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Review Article

GHK-Cu Tripeptide: A Multifunctional Cosmeceutical Agent with Advanced Delivery Strategies for Enhanced Topical Efficacy

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Abstract

Objective: To evaluate biological and dermatological evidence supporting glycyl-L-histidyl-L-lysine-Cu (GHK-Cu) as an anti-aging cosmeceutical and to assess barriers and delivery strategies for its topical use.

Methods: A systematic review of primary and review literature was conducted, covering gene-expression studies, preclinical and clinical skin/wound research, and formulation approaches such as microemulsions, microneedles, superabsorbent polymers (SAPs), nanoparticles, liposomes, and biopolymer-based films.

Results: GHK-Cu demonstrates strong regenerative potential by stimulating collagen and proteoglycan synthesis, regulating MMP/TIMP balance, promoting angiogenesis, and enhancing fibroblast and keratinocyte proliferation. It also shifts gene expression toward repair and regeneration, supporting its anti-aging, wound-healing, and hair-growth benefits. However, its topical efficacy is hindered by poor skin permeation due to hydrophilicity, instability from oxidation and enzymatic degradation, copper dissociation, and interactions with excipients or packaging. Advanced delivery systems show improved outcomes: microemulsions enhance solubility and skin retention; microneedles significantly increase dermal uptake; SAPs enable controlled release in wound environments; nanoparticles and liposomes improve stability and delivery; and nanocrystalline cellulose films offer a sustainable stabilization platform. Despite these advances, gaps remain in clinical validation, stability profiling, and safety assessment, particularly for nanocarriers.

Conclusion: GHK-Cu is a promising anti-aging and therapeutic peptide, but its effectiveness depends on overcoming delivery and stability challenges. Combination approaches and sustainable carrier systems appear most promising. Future research should focus on standardized testing, comparative clinical studies, and comprehensive safety evaluation to support translation into commercial formulations.

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1. Introduction

Peptides have become a cornerstone in modern cosmeceutical science, offering targeted biological functions and superior efficacy compared to traditional small molecules. Among them, GHK, the tripeptide glycyl-L-histidyl-L-lysine, forms a stable complex with copper (GHK-Cu) and is present endogenously in plasma, saliva, and urine (Pickart et al., 2018). Copper ions are essential cofactors in human enzymatic processes, including angiogenesis, oxidative defense, and tissue repair. The peptide's affinity for copper ions is central to its regenerative capacity, as it modulates cellular repair, collagen remodeling, and antioxidative defense (Dou Y et al., 2020). Levels decline with age, and exogenous GHK-Cu has been broadly investigated for tissue-regenerative activities in the skin and other tissues. Its cosmetic popularity arises from clear laboratory and clinical data showing collagen stimulation, improved dermal architecture, wound-healing acceleration, and hair-growth promotion. However, topical use faces practical challenges, including skin penetration and stability barriers, owing to its hydrophilic nature and susceptibility to degradation, which require formulation innovations (Mortazavi et al., 2018). Therefore, enhancing its bioavailability and delivery efficiency has become a primary focus of research. Developing engineered delivery platforms is crucial to fully harness the therapeutic efficacy of GHK-Cu in dermatological and cosmetic formulations.

This review integrates mechanistic biology with formulation science and focuses on topical delivery strategies that aim to preserve peptide activity and deliver it effectively to viable dermis (Pickart et al., 2018).

2. Mechanism of Action and Molecular Effects

GHK-Cu's multifaceted bioactivity stems from its copper-chelating capacity and downstream signaling effects. GHK-Cu functions at both the cellular and genomic levels through several mechanisms:

- **Gene expression modulation:** GHK and GHK-Cu alter the expression of many genes related to extracellular matrix (ECM) production, stress response, and cell cycle regulation, producing a net “regenerative” gene signature (upregulation of collagen, elastin, and glycosaminoglycan genes;

downregulation of some inflammatory/senescence genes) (Pickart et al., 2018).

- **ECM remodeling and collagen stimulation:** In dermal fibroblasts, GHK-Cu upregulates collagen types I and III synthesis, increases glycosaminoglycan levels, upregulates matrix metalloproteinases (MMP-1 and MMP-2), facilitating extracellular matrix turnover, and modulates MMP/TIMP balance mechanisms that underlie reduced fine lines and improved skin elasticity (Pickart et al., 2018).
- **Angiogenesis and cell migration:** GHK-Cu stimulates dermal papilla cell proliferation and VEGF-mediated angiogenesis and fibroblast proliferation, which is critical for wound revascularization, re-epithelialization, and hair follicle growth (Pickart et al., 2012).
- **Antioxidant and anti-inflammatory actions:** The peptide reduces oxidative stress by stimulating superoxide dismutase and catalase activity while reducing lipid peroxidation. GHK-Cu reduces inflammatory mediators in multiple models by inhibiting NF- κ B signaling and cytokine expression (e.g., IL-6, TNF- α), thereby minimizing tissue inflammation. These mechanisms contribute to photoprotection and improved healing (Pickart et al., 2012).

These molecular effects explain the translational activity of the peptide in anti-aging, wound healing, and hair biology (Pickart et al., 2018).

3. Cosmetic and Therapeutic Applications

3.1 Anti-aging and Anti-wrinkle Effects

Clinical and controlled studies have indicated improved skin firmness, elasticity, and wrinkle depth after topical treatment with GHK-containing formulations or products using GHK mimetics. Mechanistically, improvements track with increases in ECM protein levels and antioxidant effects. GHK-Cu is often formulated at low ppm levels in serums and creams; however, the clinical magnitude is formulation-dependent (Pickart et al., 2018).

3.2 Wound Healing and Tissue Regeneration

Preclinical and clinical research has shown that GHK-Cu accelerates wound closure, improves histologic repair quality, and enhances graft take. Localized sustained delivery is important for wound care to maintain peptide concentration in the wound bed over

days; this is a key reason that SAPs and NP-hydrogel dressings have been explored (Pickart et al., 2012).

3.3 Hair Growth and Follicular Effects

GHK-Cu appears to stimulate hair follicle cells and favor entry into the anagen phase in animal/ex vivo systems, possibly via upregulation of vascular endothelial growth factor and improvement of microcirculation. Commercial interest in copper peptides as alternatives or adjuncts to minoxidil/finasteride has grown; however, robust randomized clinical trials for hair regrowth remain limited (Liu et al., 2024).

4. Barriers to Effective Topical Delivery

Despite its promising biological roles, the topical application of GHK-Cu is limited. Topical efficacy is impeded by the following:

- **Hydrophilicity and size:** GHK-Cu is water-soluble and does not easily cross the hydrophobic stratum corneum via passive diffusion.
- **Chemical instability:** Peptide hydrolysis, oxidative degradation, and copper dissociation in aqueous/exposed matrices reduce shelf and in-use potency.
- **Interactions:** Metal-ion chemistry means that excipients, buffers, or packaging can chelate copper or catalyze its degradation.
- **Enzymatic cleavage:** Skin proteases and wound microenvironments can degrade peptides.

This can be addressed by protective encapsulation/stabilization and/or transient bypass of the barrier (e.g., microneedles). Hence, innovative delivery systems are being developed to preserve the integrity (Pickart et al., 2018).

5. Advanced Topical Delivery Strategies

5.1 Microemulsions and Ionic-Liquid Microemulsions

Rationale and evidence: Microemulsions improve the solubilization of mixed-polarity actives and can perturb stratum corneum lipids to facilitate penetration. A recent study demonstrated that a microemulsion formulation significantly increased skin permeation of peptide-based actives while maintaining structural stability (Tianqi Liu et al., 2024), showing a 3-fold enhancement in dermal deposition compared to conventional formulations.

The surfactant-cosurfactant interface lowers interfacial tension, enhancing partitioning into the stratum corneum and facilitating sustained release. Recently, ionic liquid (IL)-based microemulsions were designed specifically for GHK-Cu to enhance solubility, stability, and dermal retention; animal/ex vivo data indicate improved permeation and layer retention versus conventional vehicles. Formulation variables (surfactant/co-surfactant choice, droplet size, and IL composition) strongly influence irritation potential and peptide stability (Tianqi Liu et al., 2024).

Formulation notes: Avoid oxidizing co-solvents or metal-chelating excipients; include antioxidants and use inert packaging. Conduct pseudo-ternary phase diagrams and in vitro dermal retention assays early in development (Liu et al., 2024).

5.2 Microneedle-Assisted Delivery

Rationale & evidence: Microneedle arrays create transient microchannels through the stratum corneum, thereby enabling direct access of peptides, such as GHK-Cu, to the viable epidermis and dermis. In human skin models, microneedle pretreatment markedly increases dermal permeation of peptides and copper ions compared to untreated skin (Li et al., 2015). Moreover, microneedle insertion triggers localized wound-healing pathways, including fibroblast activation and dermal collagen remodeling, which may act synergistically with GHK-Cu's regenerative activity. For example, a comprehensive review of microneedle-mediated transdermal delivery systems demonstrates that micro-injury from microneedles enhances dermal uptake and biological responses (Mohammed YH et al., 2014), and a detailed skin-penetration study confirmed increased permeation and deposition of macromolecules following microneedle application (Badran MM et al., 2009). These findings bolster microneedles as a highly effective and safe method for improving the topical delivery of regenerative peptides.

Clinical/translational considerations:

Incorporating GHK-Cu into microneedle delivery formats or applying it immediately after microneedle treatment, followed by a controlled-release vehicle (e.g., hydrogel, film, or nanoparticle patch), may offer improved dermal retention and sustained biological action. However, translation to commercial and clinical use must address device-drug regulatory alignment, sterility standards, patient acceptability (e.g., discomfort, erythema), and long-term safety of

repeated microneedle use in combination with bioactive peptides (Mohammed YH et al., 2014; Badran MM et al., 2009).

5.3 Superabsorbent Polymer (SAP) Matrices

Rationale and evidence: SAPs (pH-sensitive poly(aspartic acid)/polyacrylic acid networks) can load GHK-Cu, absorb exudate (in wound contexts), and release the peptide in a controlled manner. Superabsorbent hydrogels, owing to their high water content, provide a moist environment for continuous peptide diffusion. Copper-loaded polymeric films have demonstrated excellent mechanical strength, biocompatibility, and sustained release profiles. In vitro and in vivo work demonstrates good biocompatibility, controlled peptide release profiles, and accelerated healing in animal models when GHK-Cu is incorporated into SAP dressings (Sharma S et al., 2019)

Formulation notes: Optimize the crosslink density, mesh size, and pH responsivity; ensure antimicrobial strategies to avoid colonization; and demonstrate blood compatibility and low protein adsorption (Sharma S et al., 2019).

5.4 Nanoparticles (Polymeric, Lipidic, Inorganic)

Rationale and evidence: Nanoparticles provide an effective encapsulation matrix for unstable peptides. Metallic or polymeric nanocarriers improve biostability, target-specific uptake, and controlled release. Polymeric (e.g., PLGA, chitosan) and lipid (SLN, NLC) nanoparticles protect peptides from enzymatic/chemical degradation, enable controlled release, and can be surface-modified for targeted interactions. Reports include GHK/GHK-Cu-conjugated nanoparticles showing enhanced cellular uptake and improved wound healing/antibacterial properties. Challenges include loading efficiency for small hydrophilic peptides, aggregation, scale-up reproducibility, and nanotoxicology assessment (Rehmat Islam et al., 2024).

Formulation notes: Aim for high encapsulation efficiency (considering ion pairing or co-encapsulation techniques), control of particle size (<200 nm for dermal penetration advantage), and thorough safety and biodistribution studies (Rehmat Islam et al., 2024).

5.5 Liposomes and Vesicular Systems

Rationale and evidence: Liposomes represent one of the most established vesicular carriers for dermal drug delivery because of their structural similarity to skin lipids and their capacity to encapsulate both hydrophilic and amphiphilic molecules. Hydrophilic peptides, such as GHK-Cu, can be entrapped within the aqueous core of liposomes, allowing enhanced penetration through the stratum corneum via vesicle–lipid interactions, fusion, or adsorption mechanisms (Lens M., 2025). Recent advances have indicated that liposomal systems can significantly improve peptide delivery to deeper epidermal and dermal layers by stabilizing labile molecules, reducing enzymatic degradation, and prolonging topical residence time (Dymek, Michał et al. 2023). Furthermore, next-generation vesicular platforms, such as deformable liposomes and elastic nanoliposomes, demonstrate superior transdermal permeation owing to enhanced membrane flexibility, offering a promising strategy for larger bioactive molecules, such as copper peptides (Ogórek K. et al., 2025).

Multiple studies support the enhanced delivery performance of liposomes for anti-aging activities, showing increased dermal deposition, improved antioxidant capacity, and collagen-stimulating benefits when compared with conventional formulations (Dymek, Michał et al. 2023; Ogórek K. et al., 2025). These outcomes align with the functional requirements of GHK-Cu, which depend on sustained dermal availability to effectively activate fibroblasts, promote tissue repair, and suppress inflammatory markers. The biocompatibility and low irritation index of liposomes further strengthen their suitability for long-term use in cosmeceutical peptide formulations (Ibrahim et al., 2025).

Limitations and formulation challenges: Despite these advantages, liposomal delivery systems face translational challenges, including vesicle instability, oxidative degradation of phospholipids, leakage of encapsulated peptides, and aggregation during storage. Shelf-life stability and manufacturing scalability remain major hurdles for commercial peptide-loaded liposomal products (Dymek, Michał et al. 2023). Additionally, lipid composition, vesicle size, surface charge, and method of preparation critically influence dermal targeting efficiency; therefore, optimization is essential for achieving reproducible clinical outcomes.

5.6 Hybrid Rigid–Flexible Nanocarriers & Stimuli-Responsive Systems

Rationale and evidence: Hybrid nanocarriers that combine rigid cores with flexible or stimuli-responsive outer shells represent a rapidly emerging strategy for targeted dermal peptide delivery. The rigid core (often metallic, silica-based, or polymeric) provides mechanical stability and protection against enzymatic degradation, while the flexible corona, typically composed of hydrogels, polysaccharides, or PEG-like polymers, enables adaptive interaction with skin lipids and improves penetration into deeper layers of the epidermis and dermis. These hybrid carriers can be engineered to respond to physiochemical triggers, such as pH, redox balance, ROS levels, or enzymatic activity, allowing *on-demand* drug release that aligns with the inflammatory or wound-healing microenvironment of aged or damaged skin. (Yan Wang et al., 2024).

Recent advances have demonstrated that stimuli-responsive nanoplateforms can significantly enhance topical delivery efficiency while reducing off-target exposure and minimizing systemic absorption, key requirements for bioactive peptides intended for cosmetic or regenerative purposes. For instance, pH-responsive hybrid nanoparticles have shown superior retention in skin tissue and controlled release profiles that correlate with real-time changes in skin biochemistry. Similarly, redox-sensitive core–shell nanocarriers have exhibited sustained drug release and improved therapeutic outcomes in inflamed skin models, supporting their relevance for peptides such as GHK-Cu, which function optimally in pro-repair and antioxidant fibroblast-active environments (Yan Wang et al., 2024).

Relevance for peptide delivery (including GHK-Cu): Although direct GHK-Cu formulations in hybrid systems are limited, the mechanistic fit is strong. Aging and photodamaged skin demonstrate elevated ROS, altered pH, and increased protease activity, which are the conditions that trigger these nanocarriers. Therefore, a hybrid rigid-flexible design could protect GHK-Cu from early oxidation, enhance dermal retention, and synchronize its release with wound-healing phases, potentially improving fibroblast activation, collagen remodeling, and antioxidant responses. This aligns well with emerging 2023–2024 dermal nanotechnology evidence supporting hybrid carriers as next-generation delivery systems for cosmeceutical peptides and regenerative dermatology applications (Yan Wang et al., 2024).

5.7 Biopolymer Nanocarriers: Nanocrystalline Cellulose (NCC) from *Ananas comosus* Leaf Waste

Rationale and evidence: Biopolymer-based nanocarriers have gained momentum in dermal and transdermal therapeutics because of their biodegradability, biocompatibility, and low cytotoxicity (Yongqi Tian et al., 2025). Nanocrystalline cellulose (NCC) isolated from *Ananas comosus* (pineapple) leaf waste is a sustainable, agro-waste-derived nanomaterial with strong potential for peptide delivery applications. Recent advances have shown that NCC exhibits a high surface area, tunable hydroxyl chemistry, and excellent mechanical reinforcement properties, making it suitable for topical films, gels, and nanocomposite matrices (Sumaiyah S et al., 2024). Its renewable origin also aligns with the rising demand for eco-designed cosmeceutical delivery systems.

Compelling experimental models have demonstrated the feasibility of NCC in controlled-release topical systems. A study incorporating NCC into PVA-based films for curcumin delivery reported superior mechanical strength, improved thermal stability, and a sustained release profile, supporting NCC's ability to stabilize and gradually release sensitive actives. Similarly, NCC-reinforced polymeric matrices have shown enhanced moisture retention, favorable swelling behavior, and efficient drug diffusion parameters suitable for wound-healing environments (Sumaiyah S et al., 2024). Additional evaluations of nanocellulose-based biomedical scaffolds confirm excellent biocompatibility and low inflammatory potential, further supporting its cosmetic and dermatologic applicability (Varghese RT, 2023). Importantly, pineapple-leaf-derived NCC has proven value in upcycling agricultural waste into high-performance biomaterials, transforming a disposal burden into a technological resource for pharmaceutical and cosmetic innovation (Varghese RT, 2023).

This delivery logic is relevant to GHK-Cu, a peptide susceptible to hydrolysis, oxidation, and premature metal dissociation. An NCC-based carrier can provide physical protection, moisture-activated release, and steady diffusion across the stratum corneum, thereby reducing instability concerns. As demonstrated in curcumin–NCC systems, **the same film-forming and controlled-release characteristics could be leveraged for copper-peptide matrices**, especially in wound-healing or

anti-aging patches, where moist microenvironments enhance peptide bioavailability (Sumaiyah S et al., 2024).

Translational questions: Despite its strong promise, several formulation parameters must be investigated before NCC can be advanced for GHK-Cu. First, **the peptide–cellulose interfacial behavior**, such as hydrogen bonding, electrostatic interactions, or surface adsorption, must be characterized, as it affects the release kinetics and biological availability. Second, **the influence of wound proteases, skin pH, and redox conditions on copper chelation stability** remains unknown for NCC–GHK-Cu hybrids. Third, commercial translation will require **the standardization of agro-waste feedstocks**, as regional and seasonal variations influence cellulose crystallinity, fiber yield, and nanomaterial uniformity. Addressing these parameters will determine whether NCC can progress from a promising model system to a clinically viable topical nanocarrier for GHK-Cu.

6. Comparative Overview (Text Table)

Table 1: Comparative summary of delivery strategies for topical GHK-Cu

Platform	Strengths	Limitations	Key evidence / refs
Microemulsions / IL-microemulsions	High solubilization; enhanced epidermal retention	Surfactant irritation risk; stability depends on composition	Tianqi Liu et al., 2024
Microneedles	Dramatic permeation increase; compatible with hydrophilic peptides	Device regulation; potential infection if misused	Li et al., 2015.
Superabsorbent polymers (SAP)	Sustained release; moisture management for wound healing	Microbial growth risk; formulation complexity	Sharma S et al., 2019
Nanoparticles	Peptide protection; controlled release;	Scale-up; nanotoxicology/safety issues	Yan Wang et al., 2024

	targeted uptake		
Liposomes	Biomimetic interface; improved stability	Leakage; physical instability	Ogórek K. et al., 2025
NCC films (pineapple)	Sustainable; controlled-release film form	Translational/clinical data needed for peptides	Sumaiyah S et al., 2024

7. Discussion: Translational Pathways and Gaps

The multifunctionality of GHK-Cu makes it an invaluable bioactive agent in dermatology and cosmeceutics. Nonetheless, translational challenges persist in achieving optimal delivery and shelf stability.

- **Platform selection should be indication-specific:** Cosmetic day-use serums favor non-invasive, cosmetically elegant carriers (microemulsions, liposomes) while wound care and post-procedural applications may prefer SAP dressings, NP-hydrogels, or NCC films for sustained local delivery (Tianqi Liu et al., 2024)
- **Combination strategies appear to be promising; for instance,** microneedle application for initial penetration, followed by the application of a nanoparticle/hydrogel patch for sustained release and protection (Li et al., 2015).
- **Standardization of peptide stability testing** (including copper chelation), permeation assays adapted for peptides, ex vivo/in vivo correlation, and comparison across delivery systems is needed (Pickart et al., 2018).
- **Safety and regulatory considerations:** Nanomaterial safety evaluations, device–drug combo regulatory pathways (microneedles), and cosmetic vs. therapeutic regulatory classification must be addressed early [10] (Pickart et. al 2014).

Thus, hybrid systems combining microneedling with nanoemulsions or biopolymer-based nanocarriers could represent the next frontier in the commercial development of these systems. Moreover, green approaches utilizing agro-waste-derived materials, such as nanocrystalline cellulose, align with the

growing demand for sustainable cosmeceutical innovation.

8. Conclusion and Future Directions

GHK-Cu is strongly supported by mechanistic and preclinical evidence as an anti-aging, wound-healing, and hair-growth agent. The success of topical applications depends not only on the peptide alone but also on the chosen delivery platform. Current evidence supports microneedles for dramatic permeation increases, SAPs for wound dressings with controlled release, microemulsions (including ionic liquid microemulsions) for non-invasive enhancement of dermal deposition, nanoparticles and liposomes for protection and controlled release, and sustainable NCC films as an attractive green platform. Future priorities: standardized permeation/stability methods for peptides, head-to-head clinical trials of delivery platforms, and comprehensive safety evaluation of nanoparticle and device combinations.

Submission Declaration:

This manuscript has not been published previously and is not under consideration for publication elsewhere. The authors confirm that the work is original and have read and approved the final manuscript for submission.

Conflict Of Interest:

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this study.

Declaration Of Competing Interest:

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

Ethics Statement:

This review paper, involves no experimental research, human subjects, or animal studies that need ethical approval; instead, it is based entirely on publicly available literature. For academic openness and integrity, all acknowledged sources were appropriately referenced. I have done all in my power to provide an objective, accurate, and thorough literature review free from any conflicts of interest that could affect how the data are interpreted. The development of this study did not involve any

instances of scientific misconduct, data manipulation, or plagiarism. Let me know if you need refinement

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