

NEWS, VIEWS, & REVIEWS

Applications of Bioactive Peptides in Dermatology

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INTRODUCTION

Most physiological processes in the body are regulated by the interaction of specific amino acid sequences, functioning either as peptides or fragments of proteins. Peptides are compounds containing two or more amino acids linked by an amide bond that transmit biochemical signals.[1] Synthetic engineering of bioactive peptides allows for the targeted promotion of physiological processes while minimizing associated side effects (Table 1). By substituting amino acids, diverse peptide analogs are created to regulate the potency, solubility, toxicity, and cost of potential therapies.[2] The ability to modify and control peptide compounds with ease is unique, as many other biological molecules are chemically challenging to alter. Consequently, bioactive peptides offer not only a broad array of potential active ingredients, but also can be developed and tailored to be made suitable for specific indications and demographics.[3]

Table 1. Advantages and Limitations of Engineered Bioactive Peptides

Advantages	Limitations
High specificity	Limited skin penetration
Limited side effects	Short half-life
Easy to modify	Low stability

Peptide Delivery

Although many advancements in peptide synthesis and therapeutic use have been made in recent decades, delivery to target sites is still a challenge. Peptides are often administered parenterally since they are unstable when administered orally due to first-pass degradation/metabolism. Yet, the typically short half-life of peptides requires frequent injections, thus alternative routes of delivery are being actively researched. Transdermal delivery is a promising alternative as this route encounters less enzymatic degradation; however, the greatest impediment is the actual target - the formidable skin barrier.[4]

Peptides require active methods of delivery through the skin given they are typically large molecular weight (>500 Da), polar and hydrophilic molecules. One approach to improve active diffusion is with the use of physical or chemical permeation enhancers.[4-6] Encapsulation within polymeric particulate delivery systems, such as phospholipid-based liposomes, which are known to penetrate the skin more easily, can improve topical delivery. Moreover, chemical modification of peptides through the addition of lipophilic derivatives is a strategy to increase encapsulation efficiency. Physical penetration enhancers include application of energy to drive delivery of peptides (iontophoresis, electroporation, or sonophoresis), minimally invasive disruption of the stratum corneum (microneedles, jet injectors), and ablation of the stratum corneum (lasers, radiofrequency, suction blister, thermal poration). Innovative technologies continue to be researched for transdermal delivery of peptides, particularly novel combinations of enhancement techniques which show promise in delivery optimization by leveraging synergistic mechanisms.[4]

Dermatologic Applications

Skin Aging

In the current era, significant efforts and research are driving the development of peptides targeting skin aging, generating a robust market in the cosmeceutical industry for peptide innovation. Ex vivo and translational studies have demonstrated that bioactive peptides increase fibroblast production of collagen, decrease collagen breakdown, and increase extracellular matrix protein expression, maintaining the skin's structural integrity and combating the natural aging process.[7-9] Additionally, peptides promote anti-aging by scavenging free radicals, chelating pro-oxidative transition metals, decreasing hydroperoxides, and enzymatically eliminating certain oxidants.[10] Currently, there are four categories of anti-ageing peptides with varying primary mechanistic processes: signal peptides, neurotransmitter-affecting peptides, carrier peptides, and antioxidants (Table 2).[10]

Table 2. Bioactive Peptide Categories and Mechanisms of Action

Peptide Categories	Primary Mechanism of Action
Signal peptides	Promote collagen synthesis by stimulating fibroblasts
Neurotransmitter-affecting peptides	Enhance botulinum toxin function to reduce facial muscle contraction thus decreasing sagging and wrinkling
Carrier peptides	Stabilize and provide essential trace elements for enzymatic processes involved in skin rejuvenation
Antioxidants	Scavenge damaging free radicals

Acne

Oral antibiotics are commonly employed in the treatment of moderate to severe inflammatory acne, however long-term

use beyond clinical guidelines can result in the emergence of antimicrobial resistance. Synthetic antimicrobial peptides (AMPs), engineered analogs of naturally occurring AMPs, have been evaluated as antibiotic alternatives. Granulysin-derived peptides are bactericidal against *Cutibacterium acnes* and possess anti-inflammatory properties.[11] The added value of these peptides has been evaluated in conjunction with isotretinoin, with data suggesting that granulysin-derived peptides improve the efficacy of isotretinoin.[12]

Wound Healing

Bioactive peptides can enhance the skin reparation and renewal processes after injury by promoting collagen and elastin production, cellular proliferation, inflammation, and angiogenesis.[10] Specifically, AMPs have been shown to promote wound healing through immunomodulation and cytokine production.[13] AMPS are effective against multidrug-resistant organisms in wound infections and may be advantageous during prolonged treatment considering the challenges associated with antibiotic resistance.[14] Only a handful of AMPs have obtained FDA approval for bacterial skin infections or wounds, including gramicidin D, daptomycin, oritavancin, telavancin and dalbavancin.[15,16]

Pigmentation

Synthetic α-MSH analogs have been evaluated for their ability to enhance melanin synthesis, imparting photoprotection. Pharmacological modifications to tetrapeptides derived from α-MSH have increase their stability and efficacy on melanocyte α-MSH receptors, reducing DNA damage from UV radiation.[3] Ongoing research on these oligopeptides may lead to topical agents that replenish or boost melanin density in the skin, potentially reducing the incidence of skin cancer and imparting protection for those with photosensitive disorders.

Conversely, inhibiting melanin synthesis is important for regulating hyperpigmentation disorders. PTPD-12, a synthetic peptide derivative, was found to induce depigmentation via an autophagy pathway when topically applied to human skin explants.[17] Decapeptide-12, a relatively new peptide, has been found to be safer than hydroquinone in reducing melanin content, with efficacy of more than 50% after 16 weeks of twice-daily treatment.[18] Building upon this promising profile, a topical formulation containing decapeptide-12 was evaluated in a randomized, split-face, placebo-controlled study and was found to significantly improve the appearance of recalcitrant melasma.[19]

CONCLUSION

The utilization of bioactive peptides in dermatology is advancing, presenting advantages difficult to achieve with conventional therapies. Nevertheless, ongoing optimization to address the two major drawbacks of peptide development in dermatology, limited skin permeability and poor in vivo stability, is necessary.[20] Additionally, continued evaluation of efficacy, dose optimization, and safety with clinical and product-specific studies is crucial.

Disclosure

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