

TOPICAL PEPTIDES AS COSMECEUTICALS

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ABSTRACT

Peptides are involved in many physiological processes including defense, immunity, stress, growth, homeostasis and reproduction. Their broad acceptance as natural molecules, relatively high stability and well defined actions make them attractive for many skin related indications most notably anti aging therapy, pigmentation therapy, innate immunity and inflammation. The latest application of peptides is their usage as cosmeceuticals. Use of penetration enhancers, chemical modification or encapsulation of peptides may enhance the transdermal delivery of peptides. The review describes the peptides that are most commonly used in cosmeceutical industry and discusses their advantages and use in dermatology.

KEYWORDS: homeostasis, penetration enhancers, encapsulation, cosmeceuticals and transdermal delivery.**INTRODUCTION**

Skin integrity is essential not only because the skin acts as a protective barrier to internal organs but also because undamaged skin is more attractive and youthful. Research studies on skin aging led to the development of cosmeceuticals that enhance health and appearance of skin. Cosmeceuticals contain biologically active ingredients to improve the health and are marketed as a combination of cosmetics and pharmaceuticals. Although they do not undergo the same testing for efficacy as pharmaceutical products, evidence of their benefits is steadily increasing. Cosmeceuticals may be available in any form like creams, lotions, serums, and ointments. They differ from nutricosmetics in the aspect that cosmeceuticals are topical preparations while the nutricosmetics are ingested.

So the question is if peptides are already present in the body, why do we need more of them? The answer is aging. We lose 1% of our remaining collagen per year after age 30.

Board-certified dermatologist Marisa Garshick of the Medical Dermatology and Cosmetic Surgery Centers helps explain that the hexapeptides brighten the skin, while tetrapeptides boost elasticity and firmness of skin.^[1]

WHAT ARE PEPTIDES?

- Peptides are defined as building blocks of proteins that are short chains of amino acids. The skin consists of proteins like collagen, keratin and elastin

which are responsible for its texture, strength and resilience.

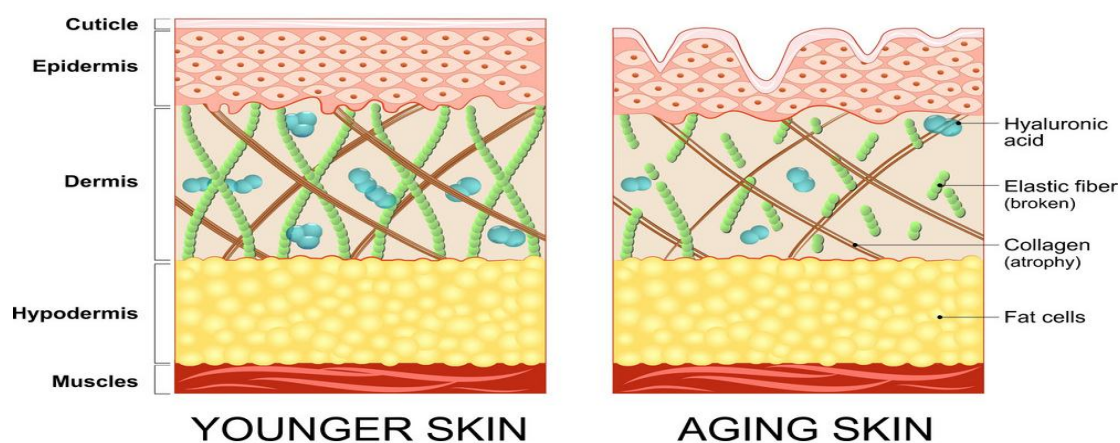
- They are important in many natural processes such as the cell proliferation, cell migration, inflammation, angiogenesis, melanogenesis and protein synthesis.^[2]
- The skin is less intact, has wrinkles, loses bouncy nature and loses firmness without peptides.
- Peptides stimulate the skin cells to perform specific functions such as building collagen and elastin thereby encouraging the skin to look and act younger.
- Peptides are present naturally in the human body, and we can also get them in our diet through fermented foods like yogurt, tofu, and pickles. They are also formed when proteins breakdown.

USES OF PEPTIDES IN SKIN CARE

1. **Improved skin barrier:** The skin is the body's first line of defense against pollution, dirt, microorganisms and ultraviolet rays. Over exposure to these toxins may damage the skin barrier. Peptides aid in help building up a stronger barrier.
2. **Reduced wrinkles:** Collagen can plump skin and lips, and when skin is firmer and plumper wrinkles and fine lines will be less visible (Fig1).
3. **More elastic skin:** The presence of elastin fibers makes skin look firmer and tauter thus reducing wrinkles.
4. **Eases inflammation:** Peptides can help ease inflammation, treat burns and repair damaged skin
5. **Can help clear breakouts:** Some peptides are antimicrobial thus can be used to prevent acne.

Table 1: Structural difference between healthy skin and aging skin.

HEALTHY SKIN	AGING SKIN
1. The epidermis holds more moisture when compared to an aging skin and therefore the skin is softer and smoother.	1. Fine lines start to appear due to lack of moisture before further deepening.
2. The dermis layer gives support and elasticity to skin as it contains elastin fibers and collagen	2. Over time the elastin fibers and collagen deplete causing the skin to wrinkle.
3. Plump skin due to presence of fat cells in hypodermis layer.	3. Fat cells diminish therefore the skin begins to sag.

**Figure 1: Structure of healthy skin and aging skin.****CONSIDERATIONS AND DRAWBACKS**

- Peptides are very expensive.
- Research on peptides is still ongoing. Other ingredients like AHAs and retinol are currently more scientifically backed as anti-aging ingredients and minoxidil for treating hair loss.
- Not all peptides have beneficial effect on skin.
- Cosmeceuticals are not regulated by US Food and Drug Act (FDA).
- Transdermal delivery is a challenge as peptides have high molecular weight and low lipophilicity.

CLASSIFICATION

There are five different categories, based on how they work.^[3]

1. Signaling peptide
2. Carrier peptide
3. Neurotransmitter inhibitor peptides
4. Enzyme inhibitor peptides
5. Structural or keratin peptides

1. SIGNALING PEPTIDES

They are the most commonly used cosmetic peptides. They increase the amount of collagen in your skin by stimulating collagen production and prevent your body from breaking down collagen.

Here are few examples of signal peptides.

- **Pentapeptide-3 (Lys-Thr-Thr-Lys-Ser, KTTKS):** It is one of the first oligopeptides to be developed for cosmeceutical use. It is used as anti-aging and

anti-wrinkling agent by increasing the synthesis of types I & III collagen, elastin and fibronectin.

- **Trifluoro tripeptide-2:** It decreases the production of progerin which is involved in the natural process of aging. It prevents wrinkle formation, elasticity and sagging of skin. It gives firmness to skin.
- **Palmitoyl Tripeptide-3/5:** It increases TGF- β activity which in turn stimulates the collagen production. Used as anti-wrinkle, firming agent and skin moisturizer.^[4]
- **Tetrapeptide (His-D-Phe-Arg-Trp):** It is an analogue of α -MSH and acts by inducing melanin synthesis. Used in treatment of vitiligo.
- **Tetrapeptide 21 (Gly-Glu-Lys-Gly):** It was developed by Farwick et al. who demonstrated its In-vitro and In-vivo capability of inducing collagen production. Used to prevent wrinkle formation.
- **Lipospondine (Elaidyl-lysine-phenylalanine-lysine-OH)** is a tripeptide linked to elaidic acid.^[5] It increases the collagen levels by activating TGF β , inhibiting and reducing the levels of collagenase.
- **Carnosine and N-Acetylcarnosine:** Carnosine is a dipeptide (β -Ala-His) and an aqueous antioxidant. It has wound healing property. It is present in high concentrations in muscle and brain tissues.

During a six-month study, 20 healthy volunteers were treated with carnosine and *N*-acetylcarnosine formulations. Carnosine showed 3.6% reduction of erythema and *N*-acetylcarnosine showed 7.3% reduction of erythema compared to the control. Both have antioxidant capacity.

- **Palmitoyl Hexapeptide-12** (Pal-Val-Gly-Val-Ala-Pro-Gly). It stimulates collagen and elastin. It acts by reducing the production of interleukin-6 (IL-6) by keratinocytes and fibroblasts. IL-6 promotes inflammation which leads to faster degradation of the skin matrix. This contributes to the development of wrinkles, and loss of skin firmness and elasticity.

2. CARRIER PEPTIDES

These are the second most popular cosmeceutical peptides. Carrier peptides adjoin to other compounds to facilitate their delivery. Carrier peptides deliver trace elements like copper and manganese, which aid in wound healing and enzymatic progress.

- **Copper tripeptide- 1 (Cu- GHK):** It is composed of glycine (G), histidyl (H), and lysine (K). The first carrier peptide GHK- Cu was isolated from human plasma. It is used in wound healing creams and in anti- wrinkle cosmeceuticals.^[6]

GHK and Gly-Gly-His (GGH) act by reducing TNF- α induced IL-6.

Cu-GHK also stimulates hair growth and collagen synthesis on the scalp thus strengthening the hair.

- **Manganese tripeptide- 1 (Mn- GHK):** Hussain et al. investigated the influence of manganese compound with GHK peptide in treating cutaneous photo damage. The damage was reduced from moderate to mild.

3. NEUROTRANSMITTER INHIBITOR PEPTIDES

Neurotransmitter inhibitors act in a similar way to Botulinum toxin. They decrease the appearance of fine lines and wrinkles by blocking the release of acetylcholine, a neurotransmitter involved in muscle contractions. They selectively modulate synaptosomal-associated protein (SNAP-25) of 25,000 Daltons which is essential for ACh release from vesicles. This inhibits the formation of soluble N-ethyl-maleimide-sensitive factor attachment protein receptor complex (SNARE). Therefore, peptides that mimic the amino acid sequence of the synaptic protein (SNAP-25) inhibit the secretion of ACh.

- **Acetylhexapeptide-3-:** Acetyl hexapeptide-3 is the most widely used neurotransmitter peptide. It is a synthetic peptide derived from the N-terminal domain of SNAP-25. It interferes with the formation of the SNARE complex which is necessary for catecholamine release from chromaffin cells.
- **Pentapeptides, including pentapeptide-3 and pentapeptide-18:** Pentapeptide-3 acts as a competitive antagonist at the Acetylcholine postsynaptic membrane receptor. This prevents sodium ion channels to open, thus inhibiting depolarization and muscle contraction.

Pentapeptide-18 (Tyr-D-Ala-Gly-Phe-Leu) acts in a similar way as enkephalins. It inhibits the catecholamine

release.^[7] It reduces fine lines and wrinkles, moisturizes the skin, and improves firmness and skin tone.

- **Tripeptide-3:** Tripeptide-3 (beta-Ala-Pro-Dab-NH-benzyl) acts as reversible antagonist of muscular nicotinic ACh receptors at the post-synaptic membrane, preventing binding of acetylcholine to the receptors. This causes sodium ion channels remain to close and depolarization does not take place, and muscles cannot contract.

4. ENZYME INHIBITOR PEPTIDES

Enzyme inhibitors inhibit the enzymes that mediate the breakdown of collagen and other skin proteins thus preventing loss of collagen. The most common types are soybean peptides, silk fibroin peptides, and rice peptides.

- **Soybean Peptides:** They are peptides consisting of 3–6 amino acids, mainly in the size range of 300–700 kDa obtained from soybean. Topically applied soy oligopeptides increases Bcl-2 protein expression and decreases sunburn cells, apoptotic cells, p53 protein expression, and Bax protein expressions in the epidermis layer of UVB-irradiated skin. Thus protecting from UVB photo damage.^[8]
- **Silk Fibroin Peptide:** Silk fibroin peptide is derived from the silkworm *Bombyx mori*. It inhibits the formation of skin lesions following exposure to Ultraviolet B.
- **Rice Peptides:** These are low molecular weight peptides (<3000 Da) obtained after processing of black rice bran. These oligopeptides inhibit matrix metalloproteinase activity and induce expression of hyaluronan synthase 2 gene in keratinocytes.

5. STRUCTURAL OR KERATIN PEPTIDES

Structural peptides prevent dehydration and dryness of skin. They're derived from protein called keratin that gives hair and nails their structure. They act by improving the skin barrier thereby allowing it to retain more water and give the skin a plumper look.

Keramino 25: It is described to have hemostatic, moisturizing, repair-promoting and potentially radio-protective properties.

HOW DO PEPTIDES INFLUENCE HAIR?

- There are a wide range of peptides with different benefits. Some can help make the skin look younger while others can help the hair look lush and dense.
- According to the American Hair Loss Association, 85% of men and 40% of women will experience hair loss by the age of 50.
- The hair growth from the hair follicles is a complex process. Different peptides act in different ways to aid in hair growth.
- Hair disorders may be caused by various factors like stress, pollution, hormonal factors, genetics and medicinal conditions.

CAUSES OF HAIR LOSS

- As people get older hair loss is normal as hairs naturally begin to lose strength and volume.
- As time goes by the follicles stop producing new hair, and the hair begins to lose its color. It becomes a problem only when there is hair loss at young age.

Some of the common causes of hair disorder are.

1. Alopecia Areata (AA)

Alopecia Areata is a non-scarring auto-immune hair loss disorder.^[9] The hairs fall out in round patches from the scalp and beard mostly. It affects both males and females and occurs due to genetic and environmental factors. Although it affects hair growth, the follicles are still very much alive and intact, and can still regrow hair.

2. Diet

It is very important to take proteins in our diet. Lack of a healthy diet may cause hair problems like dryness, dandruff, graying of hair and hair loss.

3. Stress

Telogen effluvium, a scalp disorder is a very common hair disorder which is characterized by thinning or shedding of hair due to stress. This is because the hair follicles go into a resting stage. Stress also causes premature graying as it affects the melanocyte stem cells that influence hair color.

TYPES OF PEPTIDES FOR HAIR GROWTH

1. Copper Peptides for Hair Growth

- Copper is an essential component of our body. Copper, is important for tyrosinase (an enzyme needed to produce melanin) and other cuproenzymes to function.
- Melanin is very important for pigmentation. Copper deficiency can lead to graying of hair.
- The lack of adequate copper in the body causes various problems, such as brittle hair, graying of hair, weakness, skin and muscle soreness, and hair disorders. Since the 1970s, copper peptides have been used in cosmeceuticals. Copper peptides are made of three amino acids.^[10] They prevent hair loss by.

- **Blocking of the Dihydrotestosterone (DTH)**

They inhibit the conversion of testosterone to dihydro testosterone in the scalp thereby improving hair growth.

- **Improves Microcirculation**

The hair follicles require some oxygen without which they do not function well, affecting the hair growth.

The copper peptides stimulate the angiogenesis process, which will cause an increase of oxygen and allow regeneration of new blood vessels from previously damaged vessels in the follicles thus promoting hair growth.

- **Promote Collagen and Repair Skin**

They act by increasing the collagen and elastin production which in turn increases the fat cells on the

scalp. With increase in fat cells on scalp there will be significant hair growth.

- **Other Mechanisms like** dermal fibroblast stimulation and increased expression of vascular endothelial growth factor.^[11]

2. Thymic Peptides for Hair Growth

- The thymus gland plays a key role in the immune system.
- Hair growth is one of the therapeutic applications of thymic peptides.^[12] A study was carried on volunteers with chronic telogen effluvium (TE) over a period of 6 months.
- A Lotion and a shampoo with synthetic thymus peptides were used to investigate the efficacy of the peptide on hair growth. The study consisted of 364 people (male and female) suffering from the two hair diseases.
- During the study for 24 weeks the participants applied the lotion every day, and the shampoo three times a week.
- For the TE patients, 98% improvement was recorded with no side effects.

3. Biomimetic Peptides for Hair Growth

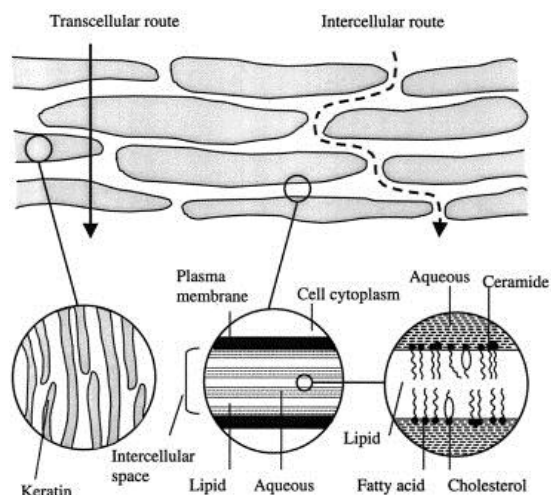
- They are synthetic peptides having similar structure to natural peptides that occur in the body.
- They regulate the synthesis proteins Ki-67 and stimulate the regeneration process thus preventing aging.
- Capixyl is one of the most common biomimetic peptide products. It is made of a blend of water, dextral, butylene glycol, Trifolium extract, and acetyl tetrapeptide-3.^[13] It aids in wound healing just like the natural peptides in the body.
- It acts on reductase enzyme, thereby preventing dihydrotestosterone, thus preventing hair loss. It also enhances dermal protein papilla, hence resulting in better hair stability and strength.

TRANSDERMAL DELIVERY OF OLIGOPEPTIDES

Transdermal delivery of a drug involves its passage through the stratum corneum of epidermis and later the dermis, into the circulation or the target site for action. The human skin consists of 2-4% of elastin and 70-80% of collagen. When the proteins diminish over time it results in cutaneous ageing. it results in cutaneous ageing. Dermis has been identified as being critical in wound healing and maintenance of normal healthy skin and therefore is the target to both cosmetic and clinical applications.

Topical administration of peptides may be possible by two pathways:

1. Intercellular route
2. Transcellular route.^[14]



But the skin is impermeable to compounds that are charged, hydrophilic and have relatively high molecular weights such as peptides. To overcome this barrier, several enhancement techniques have been used. Few of them are.

1. **Penetration enhancers:** Penetration enhancers alter the lipid structure of the stratum corneum by fluidizing the lipid structure of the stratum corneum and forming micro cavities within the lipid bilayers thereby reducing its barrier properties and increasing its permeability for peptides.^[15] Various penetration enhancers include alcohols, azones, hexanoates, Dimethylsulphoxide, pyrrolidones, urea, sugar esters, surfactants unsaturated fatty acids such as oleic acid.
2. **Facilitating peptide sequences:** Co-administration of certain peptide sequences, acting as peptide facilitators, has also been reported to increase peptide delivery.
3. **Chemical modification of the peptide itself:** Lipophilic derivatives of peptides obtained by Coupling or conjugation of a peptide to a lipophilic moiety such as lauric, palmitic, myristic, stearic or oleic acid lead to better skin permeability.
4. **Using conjugates with cell penetrating peptides (CPPs)** is also an attractive approach to deliver the peptide into the deeper skin layers. They are also known as protein transduction domains.^[16] These are short peptides with not more than 30 residues. These CPPs include Tat, transportan, Poly-Arg and penetratin.
5. **Encapsulation of peptides:** Carrier systems that possess an aqueous core surrounded by a lipid or surfactant bilayer have been very useful to deliver peptides and proteins to the dermis. Therefore different types of vesicular systems such as liposomes, transfersomes, niosomes and ethosomes are being extensively used for delivery of peptides.

MARKETED PRODUCTS

1. Peter Thomas Roth Peptide 21 Wrinkle Resist Serum

This product features a 73% complex of 21 peptides, plus two gamma proteins derived from Asian natto gum, to reduce the appearance of fine lines and wrinkles, improve skin elasticity and even skin tone and texture.

2. Neocutis Bio Cream Overnight Smoothing Cream

Known in skin care circles as the “Cadillac of peptides,” PSP[®], which stands for “processed skin cell proteins,” is a blend of proteins and polypeptides, formulated to revive skin and increase firmness, brightness and elasticity.

3. EltaMD PM Therapy Facial Moisturizer

This nighttime moisturizer is oil-free and enriched with ceramides and rice protein peptides to moisturize and repair skin while at rest. Cell growth and collagen formation within the skin is credited to peptides, resulting in a boost in elasticity.

4. Vichy LiftActiv Peptide-C Anti-Aging Moisturizer

Formulated with phyto peptides, vitamin C and mineralizing thermal water, this advanced anti-aging moisturizer works to correct multiple signs of aging, including wrinkles, dullness and loss of definition. Its creamy texture transforms into a powder-feel and hydrates skin for up to 48-hours, unveiling a lifted and firmer complexion.

CONCLUSION

Peptides have become important for the cosmeceutical industry as they play a significant role in reducing scarring, anti-ageing, wound healing, and to treat burns. With the advent of new technologies efficient delivery approaches have been developed to enhance the dermal delivery of peptides. With increasing therapeutic use of commercial peptides and advanced technology in peptide pharmacokinetics and dynamics, the use of peptides in various dermatological conditions appears promising.

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