Porcine Research

GHK-Cu (copper peptide): discovery, biology, applications, and prospects

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Abstract. GHK-Cu (glycyl-L-histidyl-L-lysine–copper) is a naturally occurring human tripeptide-copper complex exhibiting broad regenerative, anti-inflammatory, and antioxidant properties. Initially identified in the 1970s as a factor capable of reversing age-related cellular changes in human liver, GHK-Cu functions as a systemic copper carrier and epigenetic modulator, influencing gene expression, tissue remodeling, and cellular repair. Its biological activities include stimulation of collagen and elastin synthesis, angiogenesis, nerve growth, and hair follicle enlargement, alongside suppression of pro-inflammatory signaling and oxidative stress. Preclinical studies in rodents, pigs, and zebrafish support its potential for systemic wound healing, organ protection, neuroprotection, and modulation of chronic inflammatory, fibrotic, and neoplastic conditions. Clinically, GHK-Cu is most established in dermatologic and cosmetic applications, demonstrating improved skin elasticity, barrier function, and hair density with excellent tolerability. Emerging research focuses on optimized delivery systems, systemic therapeutic use, and translational studies targeting neurodegeneration, chronic lung disease, inflammatory bowel disease, and age-related tissue decline. This mini-review synthesizes current knowledge of GHK-Cu biology, therapeutic potential, and translational prospects, highlighting its multifaceted role as a regenerative and geroprotective agent.

Key Words: anti-aging, copper peptide, dermatology, gene modulation, GHK-Cu, hair growth, inflammation, neuroprotection, oxidative stress, regenerative medicine, remodeling, tissue translational research, wound healing.

Introduction. In recent years, pharmacological research has driven the rapid development and clinical adoption of novel therapeutic peptides, highlighting their transformative potential in the management of metabolic disorders. Among these, three peptides have emerged as particularly revolutionary: semaglutide, tirzepatide, and retatrutide. Semaglutide, a glucagon-like peptide-1 (GLP-1) analogue, has demonstrated potent effects on glycemic control and weight reduction through enhanced insulin secretion and appetite regulation (Kopp et al 2022; Chao et al 2023). Tirzepatide, a dual agonist of GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), represents a new class of multi-receptor peptides with synergistic metabolic benefits (Syed 2022; Alfaris et al 2024; France & Syed 2024). Retatrutide, a triple agonist targeting GLP-1, GIP, and glucagon receptors, further extends the therapeutic horizon by simultaneously modulating multiple pathways involved in energy homeostasis and glucose metabolism (Petrescu-Mag 2025a, b; Petrescu-Mag & Dăescu 2025). Collectively, these advances exemplify the capacity of rational peptide design to translate molecular insights into highly effective clinical interventions, marking a paradigm shift in modern peptide pharmacotherapy (Bailey et al 2024).

GHK-Cu (glycyl-L-histidyl-L-lysine–copper) is a naturally occurring human tripeptide-copper complex with broad regenerative, anti-inflammatory and antioxidant actions, now widely used in skin/hair products and increasingly explored as a systemic therapeutic (Pickart 2008; Pickart et al 2015; Pickart & Margolina 2018a).

The purpose of this mini-review is to provide a concise synthesis of the discovery, biological mechanisms, preclinical and clinical applications, and translational potential of GHK-Cu. Emphasis is placed on integrating molecular, cellular, and systemic data to evaluate its utility as a multi-target therapeutic peptide. By collating evidence across dermatologic, systemic, and neuroprotective domains, this review aims to inform future research directions and highlight opportunities for clinical translation beyond cosmetic and topical use.

Historical discovery and original conceptual role. GHK was discovered in 1973 during studies on age-related changes in human liver. When old human liver cells were exposed to human albumin fractions containing a small peptide, they began synthesizing proteins in a pattern resembling younger tissue; the active factor was identified as the tripeptide GHK, which tightly binds Cu(II) to form GHK-Cu (Pickart et al 2012; Dou et al 2020). This led to the original concept of GHK as a systemic "youth-associated" copper carrier, capable of resetting protein synthesis and tissue remodeling programs from an older to a younger pattern (Pickart et al 2012, 2015; Hu et al 2025). GHK circulates in plasma (≈200 ng mL^{-1} at age 20, falling to ≈80 ng mL^{-1} by 60), and its affinity for copper is similar to that of albumin's copper-binding site, supporting a physiological role in copper transport and distribution to injured tissues (Pickart 2008; Pickart et al 2015; Dou et al 2020).

Biological profile: **from copper carrier to tissue-remodeling signal**. Once complexed with Cu(II), GHK-Cu acquires a wide spectrum of actions on cells involved in repair and remodeling. In skin and connective tissues, GHK-Cu:

- attracts repair cells (macrophages, mast cells, capillary endothelial cells) and stimulates angiogenesis (Pickart 2008; Dou et al 2020; Zoughaib et al 2021);
- suppresses inflammation and oxidative stress by reducing ROS and inflammatory cytokines (TNF-α, IL-6), increasing superoxide dismutase (SOD) and glutathione, inhibiting NF-κB and p38 MAPK, and reducing thromboxane and free iron release (Pickart 2008; Pickart et al 2015; Park et al 2016; Dou et al 2020);
- increases synthesis of collagen, elastin, glycosaminoglycans, decorin, matrix metalloproteinases and their inhibitors, VEGF, FGF-2, NGF and neurotrophins, supporting matrix renewal and nerve and vessel growth (Pickart 2008; Pickart et al 2015; Pickart & Margolina 2018a, b; Dou et al 2020; Pickart & Margolina 2021; Zoughaib et al 2021);
- stimulates proliferation of fibroblasts and keratinocytes, nerve outgrowth, and enlargement of hair follicles (Pickart 2008; Pickart & Margolina 2018a; Liu et al 2023).

At the gene level, GHK/-Cu is now recognized as a broad epigenetic modifier: in connectivity-map analyses it alters expression of roughly one-third of human genes, down-regulating pro-inflammatory and pro-cancer programs and up-regulating repair, antioxidant, and anti-pain/anti-anxiety networks (Pickart et al 2012; Pickart et al 2015; Pickart & Margolina 2018b, 2021). In COPD fibroblasts and lung tissue, GHK shifts gene expression from destructive to remodeling patterns and restores collagen fibril assembly (Pickart et al 2015). In cancer gene signatures it reverses a large fraction of metastasis-associated genes toward a more normal pattern (Pickart & Margolina 2021).

Pharmaceutical development: **from wound healing to cosmetics and beyond**. The initial pharmaceutical interest focused on wound healing and tissue repair. In animal and human wound models, GHK-Cu accelerates wound contraction, epithelization, and angiogenesis, improves collagen organization, and reduces scarring (Pickart 2008; Pickart et al 2015; Pickart & Margolina 2018a, b; Dou et al 2020). It protects hepatic tissue from toxic injury, promotes healing of stomach and intestinal ulcers and bone defects, and enhances hair transplant survival (Pickart 2008; Pickart et al 2015; Pickart & Margolina 2018a).

Because of its strong effects on aged skin, GHK-Cu quickly migrated into dermatological and cosmetic development. Controlled human studies on photoaged or aged skin show tightening, improved elasticity and firmness, reduction of fine lines, wrinkles, hyperpigmentation and mottled photodamage, along with repair of barrier proteins and smoothing of roughness (Pickart 2008; Pickart et al 2015; Pickart & Margolina 2018a). These results drove its incorporation into topical anti-aging and hair-growth formulations, where it has accumulated a long record of clinical and post-marketing safety (Pickart et al 2015; Pickart & Margolina 2018a; Liu et al 2023).

More recently, pharmaceutical research has expanded into:

- respiratory disease and lung injury (acute lung injury/ARDS, silicosis, COPD) (Pickart et al 2012, 2015; Park et al 2016; Bian et al 2024);
- gastrointestinal inflammation (ulcerative colitis) (Mao et al 2025);
- neurodegeneration and cognitive decline, including Alzheimer's models (Pickart et al 2012; Dou et al 2020; Tosto et al 2023; Min et al 2024; Tucker et al 2024);
- cancer modulation via gene-level and matrix-level mechanisms (Pickart & Margolina 2018b, 2021);
- systemic oxidative-stress–driven aging and organ protection (heart, liver, skin) (Pickart et al 2012, 2015; Dou et al 2020; Hsiao et al 2020; Hu et al 2025).

Delivery-focused work has produced injectable fillers, hydroxyapatite microspheres, peptide-loaded nanocarriers, and ionic-liquid microemulsions to improve stability, skin penetration and sustained release (Zoughaib et al 2021; Liu et al 2023a, b; Wang et al 2024; Hu et al 2025).

Current stage of testing and clinical introduction. Topically, GHK-Cu is already widely used in over-the-counter skin and hair products, supported by multiple human cosmetic/dermatologic trials showing efficacy and excellent tolerability (Pickart 2008; Pickart et al 2015; Pickart & Margolina 2018a). These uses sit closer to the cosmetic/medical-device end of the regulatory spectrum rather than fully de novo drug approvals.

For systemic or high-dose therapeutic use, most evidence is still preclinical:

- in pigs, intravenous GHK-Cu at about 1.1 mg kg^{-1} produced strong systemic wound-healing effects without toxicity, with a safety margin of ~300-fold below the blood-pressure-lowering dose (Pickart et al 2012);
- gene-profiling, cell culture, and various mouse models (lung injury, fibrosis, colitis, neurodegeneration, tumors) support disease-modifying potential, but controlled human pharmacological trials beyond dermatologic and cosmetic contexts are not yet established (Pickart et al 2012; Park et al 2016; Dou et al 2020; Pickart & Margolina 2021; Bian et al 2024; Tucker et al 2024; Mao et al 2025).

Work is active on formulation and delivery systems - rigid-flexible liposomal nanocarriers, ionic-liquid microemulsions, and injectable hydroxyapatite gels - to transition from laboratory use toward more standardized clinical products, especially for skin, fillers, and localized anti-inflammatory treatment (Liu et al 2023a, b; Wang et al 2024; Hu et al 2025).

Animal data: **effects in rodents**, **pigs**, **zebrafish and other models**. The use of mammals as model organisms in pharmacology and toxicology is of critical importance, as their physiological, metabolic, and genetic similarities to humans allow for more accurate prediction of drug efficacy, safety profiles, and potential adverse effects, thereby providing essential insights prior to clinical application (Petrescu-Mag & Safirescu 2021; Proorocu et al 2022; Petrescu-Mag 2023a, b, c; Daescu & Oroian 2024; Petrescu-Mag 2025a, b). Rodent and other animal models provide the bulk of mechanistic data.

In mice and rats, GHK-Cu:

- enhances wound repair and dermal matrix regeneration, including decorin and collagen accumulation, with prolonged remodeling up to at least 22 days in rat wounds (Pickart 2008; Pickart & Margolina 2021);

- improves hair growth in young mice and in hair loss models; in some studies it rivals minoxidil with fewer systemic side-effects (Pickart & Margolina 2018a; Liu et al 2023);

- protects against bleomycin-induced pulmonary fibrosis, reducing inflammatory infiltration, interstitial thickening, and TNF-α and IL-6 expression (Dou et al 2020);

- attenuates LPS-induced acute lung injury: decreases ROS, TNF-α and IL-6, increases SOD, and histologically reduces edema and inflammatory cell infiltration (Park et al 2016);

- ameliorates experimental silicosis: reduces lung inflammation and fibrosis via binding to peroxiredoxin-6 in alveolar macrophages and limiting silica-induced oxidative stress, without systemic toxicity (Bian et al 2024);

- shows strong therapeutic effects in DSS-induced ulcerative colitis, improving weight, disease index, colon length, goblet cell number, and mucosal integrity while lowering TNF-α, IL-6, IL-1β and modulating SIRT1/STAT3 and Th17/RORγt signaling (Mao et al 2025);

- in cancer models, GHK-Cu–like copper peptides plus ascorbate markedly inhibit tumor growth and prolong survival in mouse sarcoma and Ehrlich ascites models (Pickart & Margolina 2021).

In pigs, systemic administration around 1.1 mg kg^{-1} produces robust, generalized wound-healing responses - an important translational step because pig skin and healing more closely resemble humans than rodent models (Pickart et al 2012). This dosing information also underpins preliminary human dose projections.

In zebrafish, recombinant GHK (forming GHK-Cu in the presence of copper) protects against waterborne Cu(II) cardiotoxicity. At nanomolar concentrations (as low as 1 nM), GHK prevents bradycardia and heartbeat irregularity and improves heart rate and cardiac output, without worsening other cardiac parameters, highlighting its role as a physiological copper buffer and cardioprotectant (Hsiao et al 2020).

In *in vitro* CNS models, GHK reduces copper and zinc redox activity, prevents metal-induced aggregation of bovine serum albumin, resolubilizes aggregated protein, and protects central nervous system cells from copper- and zinc-induced death, including under inflammatory or paraquat-sensitized conditions (Min et al 2024). These findings support its candidacy as a cytoprotective agent against metal-linked neurodegeneration.

Evidence in rodents or pigs in detail. Specific detailed rabbit studies were not identified among the provided references; most dermal and organ repair work uses small rodents and pigs (Pickart 2008; Pickart et al 2012; Park et al 2016; Dou et al 2020; Bian et al 2024). The pig data come from systemic wound-healing experiments where intravenous GHK-Cu produced strong repair of multiple tissues at ~1.1 mg kg^{-1}. This dose is estimated to translate to ~75 mg in an adult human and remains ~300-fold below doses causing hypotension, underscoring a wide therapeutic index in a large mammal model (Pickart et al 2012). While the underlying report is summarized rather than fully detailed in the excerpt, it indicates:

- widespread stimulation of healing in multiple wound types;

- systemic, not merely local, effects consistent with the peptide's circulating role;

- lack of overt toxicity at effective doses, a key step toward systemic human use.

Given pigs' proximity to humans in skin thickness, immune responses, and cardiovascular physiology, these results are often taken as proof-of-principle that GHK-Cu can be safely escalated to clinically meaningful systemic doses, pending formal toxicology and pharmacokinetics.

Human data: **skin**, **hair**, **organs**, **and tolerability**. Human evidence is strongest in the dermatologic and cosmetic domain. Topical GHK-Cu:

- tightens lax skin, reverses thinning of aged skin, improves firmness, elasticity, clarity and barrier function (Pickart 2008; Pickart et al 2015; Pickart & Margolina 2018a);

- reduces fine lines and wrinkles, improves skin texture, pigmentation irregularities, and photodamage, including mottled hyperpigmentation and lesions, in controlled studies on aged/photoaged skin (Pickart 2008; Pickart et al 2015; Pickart & Margolina 2018a);

- improves the success of hair transplantation and increases hair density and thickness in early clinical contexts (Pickart 2008; Pickart et al 2015; Pickart & Margolina 2018a; Liu et al 2023).

These clinical observations align with histologic and biochemical changes: increased collagen, elastin, glycosaminoglycans, decorin, and improved vascularization and nerve fiber density (Pickart 2008; Pickart et al 2015; Pickart & Margolina 2018a, 2021). Long-term cosmetic and dermatologic use - spanning decades and wide populations - has not revealed significant safety issues when used at topical concentrations, leading to consensus that small copper peptides like GHK-Cu have an excellent safety profile in this route of administration (Pickart et al 2015; Pickart & Margolina 2018a).

Systemic clinical data are more limited. Historically, GHK-Cu has been used intravenously in wound-healing contexts and to protect organs (e.g., liver) against toxic injury, but these reports are fragmentary compared with formal modern randomized trials (Pickart 2008; Pickart et al 2012, 2015). Nonetheless, no major toxicity signals have emerged in the preclinical or limited clinical literature, and animal safety margins are wide (Pickart et al 2012; Park et al 2016; Hsiao et al 2020; Bian et al 2024).

Mechanistic advances: **delivery systems and gene-level effects**. Recent work focuses on improving delivery and exploiting GHK-Cu's gene-modulatory capacity.

Rigid-flexible liposomal nanocarriers and ionic-liquid microemulsions significantly increase skin penetration and stability of GHK-Cu, enabling efficient non-invasive hair-growth therapies that activate VEGF and Wnt/β-catenin pathways with approximately three-fold higher local delivery than conventional formulations (Liu et al 2023a, b; Wang et al 2024). Injectable hydroxyapatite microspheres loaded with GHK-Cu create soft-tissue fillers that release the peptide over seven days, markedly dampen LPS-induced inflammation and ROS, increase SOD, and promote collagen deposition in vivo, providing both volumizing and anti-inflammatory/antioxidant functions (Hu et al 2025).

On the gene level, GHK-Cu is now viewed as a multi-target epigenetic regulator. It suppresses NF-κB-driven inflammatory genes, modulates antioxidant and detoxification genes, and reverses disease-associated signatures in COPD lung tissue and several cancers (Pickart et al 2012; Pickart et al 2015; Pickart & Margolina 2018b, 2021). In breast and prostate cancer cells, it influences cascades controlling survival, migration, angiogenesis, and matrix organization, partly via decorin up-regulation and tyrosine kinase modulation, supporting anti-tumorigenic activity (Pickart & Margolina 2018b, 2021). In colitis and pulmonary models it regulates SIRT1/STAT3 and peroxiredoxin-6 pathways, linking it to established aging and inflammation hubs (Bian et al 2024; Mao et al 2025).

Neurodegeneration and cognition: **emerging data**. Cognitive and neuroprotective claims rest largely on animal and *in vitro* studies. In aging mice, GHK or GHK-Cu improves cognitive performance, likely via anti-inflammatory, antioxidant and epigenetic mechanisms (Pickart et al 2012; Dou et al 2020). In 5xFAD Alzheimer's model mice, intranasal GHK-Cu (15 mg kg^{-1}, three times weekly for 3 months) delays cognitive impairment, reduces amyloid plaque burden, and lowers MCP-1-mediated inflammation in frontal cortex and hippocampus (Tucker et al 2024). Independently, GHK prevents copper- and zinc-induced protein aggregation and CNS cell death *in vitro*, suggesting a capacity to mitigate metal-driven proteinopathy and oxidative injury characteristic of neurodegenerative diseases (Min et al 2024). Biotinylated GHK-Cu derivatives further show antioxidant, antiglycation and anti-amyloid-aggregation activities *in vitro*, supporting design of targeted neuroprotective constructs (Tosto et al 2023).

Whether GHK-Cu crosses the human blood-brain barrier is not yet definitively proven, but its high uptake through skin lipids and small size suggest it may, especially with optimized carriers or intranasal delivery (Pickart et al 2012; Tosto et al 2023; Min et al 2024; Tucker et al 2024). Overall, the peptide is viewed as a promising, but still experimental, neuroprotective and anti-Alzheimer agent.

Anti-aging and systemic perspectives. By integrating its roles in copper homeostasis, antioxidant defense, inflammation control, tissue remodeling, and gene expression, GHK-Cu is increasingly conceptualized as a systemic anti-aging modulator. Age-related decline in circulating GHK parallels increasing oxidative stress and degenerative diseases; supplementation in animals:

- restores youthful patterns of collagen and matrix synthesis;
- enhances antioxidant capacity and reduces chronic inflammation;
- improves cognitive performance and attenuates neurodegeneration;
- protects lungs, liver, heart and skin from diverse toxic and inflammatory insults (Pickart et al 2012, 2015; Park et al 2016; Dou et al 2020; Hsiao et al 2020; Bian et al 2024; Hu et al 2025).

These pleiotropic effects place GHK-Cu among candidate "geroprotective" molecules, though rigorous long-term human trials in aging and degenerative conditions remain to be conducted (Pickart et al 2012; Dou et al 2020; Hu et al 2025) (Table 1).

Table 1

Major biological and therapeutic domains of GHK-Cu (summarized by Consensus, 2026)

Domain / Indication	*Key observed effects*	*Citations*
Skin aging and wounds	Collagen/elastin synthesis, barrier repair, wrinkle and pigmentation reduction, faster healing	(Pickart 2008; Pickart et al 2015; Pickart & Margolina 2018a, b; Dou et al 2020)
Hair growth	Follicle enlargement, increased density, enhanced transplant survival, Wnt/β-catenin activation	(Pickart 2008; Pickart & Margolina 2018a; Liu et al 2023)
Lung injury and fibrosis	Reduced inflammation, ROS and fibrosis in ALI, silicosis, COPD models	(Pickart et al 2012; Pickart et al 2015; Park et al 2016; Dou et al 2020; Bian et al 2024)
GI inflammation	Improved DSS colitis via SIRT1/STAT3, barrier repair, cytokine suppression	(Mao et al 2025)
Neurodegeneration	Improved cognition, reduced plaques, metal toxicity and aggregation control	(Pickart et al 2012; Dou et al 2020; Tosto et al 2023; Min et al 2024; Tucker et al 2024)
Cancer modulation	Anti-proliferative gene shifts, tumor growth inhibition in mice, decorin-mediated effects	(Pickart et al 2015; Pickart & Margolina 2018b; Pickart & Margolina 2021)
Cardioprotection and copper detox	Protection from Cu(II) cardiotoxicity in zebrafish; buffering excess copper	(Hsiao et al 2020; Hu et al 2025)

Future perspectives. GHK-Cu occupies a rare position: a physiological human peptide with decades of safe cosmetic use and an expanding mechanistic base that spans matrix biology, gene regulation, and metal homeostasis. The strongest human evidence is in topical skin and hair applications, where it functions as a highly effective regenerative and protective ingredient.

The next frontier lies in translating compelling animal data into controlled human trials for:

- chronic inflammatory and fibrotic lung diseases (COPD, silicosis, ARDS recovery);
- inflammatory bowel disease (ulcerative colitis);
- neurodegenerative diseases and age-associated cognitive decline;
- adjunctive cancer therapy and peri-treatment tissue protection;
- systemic anti-aging and organ-protective interventions.

Progress will depend on robust pharmacokinetics, optimized delivery systems, and careful dose-finding to harness its broad, gene-level modulatory capacity without off-target effects. At present, GHK-Cu can be viewed as a highly promising, multi-target peptide, already validated in human skin and hair care and moving steadily toward more formal therapeutic indications.

Conclusions. GHK-Cu represents a unique endogenous peptide with established safety in human dermatologic and cosmetic applications and extensive mechanistic evidence supporting its regenerative, anti-inflammatory, antioxidant, and gene-modulatory activities. Preclinical models demonstrate systemic therapeutic potential across multiple organ systems, including skin, lung, gastrointestinal tract, nervous system, and cardiovascular tissues. The translational frontier lies in controlled clinical trials for chronic inflammatory, fibrotic, neurodegenerative, and age-related conditions, facilitated by optimized delivery systems and pharmacokinetic studies. Its pleiotropic actions position GHK-Cu as a promising geroprotective and multi-target peptide, bridging physiological copper homeostasis with modern regenerative medicine approaches. Continued research will clarify its systemic efficacy, dosage parameters, and long-term safety in humans.

Conflict of interest. The authors declare that there is no conflict of interest.

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