ANTI-AGING ACTIVITY OF THE GHK PEPTIDE -
THE SKIN AND BEYOND

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Abstract: The human copper binding peptide GHK has been extensively studied as a wound-healing agent and widely used in anti-aging cosmetic compositions. Recent studies demonstrated this substance has a broad range of anti-aging activity. GHK is normally used as its copper 2+ complex GHK-Cu which in low non-toxic concentrations facilitates skin healing and remodeling, reduces inflammatory mediators, and increases production of important growth factors and molecular regulators such as decorin. A series of facial studies conducted by different researchers demonstrated that GHK-Cu containing creams reduce signs of aging such as wrinkles, mottled pigmentation and skin laxity. Also, GHK-Cu increases the expression of epidermal stem cell markers such as integrins and p53. GHK-Cu also repairs DNA damage in irradiated fibroblasts restoring normal functions and growth. Recently GHK and plant alkaloid securinega, out of 1309 bioactive compounds tested, were found to suppress RNA production in 70% of 54 human genes overexpressed in patients with aggressive metastatic colon cancer. GHK-Cu possesses antioxidant activity, increasing the level of antioxidant enzymes, reducing proinflammatory cytokines and oxidative damage, as well as quenching toxic products of lipid peroxidation. In conclusion, the tripeptide GHK-Cu that has a long safety record in skin care formulations possesses a range of health benefits, including skin regeneration, repair of irradiated cells, maintenance of stem cells, as well as anti-inflammatory, antioxidant and anti-cancer activity.

Key words: Anti-aging, GHK, Gly-His-Lys, skin remodeling, cancer metastasis.

Introduction

Wrinkles, sagging, pigmented spots and other signs of aging that result from accumulating damage, signify failure of skin’s defensive and regenerative mechanisms. Moreover, as recent studies point out the progressive decline in skin regenerative function may have dire consequences well beyond wrinkles, causing diverse skin diseases such as cancer (1). Hence, substances that promote skin regeneration may offer much more than “a wrinkle cure”.

The human copper binding peptide GHK has been extensively studied for the last three decades, primarily as a wound-healing agent. Its well documented skin regeneration activity prompted widespread use of GHK in anti-aging cosmetic products (2). Recent studies revealed a new array of GHK’s anti-aging activities including stem cell activation, suppression of cancer metastasis genes and restoration of damaged cell function.

Discovery and early research

Human peptide GHK-Cu was isolated in 1973 as an activity in human albumin that caused old human liver tissue to synthesize proteins like younger tissue (3). Subsequent studies established this activity as a tripeptide with an amino acid sequence glycyl-L-histidyl-L-lysine (Fig 1) with a strong affinity for copper that readily formed the complex GHK-Cu. It was proposed that GHK-Cu functions by modulating copper intake into cells (4).

By 1983, Pickart et al. had established that GHK-Cu accelerates wound healing and contraction, improves the take of transplanted skin, and also possesses anti-inflammatory actions (5-7).

Subsequent studies directed by J.P. Borel and F.X. Maquart et al. (France) demonstrated that GHK-Cu at a very low, non-toxic concentration (1-10 nanomolar) stimulated both the synthesis and breakdown of collagen and glycosaminoglycans (8, 9). It modulated an activity of both metalloproteinases and their inhibitors (TIMP-1 and TIMP-2), acting as a main regulator of wound healing and skin remodeling processes. Since only GHK-Cu, but not GHK, exhibited these properties, it was concluded that the copper-binding activity of GHK is...
essential for its wound healing and skin remodeling effects (10, 11).

![Molecular Structure of tri-peptide GHK-Cu](image)

**Figure 1.** Molecular Structure of tri-peptide GHK-Cu

In 2000, the same group demonstrated, using mRNA analysis, that GHK-Cu stimulated collagen, dermatan sulfate, chondroitin sulfate and a small proteoglycan, decorin (12). In 2001, McCormack et al. established that GHK-Cu decreased pro-inflammatory cytokine TGF-beta in human fibroblast culture (13). GHK was also found to attract immune and endothelial cells to the site of an injury (14).

Wound healing activity of GHK-Cu was confirmed in animal experiments. GHK-Cu accelerated wound healing, increased blood vessel formation and the level of antioxidant enzymes in rabbits (15, 16). This molecule induced systemic wound healing in pigs (17), and it improved diabetic and ischemic wound healing in rats, decreasing the level of TNF-alpha and stimulating collagen synthesis (18-20). It also facilitated healing of pad wounds in dogs (21).

**Current cosmetic use of GHK-Cu**

The best direct evidence that GHK is a remodeling activator was demonstrated by a series of facial studies. As a result, cosmetics containing GHK or GHK-Cu are now widely used. Howard Maibach’s group demonstrated that GHK-Cu readily penetrates the stratum corneum and accumulates in biologically effective concentrations (22, 23).

In one study GHK-Cu was found to perform better than vitamin C or retinoic acid. After one month, GHK-Cu increased collagen in 70% of those treated against 50% treated with vitamin C and 40% treated with retinoic acid (24). GHK-Cu containing facial cream reduced visible signs of aging after 12 weeks of application to the facial skin of 71 women with signs of photoaging. The cream improved skin laxity, clarity, and appearance, reduced fine lines and the depth of wrinkles, and increased skin density and thickness when compared with a placebo cream (25).

A GHK-Cu eye cream also performed better than vitamin K eye cream in terms of reducing lines and wrinkles, improving overall appearance, and increasing skin density and thickness (26). Besides improving the appearance of aging skin and increasing its density and thickness, the GHK-Cu cream was found to strongly stimulate dermal keratinocyte proliferation (27).

**Effects on skin stem cells**

In 2009, Kang et al. used a multilayered skin equivalent (SE) model to demonstrate that GHK-Cu increases proliferative potential of basal human keratinocytes and an expression of epidermal stem cell markers.

In cell cultures GHK-Cu (0.1-10 micromolar) stimulated proliferation of basal keratinocytes in a dose dependent manner and was non-toxic in these concentrations. An addition of GHK-Cu increased integrins and p63 expression in basal keratinocytes. The authors concluded that GHK-Cu was able to activate and maintain reparative capacity (“stemness”) of basal keratinocytes (28).

**Repair of cellular DNA damage after irradiation**

Anti-cancer irradiation slows cell replication by breaking DNA strands. A recent study also showed GHK-Cu’s ability to restore function of irradiated fibroblasts to that of intact cells. The researchers used cultured human fibroblasts obtained from cervical skin that was either intact or exposed to radioactive treatment (5000 rad). At a very low (1 nanomolar) concentration, GHK-Cu sped up irradiated fibroblasts growth and increased their production of growth factors bFGF and VGF to the point where it became even higher than that of both the irradiated and intact control cells (29).

**Suppression of cancer metastasis genes**

Recently GHK was selected, out of 1309 bioactive compounds, as a substance that suppressed RNA production in 70% of 54 human genes overexpressed in patients with an aggressive metastatic form of colon cancer. Hong et al. used genome-wide profiling to identify genetic biomarkers (gene expression) for metastasis prone colorectal cancer as well as their perturbagens – substances that modulated their expression. The search yielded only two substances that were able to downregulate expression of “metastatic” genes – GHK and plant alkaloid securinine. GHK produced the result at low non-toxic 1 micromolar concentration and securinine at 18 micromolar (30). The authors point out that both GHK and securinine are well-
known skin remodeling agents. Securinine activates macrophages and is a component of traditional African and Chinese medicines for skin injuries (31). These results suggest overlapping gene activity in tissue remodeling and cancer metastasis suppression.

GHK may inhibit cancer genes by increasing production of decorin, a proteoglycan (12). Decorin’s regenerative and anti-inflammatory actions (regenerating nerves and muscles, suppressing scar formation) are similar to those of GHK. Numerous studies have found decorin to suppress tumor growth and metastasis of cancerous tissue (breast, prostate, osteosarcoma) in animal models (32, 33).

**Genomic studies**

Recent genomic research suggests that GHK directly modulates gene expression, which may explain the diversity of its biological actions.

Iorio et al. used a repository of transcriptional responses to compounds, the Connectivity Map (cMap) (34), and MANTRA software (www.mantra.tigem.it) to explore networks of compounds producing similar transcriptional responses. GHK, as one of the compounds studied, increased mRNA production in 268 genes while suppressing 167 (35). Our own preliminary query with the cMap yielded a result that Gly-His-Lys, at 1 micromolar, up- or down-regulates over 3,900 genes out of approximately 20,500 human genes studied. Further research is needed in this area.

**Protective activity**

Animal wound healing studies (see above) established GHK-Cu’s ability to increase the level of antioxidant enzymes and reduce pro-inflammatory cytokines such as TGF-beta and TNF-alpha. GHK was also found to reduce oxidative damage by modulating iron level (36). Additionally, it quenches alpha,beta-4-hydroxy-trans-2-nonenal and acrolein – toxic products of lipid peroxidation that play an important role in the pathogenesis of several age related conditions (37, 38).

In two other studies, GHK-Cu was found to protect liver tissue from tetrachloromethane poisoning, maintain liver tissue’s normal functional activity and immune responsiveness (39, 40). GHK-Cu produced a 75% reduction of gastric mucosa homogenates of lipid peroxidation in the range 10-100 micromolar suggesting that copper-peptide complexes are able to effectively neutralize damaging oxygen-derived free radicals (41).

**Conclusion**

Human tri-peptide GHK-Cu exhibits a broad spectrum of reparative and protective actions including restoration of damaged tissues and cells, anti-oxidant, anti-inflammatory and anti-cancer effects, and is active at very
low, non-toxic concentrations (Fig 2). At present, GHK-Cu is successfully used in cosmetology to improve the appearance of aging skin. Its recently discovered ability to suppress cancer metastasis genes as well as stimulate skin stem cells warrants further investigation of its potential anti-aging benefits.

References


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