

Special Article - Amino Acid

Amino Acids and Short Peptides as Anti-Aging “Superfood”

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Nowadays, the requirements for anti-aging super products grow together with the aging population. The aim of innovations in the cosmetic field is not only to improve the appearance of skin but also health, well-being, and to make life easier. In this regard, the discovery of safe, natural and effective compounds with no side effects is like searching for the Holy Grail. Nevertheless, the simplest biomolecules, amino acids and short peptides creating proteins and participating in nearly all biological processes can be a secret of skin anti-aging therapy due to their unique properties and non-toxic „botox-like” non-invasive activity. Amino acids joined into peptide chain, similar to precious colored pearls in the necklace, have nourishing and beautifying relevance. *Notabene*, pearls, a symbol of natural noble beauty and longevity, containing all essential amino acids, offer a lot of benefits. Amino acids and oligopeptides are a „must-have” among superfoods for skin, used in either anti-aging skincare cosmeceuticals or in the diet. This mini-review summarizes the latest scientific findings concerning the great potential of short peptides in anti-aging strategy. It might contribute to further studies via making it readily available for researchers interested in the innovations in gerocosmetology.

Keywords: Amino acids; Oligopeptides; Anti-aging; Superfood; Skin; Nutrition**Introduction**

It's not surprising that everybody gets old. Aging, a natural and inevitable aspect of life, is defined as a progressive decrease in physiological functions [1]. Skin, an important protective barrier between the body and the external environment, is the largest human organ on which effects of aging processes are the most visible. Wrinkles on the face are the first signs of the passing time [2]. Skin aging is a complex biological process influenced by not only proper internal (known also as endogenous or intrinsic) - genetic (including cellular metabolism or hormones) but also improper external (exogenous, extrinsic) - environmental (in this chronic light exposure, pollution, ionizing radiation, chemicals, toxins, non-balanced diet) factors [3]. In other words, this is “aging mosaic” which results from destructive reactions occurring in different cells. Generally speaking, the structure of the skin is mainly made of collagen and elastin proteins. Collagen is the most important component of the extracellular matrix determining skin physiology (its structure and functions). The name collagen means glue. It determines its basic function – gluing cells together. The extracellular matrix retains water supporting healthy skin. Then collagen fibrils are strong and stretchy. Aging of the skin is related to the dysfunction of dermal fibroblasts (responsible for the production of collagen) leading to distortion of the contacts between cells and collagen of the extracellular matrix. In consequence, collagen decomposes through enzymatic hydrolysis into smaller fragments, oligopeptides. It is promoted by the combination of various damaging factors [4]. More specifically, reactive oxygen species, by-products of both extrinsic and intrinsic aging, cause bio-reactions within the skin, leading to the formation of cytokines and matrix metalloproteinases. The latter, activated by fibroblasts, evoke degradation of collagen and

dermal matrix. In turn, cytokines have an impact on the destruction of elastin. It reflects the main aspects of skin aging [5]. Changes in skin appearance can have a negative impact on the quality of life. Skin condition and its beauty are significant for “well-being” and the perception of health. Therefore, civilizations have always tried to maintain their youthful look and beauty. The first recorded use of cosmetics, which in Greek means beautification, is attributed to Egyptian since 4000 B.C. [6]. The idea of slowing down the effects of aging was reported in 1939, revealing that the reduction of caloric intake increased lifespan [7]. Besides, people were always looking for „elixir of youth” just like they did for the holly Grail. When, for example, the recipe for „*lexir de longue vie*” was reported in 1768, in a French book [8-9]. Today, collagen supplementation is considered to be such an elixir [10]. It is made up 70% of skin protein. It consists of ~34% glycine, 14% proline, 12% alanine, 10% hydroxyproline and 32% of other amino acids. Unfortunately, the skin aging process is impossible to stop. However, it can be significantly slowed down by holistic and complex prevention. A good lifestyle and health-promoting habits can reduce mainly extrinsic aging factors. Intrinsic anti-ageing effects can be improved by well-balanced diet enriched in the antioxidants. But, importantly, cosmetic treatments and skin bio-revitalization cannot be overlooked. In both aspects, amino acids and short peptides play a key role. They act as a “superfood” for skin. This term means „ordinary-extraordinary” nutrient-rich food providing extra health benefits and well-being. There is no “certified” precise or scientifically based definition. It is rather a marketing slogan. Probably, this expression was satirically used in 1915 for the first time, in Kingston, Jamaica, newspaper the Daily Gleaner „*he had changed the tenor of his mood and wisely written wine as super-food*” [11].

In the early 20th century, in a food marketing strategy, The United Fruit Company initiated a campaign to promote the import of their major product bananas, which are full of health benefits. It published informational pamphlets, including *Points About Bananas* and the *Food Value of the Banana* [12]. It should be mentioned that bananas contain various functional amino acids whose concentrations vary during ripening. The term superfood has evolved over the years. In 1998, Aaron Moss in „Nature Nutrition” stated: „humans have many options when it comes to fueling their bodies, but the benefits of some options are so nutritious that they might be labeled as superfoods”. Since then, it has become a very popular issue in relation to health-promoting properties or improving any aspect of physical/emotional condition. We proposed a slightly modified definition: high quality enriched ingredients stimulating cells to beneficial action for health and well-being.

Amino acids are the basic building blocks of peptides and proteins. They are supplied by blood circulation to cells. Thus, they play a vital role in almost all bioprocesses in organisms [13,14]. Moreover, they have important cellular signaling functions [15]. Hence, the simplest biomolecules have a very high nutritional potential in skin „beautification” and its health.

Amino acids

Amino acids are either produced within the body (non-essential amino acids) or can be found in many food sources (essential amino acids) [14]. The proper balance of amino acids level should be maintained due to the regulation of skin condition. Nevertheless, the level of amino acids decreases with age leading to the body’s inability to regenerate skin cells in an effective way. On the other hand, a diet containing amino acids (meat, eggs, tuna, eggs, salmon, hemp seeds, quinoa, Goji-red berries, nuts, hummus, tofu, chickpeas, milk or supplements) supports skin health. The continuous intake of the amino acid mixture in diet affects the body composition and skin condition, improves the skin texture [16]. All twenty standard amino acids play a role in the regulation of aging, creating and maintaining smooth, healthy, younger-looking skin. They are natural, safe, non-toxic, environmentally friendly, sustainable resources and do not cause allergic reactions. They activate collagen synthesis and have antioxidant properties. Nevertheless, some of them have more specialized roles [17,18]. In particular, alanine (but also serine and threonine) is a natural moisturizing factor acting as a water-binding molecule. Arginine plays a role in restoring skin damage. It speeds the healing of skin cell damage and wounds, similar to glutamine and glycine. It works so well, in fact, that application to frostbitten skin has been proven to prevent tissue loss. Arginine stimulates aggregation of keratin filament to build elastic structures in the *stratum corneum*. Besides, arginine is a precursor of nitrogen oxide, an important regulator of blood circulation in the dermis [19]. Aspartic acid and glutamine are involved in building the DNA of the skin cell. Glutamine (like glycine) prevents muscle, tissue breakdown. It is the precursor of arginine and glutathione [16]. Histidine helps boost UV protection. It protects skin against infections. It soothes the skin. Isoleucine is important in repair of tissue. It promotes the natural production of anti-microbial peptides. Leucine, in conjunction with glycine and proline, improves fine lines and wrinkles. Lysine helps make skin firm by reinforcing its supportive elements. It hydrates skin and helps increase strengthens the skin’s surface. It increases

immunity to viruses. Methionine protects the skin against from harmful substances. Proline has the greatest capacity of water binding. Serine is the important information of the cell membrane. It regulates the hydrophilic film. Tyrosine helps other ingredients penetrate the skin for maximum effectiveness [15]. Each amino acid is crucial in relation to skincare. However, they often work best in conjunction with each other.

To sum up, amino acids have nutritional benefits and great potential for the treatment of aging and aging-related diseases [15].

Short peptides

Oligopeptides are mini-proteins, in the form of a chain containing from two to ten amino acids, arranged like a colored precious pearls in a necklace. *Notabene*, pearls are made of amino acids and have rejuvenating features. The peptide properties depend on the nature and sequence of amino acids. The name peptide comes from pepton („digested” in Greek). The first peptides were described by Emil Fischer and Hofmeister in the early 19th century. Fischer described the first peptide as a glycyl-glycine [20,21]. The initial therapeutic discoveries of peptides were a century ago (opioids, cyclic peptide penicillin, or polypeptide insulin). The significant role of oligopeptides has been known for half a century since the discovery of the first peptide hormone oxytocin [22,23]. Short peptides have become preferable in the drug development due to their numerous advantages, such as: easy of production, *natural availability*, *selectivity*, simplicity of administration, diverse functionalization possibilities, low cost, the capability of regulation of tissue repair processes by stimulating cell proliferation and cell-cell interactions, whitening, moisturizing, soothing, antibacterial, nutritious, possibility to make a large range of hierarchical nanostructures and most importantly their high biocompatibility and biodegradability and superior pharmacodynamic properties [5]. Generally, short peptides are relatively more stable than their longer variants, non-immunogenic in nature and many of them self assemble to provide an exciting range of nanostructures, including hydrogels being a platform for biomedical applications [24]. The biological activity of short peptides within the skin has only recently been explored [25,26]. Peptides affect the functioning of the skin. They accelerate the redistribution of the nutrient and water. Consequently, the skin is improved and moisturized immediately. Peptides have „botox-like” effects, but are safer [27]. Scientists proved that short peptides are effective for reducing wrinkles [28]. Oligopeptides (with molecular weight less than 500 Da) can easily penetrate deeper layers of the skin. They are able to pass the critical, lipophilic skin barrier *stratum corneum*, the outermost layer of the epidermis. Peptides, playing the role of messengers, allow efficient communication among the main skin organs, epidermis, and dermis, promoting the synthesis of collagen. The *stratum corneum* is formed by a natural moisturizing factor which controls hydration [29,19]. Amino acids are main constituents of the natural moisturizing factor. Peptides as nutrients are supplied by blood to fibroblast in the dermis, and further to the epidermis helping skin repair itself. In other words, they transfer signals among cells and target the mechanisms underlying aging. They can mitigate aging biomarkers *via* modulation of free radical damage, telomeres length and so on. Notably, telomeres shorten with age resulting in cell aging. This phenomenon leads to a loss of valuable genetic material.

In view of the above, short peptides are valuable anti-aging

agents with no side effects and antioxidants. The possibilities of these simple biomolecules are continuously growing with the new in-depth knowledge on the relevance of peptides for the skin. They have both cosmetic and therapeutic action.

The bioactive oligopeptides are key ingredients in either cosmeceuticals or nutra-cosmeceuticals. The first term was coined in 1984 by Dr. Albert Kligman describing a hybrid category of products, which contain biologically active ingredients and refer to something between a drug and a cosmetic [30]. Cosmeceuticals are an attractive alternative to more invasive drugs. The term “nutraceutical” was coined in 1989 by Stephen De Felice from “nutrition” and “pharmaceutical” [31].

Oligopeptides can be divided into various groups.

Biomimetic peptides are synthetic compounds (longer oligopeptides consisting of ten to fifteen amino acids) identical to those synthesized by organisms. They mime mechanisms of the action and evoke effects similar to their natural analogs, leading to slowing down or preventing skin aging [27]. They can act as dispatchers in collagen support leading to firmer, thicker and more elastic skin. Hyperkinesia of skin muscles causes wrinkles. Peptides block neurotransmitter signals, which makes skin smoother and more relaxed. Skin wrinkles are also the effect of degeneration of extracellular matrix proteins. Peptides regulate fibroblasts and control the formation of components of extracellular matrix [28].

Bioactive peptides have either cosmetic or therapeutic activity. They have gained great interest due to a wide range of physiological functions and therapeutic relevance, such as angiotensin-I-converting enzyme inhibitory – antihypertensive, cardioprotective [32] and antimicrobial activity [33], antioxidative [34], immunomodulatory [35], anti-tumoral, anti-proliferative, hypocholesterolemic, anti-inflammatory activity [36,37], and multitudinous (physiological) features (oil absorption ability, protein solubility, stability, water holding, and foaming ability, gelling activity, emulsification capacity, better interaction with cell receptors) [38]. Ultra short peptides (containing 2-5 amino acids) are more easily absorbed than free amino acids [39]. Therefore, bioactive oligopeptides are used in the drugs, cosmeceuticals and functional foods (nutra-cosmeceuticals) [40]. An addition of fatty acids to these peptides leads to an increase in the lipophilic properties and the ability to penetrate *stratum corneum* barrier [41,42]. Bioactive peptides derived from natural sources to their higher biocompatibility and lower potential to induce allergies are very popular. Bioactive peptides can be classified according to their mechanism of action, as follows: signal, carrier and neurotransmitter peptides [43].

*Signal peptides

are messengers causing collagen synthesis *via* fibroblasts, which leads to firmer and youthful-looking skin. These peptides activate cellular signals. They can open protein channels enabling translocation of synthesized proteins to the active site. They act as growth factors activating kinase C responsible for the cell growth and migration. The structure of these peptides consists of three domains: a positively-charged amino-terminal domain (region n, 1-5 residues), a hydrophobic central domain (region h, 7-15 residues), a polar carboxyl-terminal domain (region c, 3-7 residues) [44].

Examples are as follows:

-*Valine-glycine-valine-alanine-proline-glycine* (VGVAPG, *Palmitoyl oligopeptide*). It stimulates the collagen synthesis and decreases the elastin synthesis. It is a chemoattractant for skin fibroblasts. The addition of palmitic acid enhances the oligopeptide penetration in the epidermis [23,28].

-*Lysine-threonine-threonine-lysine-serine* (KTTKS, *Pentapeptide 3*). It is a subfragment of procollagen type I and has a positive influence on the production of both of collagen (type 1 and 2) and fibronectin. All these substances are components of the extracellular matrix of the dermis. Palmitic acid leads to stability and ease of skin penetration [45,46].

-*Tyrosine-tyrosine-arginine-alanine-aspartame-aspartame-alanine*. It inhibits procollagen C-proteinase, which cleaves C-propeptide from procollagen-1 decreasing collagen breakdown [28].

-*Lysine-phenylalanine-lysine+elaidic acid* (*Lipospondine*) and *Lysine-valine-lysine*. They activate the latent Transforming Growth Factor-Beta (TGF- β) and inhibits collagenase. It increases the collagen level [47].

-*Phenylalanine-valine-alanine-proline-phenylalanine-proline* (*Peptamide-6*). It was extracted from yeast fermentation. It has wound healing properties [28]. It improves collagen synthesis. It has a powerful influence on skin growth factors.

**Heptapeptide acetyl-DEETGEF-OH* (*Perfection Peptide P7*). It protects cell DNA stimulating antioxidant enzymes [44].

**Oligopeptide-68* (β -*white*, *Arg-Asp-Gly-Gln-Ile-Leu-Ser-Thr-Trp-Tyr*). It is a whitening agent used in the treatment of skin affected by melasma.

**Tripeptide-41* (*Lipoxin*). It has an indirect influence on lipolysis [44].

- *Glycyl-L-histidyl-L-lysine* (tripeptide). It plays the role of both signal and carrier peptide. It increases collagen synthesis via stimulating fibroblasts. Palmitoyl of this peptide reduces the depth and length of wrinkles as well as smoothes the skin. Trifluorotriptide induces senescence. In consequence, it regulates biological mechanisms during the aging process [48].

*Carrier peptides

They stabilize and deliver copper (and manganese), which is a crucial element for angiogenesis, wound healing and various enzymatic processes. A good example can be *Glycyl-L-histidyl-L-lysine*. It is a fragment of the proteins of the extracellular matrix. It improves the firmness and texture of the skin, diminishes facial, deep wrinkles, fine lines, and hyperpigmentation [28].

*Neurotransmitter-inhibiting peptides

They are developed to mimic botulinum toxin. They block acetylcholine release (at the neuromuscular junction). They relax muscles, reduce facial muscle contractions and soften the wrinkles.

-*Acetyl tripeptide-30 citrulline and pentapeptide-18* (*Vanitryl*). They are used in wrinkle smoothing formulations. The first peptide is a signal, while the second – a neurotransmitter inhibitor peptide [49].

-*Pentapeptide 3 (Vialox)*. It has a similar action to tubocurarine (compound of curare). It acts at the postsynaptic membrane. It is a competitive antagonist at the acetylcholine membrane receptor. When the receptors are blocked, sodium ions are not released. In consequence, muscles are relaxed. It softens wrinkles and decreases the roughness of the skin [28].

-*Acetyl-glutamyl-glutamyl-methoxil-glutaminy-arginyl-arginylamide (Argireline, Acetyl hexapeptide 3)*.

It inhibits the release of the neurotransmitter and reduces wrinkles. It is similar to botulinum toxin A, but non-toxic. Interestingly, Botox has been considered effective so far. Nevertheless, it is highly toxic and its use should be controlled [50,51].

-*Leuphasyl*. It reduces the depth of the wrinkles.

The combination of Leuphasyl and Argireline gives a synergistic effect [28].

Neuropeptides are ingredients of neurocosmetics. They interact with the nervous system *via* skin mediators. Skin and brain mainly have the same embryonic organ. They are interconnected by nerves and neuron cells. Neurocosmetics play a function in skin homeostasis through activation/inhibition mediators [44]. They target nerve endings of the skin that are sensitive to cold, heat, pain, pressure. They have a soothing effect of skin. They are non-toxic, innovative and bio-active.

Conclusion

Currently, modern gerocosmetology is becoming increasingly popular among the aging population. Facial skin aging is the most noticeable and visible sign of the passing lifetime. The primary target of an aging study is to prevent age-related diseases, improve health and increase the quality of elderly life. Peptides are the latest, biggest revolution in aging skincare. They are the most powerful, effective, non-toxic and non-invasive anti-aging „botox-like” substances restoring the skin functional activity. Amino acids have antioxidant properties. They are a “must-have” not only to skin youthful-looking but also its health. Amino acids and short peptides are supernutrition for fibroblast cells to produce collagen, fibrinogen, and elastin, significantly improving the condition of the skin. Cosmeceuticals, proper diet, and supplements rich in amino acids and oligopeptides provide priceless nutritional benefits for the skin.

To sum up, the simplest building blocks of proteins can be the secret “superfood” for skin anti-aging strategy.

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