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Letter to Editor

Barriers to Commercialization of Cosmetic Peptides

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HIGHLIGHTS

- Peptides are eligible molecules to be applied in cosmetic products since they are biocompatible and effective.
- There are obstacles that limit the widespread use of peptides in the cosmetic industry.
- Conventional and in silico techniques can be employed to overcome challenges on the path to commercialization of peptides.

ABSTRACT

Consumer demand for safe and effective cosmetics has prompted the exploration of peptides due to their biocompatibility. However, challenges such as low skin permeability, susceptibility to degradation, and chemical instability limit their use. Additionally, regulatory and manufacturing complexities pose further hurdles. Strategies like chemical modifications, formulation adjustments, and advanced synthesis methods can help to overcome these issues. Notably, computational methods show promise in enhancing the efficacy and stability of peptide-based cosmetics.

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Introduction

Bioactive peptides are undoubtedly one of the most sought-after active ingredients in the cosmetic world. Peptides have valuable advantages such as biocompatibility and low immunogenicity. They play a variety of roles in skin health, from increasing skin cell proliferation to reducing skin pigmentation and inflammation (Pintea et al., 2025). They are categorized into four classes: signal peptides, carrier peptides, neurotransmitter-inhibitor peptides, and enzyme inhibitor peptides (Mortazavi et al., 2019). The signal peptides are in charge of triggering signaling cascades. These peptides stimulate the synthesis of the extracellular matrix components (e.g., collagen, elastin, fibronectin) and the proliferation of keratinocytes and epidermal cells. The melanogenesis can also be modulated by signal peptides. Palmitoyl pentapeptide-4, tripeptide-10 citrulline, and palmitoyl hexapeptide-12 are examples of signaling peptides. Trace elements essential for enzymatic

processes responsible for skin health are delivered by carrier peptides. These peptides also stimulate the collagen and elastin synthesis. Tripeptide-1 (GHK, glycine-histidine-lysine) can carry both copper and manganese across the skin layers. Both elements are essential for the well-functioning of the enzymatic anti-aging processes. Neurotransmitter-inhibitor peptides inhibit the muscle contraction process through the prevention of acetylcholine release. Acetyl hexapeptide-8 (available on the market as Argirelin®) and pentapeptide-18 reduce neuronal activity and thus wrinkles. The last class, enzyme inhibitor peptides, prevents the degradation of collagen and other proteins through proteinases and superoxide dismutase inhibition. Soy oligopeptides, silk peptides, and rice-derived peptides are examples of this class (Mortazavi and Moghimi, 2022; Ngoc et al., 2023; Pintea et al., 2025).

Despite all the benefits of cosmetic peptides, many challenges need to be addressed. These challenges can be divided into two categories: those that affect their production and incorporation into finished products, and those that affect their effectiveness in the body after skin application. Cosmetic peptides are used as active ingredients in combination with other active ingredients and excipients in semisolid or liquid formulations such as creams, hydrogels, lotions, and serums that contain water. Therefore, the probable interaction with other formulations' components as well as the maintenance of stability in the formulation are major issues. The manufacturing conditions, for example enhanced temperature and pH changes, can affect the structural integrity of peptides. In addition, there are economic concerns about the mass production of high-yield synthetic peptides. Frequently, low amounts of peptides are used in cosmetic formulations, therefore, their assay through common analysis methods is challenging (Aguilar-Toalá et al., 2019; Mortazavi and Moghimi, 2022; Ngoc et al., 2023). After application of products containing peptides on the skin, problems such as insufficient release from the formulation, low skin permeability, susceptibility to proteolytic degradation, and low binding to cell surfaces affect the bioactivity and bioavailability of peptides (He et al., 2023; Mortazavi et al., 2025). In the following, we intend to briefly discuss the strategies which hold promise to obviate these challenges.

Approaches to improve cosmetic peptides properties

Some approaches have been applied to increase the amount of cosmetic peptides in the skin target site. Chemical modification, chemical permeation enhancers (e.g., propylene glycol, pentylene glycol), metal complexation (e.g., copper or magnesium), novel formulations containing delivery systems (e.g., liposomes, transferosomes, microemulsions, liquid crystal nanoparticles), and physical enhancement approaches (e.g., microneedles, iontophoresis) have been investigated to enhance skin absorption of peptides (Mortazavi and Moghimi, 2022). Among others, chemical modification is a considerable technique to overcome the low skin bioavailability of peptides. Modified cosmetic peptides have been on the market for years. Peptides are mostly hydrophilic compounds with low affinity to intercellular lipids in the stratum corneum. The backbone modification, as well as conjugation to hydrophobic moieties, cell-penetrating peptides, biologically effective moieties (e.g., ascorbic acid or lipoic acid), etc. can enhance the partitioning, diffusion, or activity of peptides. In addition to enhanced bioavailability, the modified peptides are to some extent less susceptible to enzymatic degradation (Mortazavi et al., 2021a; Mortazavi and Moghimi, 2022). KTTKS (lysine–threonine–threonine–lysine–serine), GHK, and GQPR (glycine-glutamine-proline-arginine) are well-known signal peptides that benefit from chemical modification. Palmitic acid is a 16 carbon-fatty acid that converts these hydrophilic peptides, to palmitoylated conjugates with enhanced log P (i.e., Pal-KTTKS, Pal-GHK, and Pal-GQPR) (Rasouli et al., 2023; Mortazavi et al., 2025). Although, based on the published data, it seems palmitic acid is the first hydrophobic moiety used to synthesize conjugated anti-wrinkle peptides, the studies showed that the conjugation of shorter chain length fatty acids could be more effective (Mortazavi et al., 2025; Sayed Tabatabaei et al., 2025). Fatty acids with various chain lengths from C6 to C18 were conjugated to KT peptide by our group. The results revealed that C8-KT (lysine–threonine) had the highest skin permeability (Sayed Tabatabaei et al., 2025). These indicated that an optimum length/molecular weight of moieties is required to reach the highest skin absorption. Mortazavi et al., (2021b) and Choi et al., (2014) investigated the skin permeation of Pal-KTTKS. The result showed that no detectable amount of this palmitoylated peptide appeared in the receptor phase of diffusion cell. (Choi et al., 2014; Mortazavi et al., 2021b). Since palmitic acid is a main component of the intercellular lipid matrix of stratum corneum and since Pal-KTTKS has a long linear structure, this was attributed to the entrapment of Pal-KTTKS in the lipid matrix. Terpenes which are skin permeation enhancers have also been conjugated to KTTKS and enhanced its skin permeability (Mortazavi et al., 2021b).

The backbone of acetyl hexapeptide-8 was modified to achieve derivatives with enhanced skin permeability. To do so, esterification of glutamic acids' side chains, conversion of guanidine functional groups to acetamide functional groups, and so on were performed (Lim et al., 2018). Note that chemical modification despite all the benefits provides for cosmetic peptides, can pose new challenges for them, such as reduced biological activity and even reduced skin permeability (Mortazavi et al., 2021a; Mortazavi and Moghimi, 2022).

Signal peptides should interact with cell surface molecules to trigger the signaling process. The cell-targeting molecules are another type of moieties that can be grafted to cosmetic peptides to increase their concentration at the cell surfaces. Chondroitin sulfate and integrin αvβ3 are expressed in the skin cell surface. He et al., (2023) synthesized two derivatives of GHK using integrin αvβ3 binding moiety (i.e., RGD sequence; arginine-glycine-asparagine) and chondroitin sulfate binding moiety (i.e., sOtx2) (**Fig. 1**). The enhanced interaction between peptide and oxidative cell surface led to the enhanced anti-apoptotic, anti-oxidative and anti-aging features of novel GHK derivatives. The in-vitro permeation of GHK and RGD-GHK across porcine skin was also evaluated using Franz diffusion cells. Around 5% and 0.5% of RGD-GHK and GHK were measured in the receptor cells, respectively, indicating that this targeting moiety, despite being hydrophilic, did not reduce the permeability of GHK (He et al., 2023).

In silico methods

In general, molecular engineering to achieve cosmetic peptides with enhanced efficacy, permeability, and stability is essential. To decrease the time and cost associated with experimental screening, in silico techniques such as molecular dynamic simulations, quantitative structure-activity relationship models, virtual libraries, and machine learning algorithms can be applied (Adelusi et al., 2022, Hashemi et al., 2024). There are a few studies on using in silico techniques for designing cosmetic peptides. A comprehensive review has been published recently, which discussed strategies to design cosmetic peptides with optimized anti-melanogenic activity (Putri et al., 2025). Melanin pigments protect human skin against radiation; however, their abnormal accumulation leads to skin aesthetic concerns. The main therapeutic agents such as hydroquinone and kojic acid have considerable side effects. Natural compounds like peptides could be good alternatives for chemical skin-lightening therapeutic agents (Putri et al., 2025).

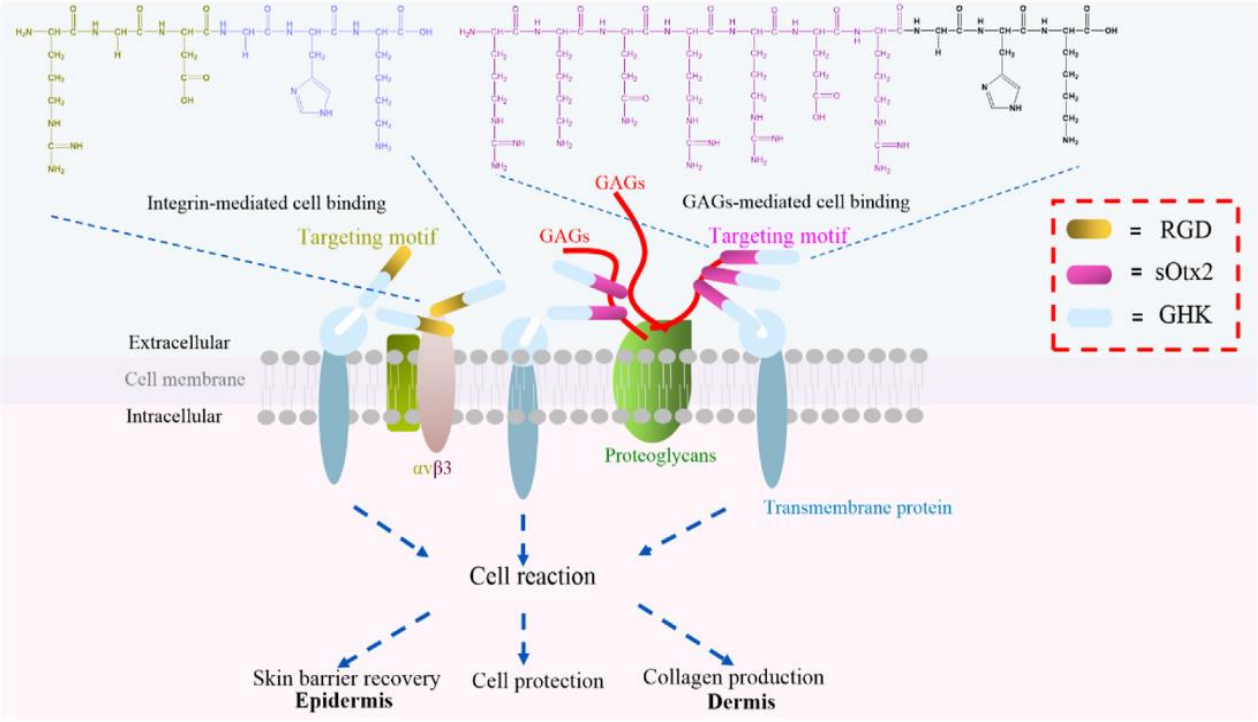

Figure 1: Schematic illustration of RGD-GHK and sOtx2-GHK interaction with cell surfaces (He et al., 2023). Reprinted from an open-access journal under the Creative Commons CC-BY license (https://creativecommons.org/licenses/by/4.0/).

Peptides indicated potential for tyrosinase inhibition, a key enzyme in melanogenesis. Structure-activity relationship study showed that the size of peptides was important in tyrosinase inhibition. Peptides with a molecular weight in the range of 0.5 to 2 KDa have formed hydrogen bonds with certain amino acid residues on tyrosinase (Ji et al., 2022). Furthermore, studies showed that the presence of aromatic residues such as tyrosine and phenylalanine in the sequence of oligopeptides led to effective tyrosinase inhibition. Such peptides could bind efficiently to tyrosinase and stabilize the enzyme-peptide complex (Kongsompong et al., 2021). Cyclization is another technique to strengthen inhibitory activity against tyrosinase. Cyclization of peptides not only improves receptor target affinity and stability but also enhances skin penetration and cellular uptake (Putri et al., 2025). A good example is cyclic tetrapeptide massiliamide with strong anti-tyrosinase activity which is an isolated Gram-negative bacterium *Massilia albidiflava* (Frediansyah et al., 2021).

In the case of the prediction of cosmetic peptides' skin permeability through in silico techniques, no published data was found. However, a recent research study addressed this challenge for FDA-approved drugs using artificial intelligence algorithms (Abdallah et al., 2024). These researchers aimed to achieve nonlinear models for predicting Log K_p (permeability coefficient) values of compounds based on their chemical structures. Initially, they analyzed a skin permeability dataset consisting of 140 molecules with diverse Log K_p values and found out lipophilicity and hydrogen bond donors and acceptors as well as topological polar surface area were key descriptors affecting skin permeability. They then applied various machine learning models for regression analysis and concluded that the LGBM model had superior performance for predicting Log K_p. The cluster analysis of 2326 FDA-approved drugs dataset was also performed, and the results showcased four discrete clusters with considerable differences in molecular properties (molecular weight, polarity, saturation, aromaticity, etc.). Subsequently, the LGBM model was applied to predict the Log K_p of FDA-approved drugs. The predicted Log K_p values and permeability profiles of the mentioned clusters were significantly different (Abdallah et al., 2024). Such information can pave the way for identifying potential candidates for skin permeability.

Conclusion

Consumer demand for highly effective and safe cosmetic products has driven the cosmetic industry to achieve more efficient products. Peptides are eligible molecules to be used in cosmetic products since they are biocompatible and effective. However, some obstacles limit their widespread use in the cosmetic industry. Due to low skin permeation and susceptibility to degradation by skin proteolytic enzymes, peptides suffer from low bioavailability. Chemical instability in environmental conditions makes it difficult to achieve long-lasting cosmetic products containing peptides. Furthermore, the regulatory challenges and manufacturing complexities are other significant issues. However, various strategies have been employed to overcome these barriers. Chemical modification, formulation adjustment, novel drug delivery systems, efficient packaging, advanced synthesis methods, and so on could be considered to obviate barriers. Nevertheless, using computational methods seems highly promising to overcome these obstacles as quickly and effectively as possible.

Ethical Statement

This work did not contain any animal or human studies performed by the authors.

Competing Interests

The authors declare no conflicts of interest.

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Data Availability

All relevant data has been reported in the manuscript.

Authors Contribution

S.M. Mortazavi prepared the manuscript draft. S.M. Mortazavi and H.R. Moghimi prepared and reviewed the final manuscript.

Declaration of AI Tools Usage

Authors gratefully acknowledge the use of the artificial intelligence (AI) tools of Grammarly AI, solely for the purpose of linguistic revision and to improve the clarity of the manuscript.

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