

Biomimetic peptides in cosmetology

Peptydy biomimetyczne w kosmetologii

ABSTRACT

Innovation and efficacy are among the most desired qualities in the cosmetics industry. In recent years, biomimetic peptides, which are synthetic analogues of peptides naturally found in tissues, have gained particular significance.

This study aimed to present selected biomimetic peptides, their properties, and potential applications.

In cosmetology, biomimetic peptides are classified into signalling peptides, peptide neurotransmitter inhibitors, and transport peptides. They constitute an innovative and promising group of active substances, and further research into them may contribute to the development of more effective, personalised skincare strategies to help maintain healthy, youthful-looking skin.

Keywords: biomimetic peptides, signalling peptides, neurotransmitter inhibitors, transport peptides, penetration.

STRESZCZENIE

Innowacyjność i skuteczność surowców należą do najbardziej pożądanых cech w branży kosmetycznej. W ostatnich latach szczególne znaczenie zyskały peptydy biomimetyczne, które stanowią syntetyczne odpowiedniki peptydów naturalnie występujących w tkankach.

Celem pracy było przedstawienie wybranych peptydów biomimetycznych, ich właściwości oraz potencjalnych zastosowań.

Peptydy biomimetyczne w kosmetologii dzieli się na peptydy sygnałowe, peptydowe inhibitory neuroprzebieżników oraz peptydy transportujące. Stanowią one innowacyjną i perspektywiczną grupę substancji aktywnych, których dalsze badania mogą przyczynić się do opracowania bardziej efektywnych, spersonalizowanych strategii pielęgnacyjnych, wspierających zachowanie zdrowia i młodego wyglądu skóry.

Słowa kluczowe: peptydy biomimetyczne, peptydy sygnałowe, inhibitory neuroprzebieżników, peptydy transportujące, przenikanie.

INTRODUCTION

Biomimetic peptides have found application in cosmetology and aesthetic medicine clinics as ingredients in next-generation cosmetic formulations. The most desirable qualities of these components include their biological activity, safety of use, innovativeness, and relatively small molecular size, which facilitates penetration into the skin. Meeting these criteria ensures that the final product is effective and meets the expectations of both potential consumers and companies introducing the product line to the market [1].

The scope of action of biomimetic peptides is broad; from a purely cosmetic perspective, the preparations are

applied topically to prevent or alleviate skin dysfunctions, primarily signs of aging. The most common indications are emerging wrinkles, discoloration, and skin damage. These compounds are highly functional; they stimulate skin cell renewal processes and the synthesis of specific connective tissue components (i.e., collagen, glycosaminoglycans), which positively affect skin regeneration and elasticity [1, 2]. The uniqueness of biomimetic peptides lies in their bioactivity. They are gaining popularity year after year since they can achieve the desired result by triggering natural repair and regeneration mechanisms [1, 3]. Currently, many cosmetic

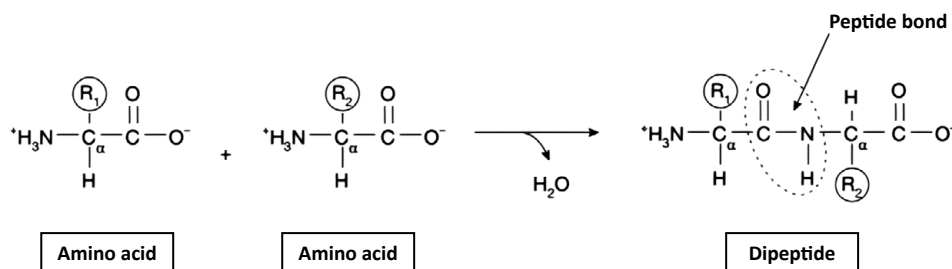


Fig. 1. Schematic diagram of peptide bond formation. Source: [4].

companies are incorporating low-molecular-weight peptides into their product formulations, both in cosmetics available at drugstores and in professional products [1, 2].

PEPTIDES

Due to the functions they perform in living organisms, peptides are a vital component of biological processes. Their significance is highly versatile, ranging from their role as cellular signalling molecules, through the regulation of metabolic processes, to their participation in the body's defence mechanisms. The field of medicine known as endocrinology shows particular interest in peptides, as many hormones naturally occurring in the human body are peptide hormones. In recent years, the cosmetics industry has also turned its attention to this area, conducting numerous studies on the benefits of applying peptide-containing formulations to the skin [4].

Peptides are organic chemical compounds composed of at least two amino acid residues linked by peptide bonds. Their structure, functions, and biological properties are determined, among other factors, by the types, number, and sequence in which the amino acid residues are linked [4-6].

The basic classification of peptides is based on the length of the amino acid chains. According to most sources, a chain containing two to a dozen or so amino acid residues is defined as an oligopeptide, a polypeptide comprises several dozen amino acid residues, while a chain composed of over 100 amino acid residues and with a molecular weight exceeding 10,000 Da is classified as a protein [5]. A peptide resulting from the reaction of two amino acid subunits is a dipeptide. Upon the sequential addition of one additional amino acid molecule at a time, tri-, tetra-, penta-, hexa-, hepta-, octa-, nona-, and decapeptides are formed [6, 7].

Amino acids

Amino acids are chemical compounds derived from organic acids. Characteristic features of their structure include the presence of an amino group (-NH₂) and a carboxyl group (-COOH), which enable the formation of peptide bonds between individual amino acid residues [5, 6].

Peptide bond

A peptide bond, which is also an amide bond, is a bond formed between the carbon of the α-carboxyl group of one amino acid and the nitrogen of the α-amino group of another amino acid. During bond formation, fragments of the amino acid molecules are released: -OH from the carboxyl group and -H from the amino group. This process explains why amino acids in peptides and proteins are referred to as amino acid residues (Fig. 1) [5, 6].

BIOMIMETICS

The term "biomimicry" refers to a field of study focused on identifying and designing solutions inspired by nature and the biological processes occurring within living organisms. The word "biomimicry" derives from the Greek words "bios", meaning life, and "mimesis", meaning imitation. Since it is widely acknowledged that mechanisms optimally adapted to a particular environment have evolved, it is more efficient to observe and thoroughly examine the current solutions that have been naturally selected rather than continuously creating new ones [7]. To illustrate the history of biomimetics, the discovery of Swiss inventor George de Mestral is most often cited. In 1955, he patented a fastening system commonly known today as velcro. The origin of the entire project was a seemingly ordinary walk with his dog, during which the man noticed that burdock seeds (*Arctium lappa* L.) cling to the surface of his clothing and the animal's fur, but removing them is quite troublesome. After analysing the structure of this part of the plant under a microscope and understanding its mechanism of action, he designed a tape that mimics burdock, which is still used today in shoe fasteners, among other applications [7, 8].

BIOMIMETIC PEPTIDES

Biomimetic peptides are compounds synthesized in laboratory conditions to mimic peptides naturally occurring in living organisms [1-3]. Their amino acid sequence is identical to natural peptides, enabling them to bind to specific cellular receptors and initiate various processes [1, 3]. Examples of biomimetic peptides used in cosmetology are presented in table 1.

Tab. 1. Examples of biomimetic peptides used in cosmetology.
Source: Compiled by the authors based on [7, 9, 10].

Peptide type	Trade name	INCI Name
Signalling peptide	Pal-KTTKS	Palmitoyl Pentapeptide-4
	SYN®-COLL	Palmitoyl Tripeptide-5
	Decorinyl™	Tripeptide-10
	GHK	Tripeptide-1
Neurotransmitter	Argireline®	Acetyl Hexapeptide-3 Acetyl Hexapeptide-8
	SNAP-8™	Acetyl Octapeptide-3
	Syn-Ake®	Dipeptide-3 Acetyl Heptapeptide-10
	Leuphasyl®	Pentapeptide-18
Transport peptide	Copper peptide/ GHK-Cu	Copper Tripeptide-1
		Manganese Tripeptide-1

Signalling peptides

Signalling peptides delivered to the dermis act by initiating, or triggering, signals that promote fibroblast growth and the synthesis of extracellular matrix components. They also inhibit collagenase activity [9]. A common name used for signalling peptides is “matrikines” [11]. Matrikines are bioactive low-molecular-weight peptides formed during the partial proteolysis of extracellular matrix macromolecules, both during physiological skin aging and pathological injuries. Most often, these are fragments derived from collagen or elastin. Matrikines bind to specific receptors present in the cell membrane, enabling them to regulate cellular activity, including the remodelling and repair of damaged tissues [9, 11].

KTTKS and its derivative Pal-KTTKS

One representative of signalling peptides is a pentapeptide with the sequence Lys-Thr-Thr-Lys-Ser, known as KTTKS, a name derived from the one-letter abbreviations of the amino acids. This peptide belongs to the group of matrikines naturally occurring in the extracellular matrix of the skin. It is formed as a result of proteolytic hydrolysis of collagen, which is why it was identified in 1993 as a fragment of type I procollagen [9, 11].

Mechanism of action and biological activity

The primary function of KTTKS is to stimulate skin cells to synthesize components of the extracellular matrix, which consists of fibrillar proteins (such as collagen, elastin, fibronectin, and others), non-fibrillar proteins (like laminin, tenascin, nidogen, and others), proteoglycans along with their attached glycosaminoglycans (GAGs), and various proteases. This structure helps maintain the integrity of connective

tissue, however, over the years, the rate of extracellular matrix component synthesis decreases, and their degradation intensifies, contributing to visible signs of skin aging [12]. The literature most frequently reports that KTTKS has a positive effect on the synthesis of fibronectin (a glycoprotein) and type I and III collagens [12, 13], which account for up to 85% and up to 15% of collagen in the skin of an adult, respectively [14].

Neurotransmitter inhibitors

A class of peptides known as neurotransmitter inhibitors limits nerve impulse flow by preventing the release of neurotransmitters. This results in a reduction in muscle contraction intensity. These preparations are used primarily to reduce existing expression lines and prevent the formation of new ones, particularly around the eyes, cheeks, and forehead. This group of substances includes botulinum neurotoxin, commonly known as Botox, and Botox-like compounds, which are designed to mimic the activity of botulinum toxin [7].

Botox-like compounds may be natural substances, derived, for example from snake or jellyfish venom, or synthetic substances obtained through chemical synthesis, modeled on animal-derived neurotoxins [7]. The key advantage of these products is that they do not require subcutaneous injections and can be self-administered, while also being gentler on the body and free of side effects, which makes them suitable for long-term use [15].

Argireline

Understanding the mechanism of action of botulinum toxin and years of research into its synthetic substitutes have led to the development of a biomimetic peptide called argireline [7]. It is a hexapeptide with a structure mimicking the N-terminal domain of the SNAP-25 protein, with the sequence: Glu-Glu-Met-Gln-Arg-Arg. This substance is also commonly known as acetyl hexapeptide-3 or acetyl hexapeptide-8 [15].

Mechanism of action and biological activity

The SNAP-25 protein is one of the components of the SNARE complex, which enables the synaptic vesicle to approach and fuse with the presynaptic membrane of a nerve cell's axon. This process occurs in the presence of calcium ions. As a result, neurotransmitters are released into the synaptic cleft, which then bind to their respective receptors on the postsynaptic membrane of the dendrite of the neighbouring nerve cell [16, 17].

Argireline's mechanism of action involves competing with the SNAP-25 protein for participation in the formation of the SNARE complex, thereby inhibiting its formation. This causes the entire complex to become unstable and inhibits the release of the neurotransmitter acetylcholine by exocytosis. Disruption of nerve impulse transmission to the muscles leads to weakened contraction and relaxation, which reduces the formation of expression lines [15].

The anti-wrinkle effect of argireline has been confirmed in numerous scientific publications, as many studies have been conducted in this area. In a study involving a group of 10 women who applied an O/W emulsion containing a 10% argireline solution twice daily for 30 days, a reduction in the depth of the subjects' wrinkles by as much as 30% was observed [15,16]. The use of a W/O/W emulsion also enhanced the penetration of argireline [16].

Argireline as an alternative to botulinum toxin

Argireline is often described as a non-invasive and safe alternative to botulinum toxin in cosmetic applications. This statement is valid, but its accuracy depends on the expected results. The anti-wrinkle benefits of argireline are not as strong as those of botulinum toxin. Argireline-containing products should be incorporated into a daily skincare routine and applied to cleansed and toned skin. Only regular and consistent use yields the desired results. In light of the latest reports and studies, argireline is considered well-tolerated and safe. This is an alternative to Botox therapy, eliminating the need for injections required to deliver botulinum toxin to the tissues, and reducing the risk of toxicity and potential side effects following the procedure [15,17].

Transport peptides

Transport peptides, also known as carrier peptides, have the ability to bind and transport substances essential for the proper functioning of metabolic processes in the skin. The transported elements may include trace elements such as copper or manganese ions [3]. Thanks to this property, these peptides play a significant role in maintaining cellular homeostasis and supporting regenerative processes. The metal ions they transport often act as cofactors for enzymes involved in the synthesis of structural proteins, including collagen and elastin. As a result, these peptides have a beneficial effect on tissue regeneration, accelerate repair processes, and improve the overall quality and appearance of the skin. For this reason, they are used in cosmetic formulations with restorative and anti-aging properties [3,18].

Copper peptide

One of the most popular metal ion-transporting peptides is the GHK tripeptide with the sequence Gly-His-Lys, composed of glycine, histidine, and lysine residues linked by a peptide bond. GHK exhibits a high affinity for copper (II) ions (Cu^{2+}), resulting in the spontaneous formation of a GHK-Cu complex, known as the copper tripeptide. It is believed that GHK facilitates the uptake of copper ions by cells, acting as both a carrier and a stabilizer [19,20].

Mechanism of action and biological properties

The GHK peptide was first isolated from human plasma in 1973 by Loren Pickart, PhD. It also occurs naturally in saliva

and urine. This discovery was made during an experiment where young people's blood plasma was mixed with liver tissue from elderly people. It has been shown that hepatocytes have an increased ability for regeneration when exposed to plasma from young individuals. It was shown that the obtained tissue synthesized more distinctive proteins and functioned similarly to younger tissues. Subsequent studies confirmed that GHK, which has a strong affinity for copper ions, is responsible for this activity. It was then suggested that this tripeptide functions as a complex with copper. The concentration of GHK in blood plasma is highest in young, healthy individuals and decreases from approximately 200 ng/mL at ages 20-25 to approximately 80 ng/mL at age 60. It is believed that this decline may be associated with a reduction in the body's regenerative capacity with age [19,21], although this hypothesis has not yet been conclusively confirmed [22].

The tripeptide GHK, when used alone, is classified as a signalling peptide because it stimulates, among other things, the synthesis of skin building blocks. Its primary function, however, remains the transport of copper to cells. In the 1980s, it was proposed that GHK may function as an early signal in the event of skin damage. This is associated with the release (at the site of injury) GHK amino acid sequences, which are part of the alpha 2(I) chain of type I collagen, the most common type of collagen, found in the skin. This is because skin damage activates proteolytic enzymes, which catalyze the hydrolysis of peptide bonds [20].

A significant effect of the GHK tripeptide on the activity of matrix metalloproteinases (MMPs), enzymes that catalyze the degradation of extracellular matrix proteins, and tissue inhibitors of metalloproteinases 1 and 2 (TIMP-1, TIMP-2) has also been observed. Its influence is described as regulatory in terms of protein breakdown in the skin, preventing the accumulation of damaged proteins as well as excessive matrix breakdown, which may influence regeneration and improve skin appearance [20].

Copper tripeptide also has a beneficial effect on fibroblasts. These cells are extremely important components of the connective tissue of the dermis. They are responsible for the synthesis of growth factors and glycosaminoglycans (GAGs), which include, among others, chondroitin sulfate, dermatan sulfate, and hyaluronic acid, as well as collagens, which form collagen fibers, and elastin, which forms elastic fibers [20]. Due to its beneficial impact on fibroblast function, the synthesis of the aforementioned skin building blocks is also stimulated, which translates into the skin's ability to repair damage and less visible signs of aging.

GHK-Cu, as a copper ion transporter, plays a significant role in the synthesis of collagen and elastin. Lysine oxidase plays a role in the formation of so-called cross-links between adjacent tropocollagen molecules during their aggregation into collagen fibers, and its activity depends on the presence

of copper ions. A similar process occurs in the cross-linking of elastin [23].

The effect of GHK-Cu in the wound healing process has been confirmed in numerous animal studies. In rabbit wounds, the use of the tripeptide improved wound contraction and granulation tissue formation. The antioxidant enzyme activity was also increased, and there was an expansion of the blood vessel network. Studies conducted on healthy rats and rats with induced diabetes showed that the use of collagen dressings containing GHK resulted in faster wound healing in both groups. GHK-Cu promoted the healing of diabetic and ischemic wounds in rats. A decrease in the levels of MMP-2 and 9 and tumor necrosis factor α (TNF - α) was also observed [20].

In wound healing, excessive inflammation can delay the process and lead to scarring. It has been demonstrated that complexes of copper and the GHK peptide reduce the secretion of pro-inflammatory interleukin 6 (IL-6) induced by TNF- α in skin fibroblasts [19].

Another important factor promoting wound healing is the growth of blood vessels and nerves. This tripeptide supports tissue remodelling by increasing blood flow to damaged areas through the stimulation of angiogenesis. It has been shown that GHK-Cu also promotes the regeneration of nerve fibers. When severed rat nerves were placed in a collagen tube impregnated with GHK, an increase in the number of axons and faster regeneration was observed compared to the control group [20].

Superoxide dismutase (SOD) can be used as an example to show how GHK-Cu affects antioxidant capabilities. This enzyme functions as an antioxidant by neutralizing free radicals, and its activity is dependent on metal ions like copper and zinc. This has a major effect in preventing damage to cellular structures and extracellular matrix fibrillar proteins (like collagen or elastin) as the skin ages [24, 25].

PEPTIDE PERMEABILITY THROUGH THE SKIN

The epidermis, and more specifically its stratum corneum, as the outermost layer of the skin, serves as the primary barrier to active compounds. The thickness of the epidermis averages approximately 0.1 to 2 mm. The stratum corneum is composed of flat, organelle-free cells known as cornified cells. The cells in the outermost rows of this layer are tightly packed, but as they move further out and desmosomes degrade, they take on a loose structure and undergo desquamation [14, 23].

A single cornified scale consists of a keratin core and a cellular envelope composed of proteins, including involucrin, loricrin, and SPR protein [14]. Additionally, there is also an extracellular lipid bilayer that acts as a seal for the epidermis, composed of lipids, particularly ceramides, cholesterol, and free fatty acids [14, 27]. Because of its lipophilic character, this structure is most easily penetrated by substances that have an affinity for lipids. The live layers of the epidermis that are closer to the dermis, which is made up of the reticular

and papillary layers, are more hydrophilic; nevertheless, a substance must first cross the lipid barrier to reach these layers [27, 28]. Active substances can penetrate deep into the skin through the epidermis and its appendages (hair follicle openings and the openings of sweat and sebaceous glands). In the case of substance transport through the epidermis, two possible pathways are distinguished: intercellular – between cells – and transcellular – through cells. Intercellular penetration is significantly more effective; however, it works best for lipophilic or amphiphilic molecules, as it occurs in a lipid environment [27, 29].

In early studies, it was assumed that the molecular weight of biomimetic peptides should not exceed 3,000 Da. In 2000, the so-called 500 Da Rule was introduced, based on the molecular weight of contact allergens and topically applied pharmacological agents that penetrate the skin, whose molecules do not exceed 500 Da. However, this requirement was challenged in 2005 when it was demonstrated that molecules with a molecular weight of 1200-1600 Da could penetrate transdermally; nevertheless, the smaller the molecules, the greater their ability to penetrate on their own [30]. Due to their structure, peptides are hydrophilic compounds. Depending on the length of the amino acid chain, individual molecules can reach sizes of up to several thousand Da. Sources indicate that only dipeptides and tripeptides are capable of penetrating the skin. A key issue is increasing the degree of peptide penetration and facilitating their ability to overcome skin barriers, which makes it possible to achieve visible results. To this end, various supportive methods are most commonly used, such as transport promoters and carrier systems for substances in cosmetics, as well as treatments such as microneedle/needle mesotherapy and physical methods such as sonophoresis, iontophoresis, and electroporation [3, 28].

SUMMARY

According to the latest scientific reports, biomimetic peptides represent a promising group of active ingredients used in cosmetology and aesthetic dermatology. They are characterized by a high safety profile and a mechanism of action based on mimicking and modulating the natural biological processes occurring in skin cells. They exhibit a broad spectrum of activity, including regenerative, revitalizing, and anti-aging properties, making them an essential component of modern skincare strategies. Due to their multifaceted action and good biological tolerance, they can be used in formulations designed for various skin types, regardless of age. Current research confirms the effectiveness of biomimetic peptides in improving skin condition by stimulating fibroblast proliferation, collagen synthesis, and regulating repair processes within the extracellular matrix. In the context of anti-aging therapies, their use may serve as an alternative or complement to traditional methods, such as treatments

using acids, retinoids, or fillers. Despite the growing number of scientific publications, further well-designed clinical trials are necessary to precisely determine the mechanisms of action of individual peptides, their bioavailability, and long-term safety of use. In the context of the development of evidence-based cosmetology, biomimetic peptides may represent a key direction for research into effective and safe active ingredients that support skin regeneration processes.

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