaller elements, one of which is β -casomorphine (position 60-70, sequence Tyr-Pro-Phe-Pro-Gly-Pro-Ile-Pro-Asn-Ser-Leu; see Table 1) that binds to μ opioid receptors. For example β -casomorphine-7 (Tyr-Pro-Phe-Pro-Gly-Pro-Ile) has activity in nervous, digestive and immunological system. It is digested by proline dipeptidylpeptidase IV and goes through intestine barrier (Fiedorowicz 2014).

α -casein in turn can be source of exorphines corresponding to fragments 90-96 (Arg-Tyr-Leu-Gly-Tyr-Leu-Glu), 90-95 and 91-96 and binds to δ receptors (Meisel 2000).

From whey come α -lactorphines (Tyr-Gly-Leu-Phe) and β -lactorphines (Tyr-Leu-Leu-Phe). α -lactorphine has weak opioid activity that smooth muscles, while β -lactorphine smooth muscle contracting effect and improve arterial functions in spontaneously hypertensive rats (Haque 2009).

From plasma albumin a serorphine was extracted (Tyr-Gly-Phe-Asn-Ala) that is an opioid agonist (Meisel 2000).

κ -casein can be source of casoxines: casoxine A (Tyr-Pro-Ser-Tyr-Gly-Lys-Asn-Tyr), casoxine B (Tyr-Pro-Tyr-Tyr), casoxine C (Tyr-Ile-Pro-Ile-Gln-Tyr-Val-Leu-Ser-Arg). They bind to μ and κ receptors and act as opioid antagonists.

From lactoferrin can be extracted lactoferricin A (f339-344;), B(f544-548) and C(f681-687) that act similarly to casoxins and has antagonistic influence on μ receptors (Meisel 2000).

Table 1. Peptides derived from milk.

Precursor protein	Peptide	Fragment	Sequence	Ref.
β -casein	β -casomorphins	60-70	Tyr-Pro-Phe-Pro-Gly-Pro-Ile-Pro-Asn-Ser-Leu	Meisel 2000
	β -Casomorphin-8	60-67	Tyr-Pro-Phe-Val-Glu-Pro-Ile-Pro	Righard 2014
	β -Casomorphin-7	60-66	Tyr-Pro-Phe-Val-Glu-Pro-Ile	Righard 2014
	β -Casomorphin-11	60-70	Tyr-Pro-Phe-Pro-Gly-Pro-Ile-Pro-Asn-Ser-Lys	Haque 2009
	β -Casomorphin-5	60-64	Tyr-Pro-Phe-Pro-Gly	Meisel 2000
α -casein	α -casein-exorphin	90-96	Arg-Tyr-Leu-Gly-Tyr-Leu-Glu	Meisel 2000
α -lactalbumin	α -lactorphin	50-53	Tyr-Gly-Leu-Phe	Meisel 2000
β -lactoglobulin	β -lactorphin	102-105	Tyr-Leu-Leu-Phe	Meisel 2000
plasma albumin	serorphine	399-404	Tyr-Gly-Phe-Asn-Ala	Meisel 2000

κ-casein	casoxin A	35-42	Tyr-Pro-Ser-Tyr-Gly-Lys-Asn-Tyr	Meisel 2000
	casoxin B	58-61	Tyr-Pro-Tyr-Tyr	Meisel 2000
	casoxin C	25-34	Tyr-Ile-Pro-Ile-Gln-Tyr-Val-Leu-Ser-Arg	Meisel 2000
	casoxin 6	33-38	Ser-Arg-Tyr-Pro-Ser-Tyr	Kastin 2006
αS1-casein	casoxin D	158-164	Tyr-Val-Pro-Phe-Pro-Pro-Phe	Teschemacher 1998
lactoferrin	Lactoferroxin A	318-323	Tyr-Leu-Gly-Ser-Arg-Tyr	Sienkiewicz-Szłapka 2009
	Lactoferroxin B	536-540	Arg-Tyr-Tyr-Gly-Tyr	Tani 1990
	Lactoferroxin C	673-679	Lys-Tyr-Leu-Gly-Pro-Gln-Tyr	Tani 1990

Most commonly used opioid is morphine that reduces pain e.g. in patients after chemotherapy. Most common route of intake is oral, but opioids can be also used externally, on skin. Such way is a preferred path of pain therapy development as it enables elimination of some of side effects occurred by traditional drug administration. Among most burdensome effects are sedation, nausea, respiratory depression and constipation which can be so strong that patients often decide to withdraw drug intake only to avoid those side effects. Topical administration of drugs, on skin, wound or surface changed by disease, enables local administration that limits systemic absorption. It is possible that in such administration route effective dosage of drug could be reduced as the transport path to target place is shorter and distributive losses are minimalized (Twillman 1999).

Other studies considered administration of 10mg of diamorphine in form of hydrogel patches to three patients suffering from malignant skin ulceration and decubitus ulcers. All patients felt strong relieve (Jepson 1992). In studies conducted by Twillman et al. on 9 patients with skin ulcerations, where morphine was administered to the wound in form of hydrogel, good analgesic effect were reached in 7 patients, moderate effect in 1 patient and lack of analgesia in 1 patient.

Conducted research show that opioid compounds can be used in topical pain therapy. Solutions where high analgesia and limited side effects occur has high potential. Such combination is possible using peptides derived from natural sources – milk opioids – that have higher bioavailability than chemically derived preparations. If delivered in form of topical preparation – cosmetic or cosmeceutical (ointment, cream, hydrogel), local analgesia can be obtained. Studies conducted by co-authors of the publication showed that a preparation in form of cream containing milk derived opioid peptides gives good analgesic effects in topical administration. The preparation is a derivative of peptide fragment of casomorphin and acts also as a soothing factor and stimulates fibroblast cells to grow which gives a regenerative effect. The solution is under patent examination process.

2. 5. Marine peptides

Marine products such as seafood and algae are gaining on popularity in cosmetics. Algae are rich in polysaccharides, proteins, lipids, phenolic compounds, pigments, vitamins, macro- and microelements. Peptides derived from them may be used in cosmetics as radical scavengers, antioxidant, anticancer and chelating, antifungal or anti-inflammatory agents. Examples of such activity are *Ecklonia cava*, *Ancanthophora dellei*, *Scytosiphonlomentaria* and *Spirulina sp.*. Apart from that, algae proteins are used as moisturizers for skin and hair (Fabrowska 2015). A source of peptides can be also Hawaiian red seaweeds that are incorporated with some cosmeceuticals to enhance collagen formation and firmer skin appearance. Also some seaweeds are source of antioxidant peptides and chitoooligosaccharides (Kim 2014).

3. CONCLUSIONS

Innovations in cosmetics are based on some global trends in adding new bioactive ingredients to their formulas. Those are usually vitamins, oils, ceramides, but most often peptides and protein hydrolysates. Their usage can vary between most common anti-aging formulas, antibacterial products to even therapeutics such as analgesics or antihypertensive factors. As the population awareness is increasing, consumers are looking for more natural sources of cosmetics and drugs which stimulates higher potential for products derived from natural sources like plants, animal fat or milk.

The research on new cosmetics and cosmeceutical ingredients are still being globally conducted in order to produce new formulas that may simplify life, improve health and appearance but simultaneously limit side effects obtained by traditional applications.

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