



# Copperceuticals and the Skin

**Loren Pickart PhD**

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Reversing of the effects of aging on human skin was a primary goal of ancient alchemists and their successors, modern cosmetic chemists. During human aging, skin becomes thinner and accumulates various blemishes, lesions and imperfections. The structural proteins are progressively damaged causing collagen and elastin to lose their resiliency. The skin's water-holding proteins and sugars diminish, the dermis and epidermis thin, the capillary network becomes disorganized, and the subcutaneous fat cells diminish in number. These effects are further intensified by decades of exposure to ultraviolet rays, irritants, allergens, and various environmental toxins. The result is a dry, wrinkled, inelastic skin populated by unsightly lesions.

Restoration to a biologically younger skin morphology requires two linked processes: the removal of damaged proteins and aberrant skin lesions, and their replacement with normal, blemish free skin. This process is similar to the remodeling phase of wound healing in which scar tissue is removed over several years to slowly restore the skin to its original state. In young children this process functions efficiently and skin damage is rapidly removed. But in adults this process slows drastically and various skin lesions may persist for years or decades.

Various skin renewal methods that have been developed that produce a limited type of skin restoration but all have drawbacks. Retinoic acid slowly remodels skin but at the price of chronic irritation and redness. Collagen inducing peptides, melatonin, and vitamin C increase skin collagen but skin also needs to increase its micro-circulation and rebuild of elastin, water-holding proteoglycans. Collagen stimulatory molecules, such as TGF-beta-1 and fibronectin-binding peptides, were tested in wound healing studies but produced unacceptable skin thickening and scarring. Controlled skin damage (i.e., peels, dermabrasion, lasers,) works well only if there is a vigorous post-therapy regenerative response by the damaged skin.

The good news today is that certain types of copper peptides possess all the necessary biochemical actions that can, in a morphological sense, restore skin to a younger state without causing skin irritation. Such types of copper peptides are increasingly used in cosmetic skin care products such as Neutrogena's Active Copper line. These copper peptides also are used to improve post-treatment skin recovery after dermatological skin renewal procedures, such as chemical peels, laser resurfacing, and dermabrasion. Unlike most purported skin improvement therapies, the skin regenerative actions of such types of copper peptides are documented by numerous well-controlled, published studies from leading laboratories and universities.

## **GHK-Copper for Skin Renewal**

A human copper peptide complex forms the basis for these developments. The complex is glycyl-L-histidyl-L-lysine:copper(II) or GHK-Cu. The tripeptide, which I discovered while searching for methods to reverse human aging, is generated by proteolysis after tissue injury or skin turnover. Its high affinity for copper(II) allows it to obtain copper from carrier molecules such as albumin and form GHK-Cu. The complex is a normal constituent of human plasma, saliva, and urine. (1-5)

When injected into skin or applied to the skin's surface, GHK-Cu activates the processes that remove scarred or damaged tissue and deposit new tissue. Francois Maquart and colleagues (Universite de Reims) have published several reports demonstrating the role GHK-Cu in wound healing.

- GHK-Cu acts as an inducer of the second phase of healing when skin remodeling processes remove scars and tissue debris while rebuilding healthy skin. (5-11)
- GHK-Cu concomitantly stimulates the degradation of existing collagen and synthesis of new collagen.
- At the molecular level, GHK-Cu aids the rebuilding of new skin by increasing angiogenesis, the production of m-RNA for collagen, elastin, proteoglycans, glycosaminoglycans and decorin, while simultaneously stimulating the m-RNA production of, and synthesis of, certain metalloproteinases and anti-proteases that clear damaged protein and remove scars. (10-12)
- In addition, GHK-Cu suppresses secretion of scar-forming TGF-beta-1 by fibroblasts. (13)
- GHK-Cu also acts indirectly as a chemoattractant for cells that stimulate repair, such as macrophages and mast cells, which release protein growth factor proteins that stimulate tissue repair. (6)

GHK-Cu also appears to function in humans as a circulating non-steroidal anti-inflammatory. (14) After episodes of tissue damage, ferric ion is released from ferritin and catalyzes damaging tissue oxidations. GHK-Cu counters this action by blocking ferritin channels and stopping the release of oxidizing iron ions. (15) GHK blocks the oxidation of low density lipoproteins by loosely bound copper. (16) Interleukin-1beta is also released after tissue injury producing cellular damage. At hormonal levels, GHK-Cu prevents damage to pancreatic cells by interleukin-1. (17)

### **Dermatological Actions of Copper Peptides**

In 1985, I started a company called ProCyte to develop products based on GHK-Cu. We found that the application of GHK-Cu-containing creams to the human skin increased the thickness of the epidermis and dermis, increased skin elasticity, reduced wrinkles, and resulted in a removal of skin imperfections such as blotchiness and sun damage marks, while producing a significant increase in subcutaneous fat cells.

Recently, more extensive and statistically significant human studies solidified these observations. Abulghani et al. reported (18) GHK-Cu was more effective in stimulating new collagen development than vitamin C, retinoic acid, or melatonin. Abba et al. reported (19) that in 8 weeks, a GHK-Cu-containing liquid foundation improved epidermal thickness, increased skin elasticity, and improved skin appearance. Leyden et al. found (20) such creams to reduce visible signs of photodamage and increased skin density in 8 weeks on facial skin. A second placebo-controlled study by this group (21) (71 females, 12 weeks) by this group found that GHK-Cu-containing face creams reduced wrinkles and fine lines while increasing skin elasticity, density and thickness. A third placebo-controlled study (22) (41 females, 12 weeks) found that a GHK-Cu-containing eye cream reduced wrinkles and fine lines and improved eye appearance.

However, despite these promising properties, GHK-Cu failed in clinical trials conducted by the U.S. Food and Drug Administration (FDA) on the healing of indolent wounds such as venous stasis and diabetic ulcers. The actions of GHK-Cu are limited by its fragility and tendency toward breakdown and also its lack of adhesion to the skin surface.

Therefore, in 1994, I started Skin Biology to develop an improved second generation of skin regenerative copper peptides with enhanced potency, breakdown resistance, and high adherence to skin. We isolated a fraction of peptide fragments from soy protein that possessed the desired qualities when chelated to copper (II). Such soy peptides have a long history of safe use in cosmetic products. Howard Maibach and colleagues (University of California at San Francisco) tested these new copper peptides in four small, placebo-controlled human studies. They found that creams made from these new copper complexes produced significantly faster skin healing and

reduced redness and inflammation after mild skin injuries induced nickel allergy inflammation (23), tape stripping (24), 24-hour detergent irritation (25), and acetone burns (removal of skin lipids) (26).

## **Scarless Healing**

Copperceuticals like those studied by Maibach et al. are opening an approach to scarless or nearly-scarless healing of surgical incisions. GHK-Cu markedly reduces scarring after surgery if injected (an aqueous solution of 1 mg/ml) down the incision line. However, the second generation copper peptides appear to be superior for such uses.

In veterinary studies, the application of second generation copper peptides in creams immediately after surgery produced rapid and scarless healing in dogs after spaying operations and in young horses after leg-straightening operations. This allowed the dogs to be returned to their owners in four days instead of the usual five, while the foals were returned in five days instead of seven. For such uses, the incisions should be left open to air or only lightly covered with gauze. Occlusive dressing and wet bandages nullify the positive effect.

## **Post-Procedure Treatments**

Both GHK-Cu and the second-generation copper peptides function well to improve the recovery of skin after procedures such as deep peels, laser resurfacing, and dermabrasion. If the skin is treated with copper peptides within two hours after the procedure, post-treatment redness and inflammation is avoided without the use of corticosteroids. Skin rebuilding is hastened while scars and infections are greatly lessened.

We developed a water based product called CP Serum, which works especially well. This is often followed by either emu oil or squalane which act as moisturizers and as penetrating agents that push more copper peptide into the skin.

## **Removal of Skin Lesions**

The second-generation copper peptides work well for the removal of skin lesions. Our research finds that most skin imperfections (hypertrophic scars, pitted scars, skin tags, moles, actinic keratosis) can be removed or greatly reduced by repeated daily use of hydroxy acids to loosen and dissolve the lesions followed by strong copper peptides to aid skin regeneration.

Hydroxy acids such as 2% salicylic acid (pH=3.2) or 14% glycolic acid (pH=3.9) are effective with copper peptides but obtaining a cosmetically satisfying result may require several months of applications.

>The use of stronger hydroxy acids, followed by the application of copper peptides greatly speeds the removal of lesions and scars, but can be very irritating if not expertly applied. For example, to remove moles, 70% glycolic acid is applied for 6 minutes, washed off, then the strong copper peptides are applied to the moles. Two to three days of this procedure often removes moles permanently.

## **Safety of Copper Peptides**

Numerous safety tests of skin regenerative copper peptides have failed to find any toxicity problem. Extremely small amounts penetrate the skin and no rise in blood copper has ever been found in animals or humans treated with copper peptides.

Further reassurance as to the safety of copperceuticals is that in nutritional studies, increased supplementation with copper has been reported to (27)

- Increase DHEA levels;
- Raise brain enkephalins;
- Reduce carcinogenesis and cancer growth;
- Reduce protein glycation and deleterious peroxidation of fats;
- Reduce brain developmental defects in offspring;
- Increase anti-oxidant defenses by activation of superoxide dismutase.

## **Formulating Copper Peptides**

When formulating copper-peptide products, great care must be taken to minimize interactions with the ionic copper. Other ingredients of creams, lotions, and solutions may interact with the ionic copper and neutralize the positive copper-peptide actions and, in some cases, generate copper-complexes that inhibit cell replication.

All products should be carefully tested for their effects on skin repair. Not all copper peptide complexes are skin regenerative; some may even inhibit skin repair. The existing products based on GHK-Cu or the newer complexes are supported by credible, published evidence of efficacy. (27)

## **Future Developments**

Since the patent (28) held by ProCyte Corporation on cosmetic uses of GHK-Copper expires in May 2004, we can expect a greatly increased use of this complex in cosmetic products thereafter. The newer copper peptides under development at Skin Biology will provide an alternative type of higher potency skin renewal products that may be especially useful for improving skin recovery after dermatological procedures. (27)

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