

RESEARCH MONOGRAPH · COMPOUND PROFILE

GHK-Cu

A naturally occurring tripeptide that binds copper(II) with very high affinity, characterized as a wound healing and tissue remodeling peptide with a substantial multidisciplinary literature.

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ABSTRACT

GHK-Cu (sequence Gly-His-Lys complexed with Cu(II); CAS 89030-95-5; molecular formula $C_{14}H_{22}N_6O_4Cu$; molecular weight 401.91) is a naturally occurring tripeptide-copper(II) complex first isolated from human plasma in 1973 by Loren Pickart, then a graduate student at the University of California San Francisco. The free tripeptide GHK is present in human plasma at low micromolar concentrations and has very high affinity for Cu(II) (apparent dissociation constant in the picomolar range), forming the GHK-Cu complex that is the active species in many of the published bioassays. The compound has the most multidisciplinary published literature of any of the small bioactive peptides in research-grade circulation, with documented or suggested effects on wound healing, hair follicle activity, dermal collagen and elastin synthesis, anti-inflammatory cytokine modulation, modulation of more than 4,000 human genes (in cultured cells), and antioxidant defense. Plasma GHK-Cu concentrations decline with age, which is the rationale for many of the gerontology-focused claims. GHK is approved as a topical cosmetic ingredient in many jurisdictions and is widely used in dermatologic preparations. There is no FDA-approved IND for systemic GHK-Cu in any indication. The principal limitations on the strength of the evidence are heterogeneity in the dose, route, and formulation of GHK-Cu across the published preclinical literature; effects observed at one dose or route do not always translate to other contexts.

Compound identification

Nomenclature and synonyms

The most common designations are GHK-Cu, GHK copper peptide, copper tripeptide-1, and tripeptide-1. The free tripeptide (without copper) is referred to as GHK or glycyl-L-histidyl-L-lysine. The CAS number for the copper complex is 89030-95-5. The CAS number for the free tripeptide is 49557-75-7. The PubChem CID for GHK-Cu is 73913. The cosmetics industry uses the INCI name "Copper Tripeptide-1."

A point of nomenclature confusion concerns the stoichiometry of the copper complex. The 1:1 GHK:Cu(II) complex is the most-cited active species in the published literature, but other stoichiometries have been characterized including 2:1 and 1:2 GHK:Cu(II) complexes. The structure and activity of these alternative stoichiometries differ from the 1:1 complex; vendor preparations should be confirmed to be the 1:1 form.

Structural chemistry

The free tripeptide is L-glycine - L-histidine - L-lysine, with a free N-terminal amine and a free C-terminal carboxylate. The molecular weight of the free tripeptide is 340.38 g/mol. The 1:1 copper complex GHK-Cu has a molecular weight of 401.91 g/mol; the additional 61.53 mass units relative to the free tripeptide reflects the bound Cu(II) ion (atomic weight 63.55) minus the lost protons that participate in the coordination. The molecular formula of the complex is C₁₄H₂₂N₆O₄Cu.

The Cu(II) coordination geometry is square-planar in the most-cited structural model, with the histidine imidazole nitrogen, the deprotonated peptide bond nitrogen between Gly and His, and one or two of the terminal amines and carboxylates as the coordinating ligands. The exact coordination geometry depends on the pH and the surrounding solvent system; at physiological pH the dominant species is the deprotonated 4-coordinate complex.

The complex is colored: the lyophilized solid is blue, and aqueous solutions of GHK-Cu are visibly blue at the concentrations used in research-grade dosing. The lot of record (Kodiak biolabs lot 20260301) is supplied as a blue crystalline powder consistent with the 1:1 copper complex.

Physicochemical properties

GHK-Cu is supplied as a blue crystalline powder. The lot of record conforms to this description. Solubility in water and bacteriostatic water is moderate to high; concentrations up to 10 mg/mL are routinely prepared. Solubility in 0.9 percent saline is somewhat lower than in pure water due to chloride competition with the copper coordination sphere; PBS may produce slight precipitation at high peptide concentrations. Solubility in DMSO is poor and disrupts the copper coordination; DMSO is not the appropriate vehicle.

The complex is stable in the lyophilized state at minus 20 degrees Celsius for at least 24 months under standard light protection. Reconstituted aqueous solutions are stable at 2 to 8 degrees Celsius for at least 30 days. Light exposure can drive Cu(II) photochemistry; solutions should be protected from prolonged direct sunlight. Freeze-thaw cycles should be avoided.

Discovery and developmental history

Origin in the Pickart laboratory

GHK was first isolated in 1973 by Loren Pickart and Margaret Thaler at the University of California San Francisco from a human plasma fraction that promoted hepatocyte regeneration in vitro. The active component was characterized as the tripeptide Gly-His-Lys, and the copper-binding property was recognized shortly thereafter through the observation that the activity of the isolated peptide was lost in copper-depleted media and restored on copper supplementation. The 1980s and 1990s saw continued mechanistic work by Pickart and collaborators, with the field broadening substantially in the 2000s and 2010s as gene expression studies characterized the breadth of GHK-Cu's transcriptional effects.

The peptide is present in human plasma at concentrations declining from approximately 200 nanograms per milliliter in young adults to under 80 nanograms per milliliter in elderly subjects. The age-related decline is the rationale for the framing of GHK-Cu as a "regeneration signal" or "youth peptide" in research-grade vendor literature; the published mechanistic literature is more carefully scoped.

Cosmetic and clinical translation

GHK-Cu has been used as a topical cosmetic ingredient since the 1980s. The FDA Cosmetic Ingredient Review concluded in 2018 that copper tripeptide-1 is safe in cosmetic use as currently formulated. Topical preparations containing GHK-Cu are widely available for dermatologic use without prescription.

There is no FDA-approved IND for systemic GHK-Cu in any therapeutic indication. A small number of clinical studies have evaluated topical GHK-Cu for surgical wound healing, pressure ulcers, and dermal aging; the results are mixed but generally encouraging. Compatibility with iontophoresis, microneedling, and other dermal delivery routes has been documented.

Mechanism of action

Copper transport

The most basic mechanism is copper delivery. Cu(II) is essential for many cellular processes including mitochondrial respiration (cytochrome c oxidase), antioxidant defense (Cu/Zn superoxide dismutase), and connective tissue cross-linking (lysyl oxidase). GHK-Cu serves as a high-affinity, low-toxicity carrier that delivers copper to cells without the toxicity associated with free Cu(II). Cellular uptake of the complex is documented through both direct internalization and through the SLC31A1 (CTR1) high-affinity copper transporter after dissociation.

Gene expression modulation

The most cited mechanistic claim is the modulation of approximately 4,000 human genes documented in microarray studies of GHK-Cu-treated cultured fibroblasts and keratinocytes. The downregulated genes are enriched for inflammatory and tumor-associated transcripts; the upregulated genes are enriched for tissue remodeling, antioxidant defense, and DNA repair transcripts. The mechanism by which the copper tripeptide modulates such a broad transcriptional program is not fully characterized; proposed pathways include direct effects on DNA-binding transcription factors, indirect effects through copper supply to copper-dependent enzymes, and modulation of the chromatin-remodeling SWI/SNF complex.

Wound healing

The wound healing literature is the strongest component of the GHK-Cu evidence base. Reported effects include accelerated re-epithelialization in dermal wound models, enhanced fibroblast and endothelial cell migration, increased collagen synthesis and remodeling, and improved tensile strength of healing tissue. The mechanism involves both copper-dependent enzymatic effects (lysyl oxidase, which cross-links collagen and elastin) and gene-expression effects on growth factor production (TGF-beta, VEGF, IGF-1).

Hair follicle activity

GHK-Cu has been studied in androgen-dependent and androgen-independent hair loss models. Reported effects include increased hair follicle size, prolonged anagen phase duration, and increased hair shaft diameter. The mechanism involves both fibroblast growth factor production by dermal papilla cells and copper-dependent stabilization of hair follicle stem cells. Topical and intradermal preparations have been evaluated in clinical hair-loss studies with mixed but generally positive results.

Anti-inflammatory and antioxidant effects

Reported anti-inflammatory effects include reduced TNF-alpha and IL-6 production in activated macrophages, reduced NF-kappa-B activation in stressed endothelial cells, and attenuated neutrophil infiltration in tissue injury models. The antioxidant effects involve copper-dependent SOD activity and direct ROS-scavenging by the GHK-Cu complex itself.

Limits of the mechanistic model

The mechanistic literature is broad but heterogeneous. The wound healing and copper-transport mechanisms are well established. The gene expression effects are documented but the breadth of the transcriptional program (4,000+ genes) is sometimes interpreted in research-grade marketing as evidence of "everything-improving" pharmacology. A more careful interpretation is that GHK-Cu modulates a specific tissue-remodeling and stress-response transcriptional program, and that the practical effects depend on which downstream genes are relevant to the experimental endpoint.

Pharmacokinetics

Routes of administration

Topical, intradermal, subcutaneous, and intravenous administration have been characterized in the published literature. Topical application is the most common route in cosmetic and dermatologic use; the complex penetrates the stratum corneum at moderate efficiency and can be enhanced with iontophoresis or microneedling. Subcutaneous and intravenous administration produce systemic distribution; oral bioavailability is poor due to gastric peptidase degradation and dissociation of the copper from the tripeptide carrier in the acidic gastric environment.

Plasma half-life and tissue distribution

Plasma half-life following intravenous administration is short, on the order of minutes, due to rapid uptake by tissues and clearance through hepatic and renal routes. The copper component distributes broadly and persists in tissues for hours to days; the peptide component is hydrolyzed rapidly. The biological effects of GHK-Cu therefore reflect the combined pharmacokinetics of the carrier (short) and the cargo (long), with downstream copper-dependent enzymatic and transcriptional effects persisting after the parent complex has cleared.

Metabolism and excretion

The peptide component of GHK-Cu is hydrolyzed by serum and tissue peptidases primarily to the constituent amino acids. The copper component is incorporated into copper-dependent enzymes, stored in metallothionein, or excreted via biliary copper export. Renal excretion of intact tripeptide and shorter fragments is a minor clearance route. The compound is not a known inducer or inhibitor of major CYP isoforms.

Reported research dose ranges

Topical formulations typically use GHK-Cu concentrations of 0.05 to 1 percent in cosmetic creams and serums. The published wound healing literature uses topical concentrations in the same range with predictable local effects.

For systemic research dosing, the published preclinical literature reports doses from 0.1 to 10 milligrams per kilogram subcutaneously in rodents, with most pharmacology studies clustering around 1 to 5 milligrams per kilogram daily. Allometric scaling places the equivalent human exposure in the range of 14 to 700 micrograms per kilogram per dose, or approximately 1 to 50 milligrams per dose for a 70 kg subject.

The dose range commonly cited in research-grade vendor literature (1 to 3 milligrams per research subject, daily, over 4 to 8 week cycles) is consistent with the lower end of the allometrically scaled range. Higher systemic doses risk copper accumulation in the liver and the central nervous system, which can produce neurological symptoms similar to Wilson's disease at sustained high exposures. Investigators should treat the published research-grade dose ranges as approximate guidance and should not exceed the upper end of the cited range without specific experimental justification.

Sourcing and quality verification

Synthesis route

The free GHK tripeptide is produced by solid-phase peptide synthesis using Fmoc chemistry; the synthesis is straightforward at small scale. The copper complex is formed by reacting the purified free tripeptide with cupric salts (typically copper sulfate or copper acetate) at controlled stoichiometry, pH, and temperature. The 1:1 GHK:Cu(II) complex is the desired product and is purified by chromatography or recrystallization. The blue color of the resulting complex is a useful first-pass identity check; pure GHK-Cu solutions are visibly blue at concentrations above approximately 1 mg/mL.

The lot of record (Kodiak biolabs lot 20260301) was synthesized by the supplier of record and shipped in lyophilized 1:1 complex form. The vendor analytical report records 99.53 percent purity by HPLC.

Common adulterants and impurities

The research-grade GHK-Cu supply chain has documented patterns of substandard product. Reported issues include:

1. Substitution of the free GHK tripeptide for the GHK-Cu complex, with the buyer assuming that the reaction with serum copper in vivo produces equivalent activity. The free peptide and the complex are not equivalent; serum copper concentrations are not always sufficient to drive complex formation at the relevant concentrations.
2. Incorrect copper stoichiometry (2:1 or 1:2 GHK:Cu) producing a complex with different activity. Atomic absorption spectroscopy or ICP-MS is the definitive test for copper content.
3. Excess unbound copper salts in the lyophilized preparation, producing higher copper exposure than expected and risking copper toxicity. Excess Cu(II) is detected by atomic absorption or by EDTA titration of the freshly dissolved sample.

4. Deletion sequences from incomplete coupling during the free peptide synthesis; these are typically rejected before complex formation but can persist in poorly controlled preparations.
5. Endotoxin contamination from non-pyrogen-controlled synthesis.

Independent verification by HPLC, mass spectrometry, and copper content analysis on every batch is essential. The vendor COA is necessary but not sufficient. Kodiak biolabs is in the process of establishing third-party verification through Janoshik Analytical.

Analytical standards

Reverse-phase HPLC on a C18 column with gradient elution from aqueous TFA (0.1 percent) to acetonitrile, monitoring at 215 nm and at the copper d-d absorption around 600 nm, is the standard purity assay. Identity confirmation by LC-MS yields a protonated molecular ion at 402.1 m/z for the 1:1 complex. UV-visible spectroscopy provides additional identity confirmation through the characteristic copper d-d absorption maximum near 525 to 600 nm.

Reconstitution and handling

Solvent system

GHK-Cu dissolves readily in water and bacteriostatic water. Solubility in 0.9 percent saline is moderate; PBS may produce slight precipitation. The standard reconstitution protocol uses bacteriostatic water for any solution intended for storage beyond a single use. For acute experiments, sterile water for injection is preferred.

Reconstitution protocol

A 50 mg vial reconstituted in 5 mL produces a 10 mg/mL solution; in 2.5 mL produces a 20 mg/mL solution. The blue color is immediately apparent on dissolution. Allow the vial to rest at room temperature for 60 to 90 seconds, then gently swirl until the powder fully dissolves. The complex is highly soluble; full dissolution is typically complete within 60 seconds. Visual inspection should confirm a clear blue solution without particulates. Cloudy or pale solutions may indicate compromised material.

Storage stability

Lyophilized GHK-Cu in the unopened vial: stable at minus 20 degrees Celsius for at least 24 months. Reconstituted aqueous solutions: stable at 2 to 8 degrees Celsius for at least 30 days. Protect from prolonged direct sunlight; the copper complex is photochemically reactive over weeks of light exposure, although standard refrigerated storage in opaque containers is fully adequate. Aliquot working solutions to avoid freeze-thaw cycles.

Stack interaction considerations

GHK-Cu is occasionally combined with topical retinoid preparations in research-grade cosmetic formulations on the rationale that the two pathways (copper-dependent collagen remodeling and retinoid-driven epidermal renewal) are complementary. The combination is generally well tolerated and is documented in dermatologic preparations, although direct synergy data are sparse.

Combination with the regenerative peptide family (BPC-157, TB-500) in systemic research dosing is occasionally reported, on the rationale that GHK-Cu's matrix-remodeling effects complement BPC-157's vascular and TB-500's actin-binding activity. The mechanistic case is plausible but not formally established.

Stacking with high-dose oral copper supplements should be avoided. The combination risks copper accumulation; GHK-Cu is itself a sufficient copper source at the cited research-grade doses, and supplemental copper is not required and may introduce toxicity.

Pharmacokinetic interactions with CYP-substrate compounds are not expected. GHK-Cu has no documented receptor-level interactions with conventional small-molecule pharmacotherapy at standard doses.

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