COPPER TRIPEPTIDE-1 GROWTH FACTOR USES IN AESTHETIC MEDICINE

Charlene DeHaven discusses the skin repair and renewal properties of copper tripeptide-1 and its many applications in aesthetic medicine

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ABSTRACT

Copper tripeptide-1 is a bio-identical growth factor used throughout the human body for purposes of tissue regeneration and repair. Although the main focus in this article relates to the skin functions of this compound, it is widely distributed in all tissue. Its physiologic role in tissue other than skin will also be discussed.

This molecule exhibits diverse functions related to the healing and replacement of injured tissue, including damage occurring throughout life through injury and ageing. Copper tripeptide-1 is a member of the group of emergency response molecules devoted to diverse processes of tissue remodeling and maintenance. As such, it has wide applications in accelerating healing for all types of wounds and tissue survival. Some of its more specific actions include anti-senescent effects, DNA repairing effects, antioxidant effects, and anti-neoplastic effects. Its general effects include a wide variety of regenerative properties for numerous tissues as well as the ability to decrease the velocity of several age-related diseases.

Its safety profile has also been extensively documented since the beginning of initial research on the compound in the early 1980s. It is remarkable that no adverse issues have been found with use of this compound in skin or human wound healing studies.

Even though it has been exhaustively investigated in many fields of medicine for over 35 years it is just now becoming of greater interest in skincare. Its numerous applications in aesthetics will herein be emphasized.

KEYWORDS

Growth Factors, Peptides, Copper Tripeptide-1, Wound Healing, Tissue Remodeling, Anti-senescence, Procedural Results Optimization

IN 1986, THE NOBEL PRIZE FOR PHYSIOLOGY or Medicine was awarded jointly to Stanley Cohen and Rita Levi-Montalcini for their discovery of the growth factors—nerve growth factor (NGF) and epidermal growth factor (EGF), respectively[1]. This sparked a new era of scientific expansion in all areas related to the regulation and direction of cell growth as mediated by growth factors and cytokines.

It is not surprising that one of the first areas to benefit from this new body of knowledge was that of wound care. Around the time of this discovery, numerous articles appeared in the medical literature investigating the use of cell cultures and growth factors for burns[2-4] and numerous other wound types[5]. In these situations, laboratory-grown sheets of cells from small volumes of harvested tissue[6,7] known as 'tissue-engineered skin substitutes' came into use for a wide variety of surgical and medical situations.

One of these techniques incorporated neonatal foreskins harvested during circumcision for the purpose of culturing epidermal cells[8] for tissue intended for grafting. The use of the same basic technology, i.e. cell cultures obtained from neonatal foreskins, remains available today and has also been incorporated into cosmeceutical products[9] through the use of cytokines and growth factors extruded into the nutrient media of such cell cultures. Other technologies use cytokines and growth factors from other types of discarded cultured human tissue, such as discarded fetal tissue[10,11], and is also available in cosmeceutical products.

Not all of these cosmeceutical products share the same availability to consumers worldwide. European regulations are sometimes considered more stringent[12].

Market interest in cosmeceuticals incorporating growth factors

Despite variances worldwide in the availability of products containing growth factors, market interest in this product category is high. Many cosmetic dermatologists are selling some type of growth factor skincare. Consumers seem better educated on product ingredients and are willing to spend money on products that they believe will deliver better results. 'Consumers are particularly interested in product ingredients, including peptides and other growth factors that activate skin stem cells to boost collagen production and facilitate cell renewal'[13].

Considering these factors, growth factor products with global cosmetic regulatory acceptance and positive ingredient effects well-documented in the medical literature, should have considerable consumer interest ▷

> “Consumers seem better educated on product ingredients and are willing to spend money on products that they believe will deliver better results.”

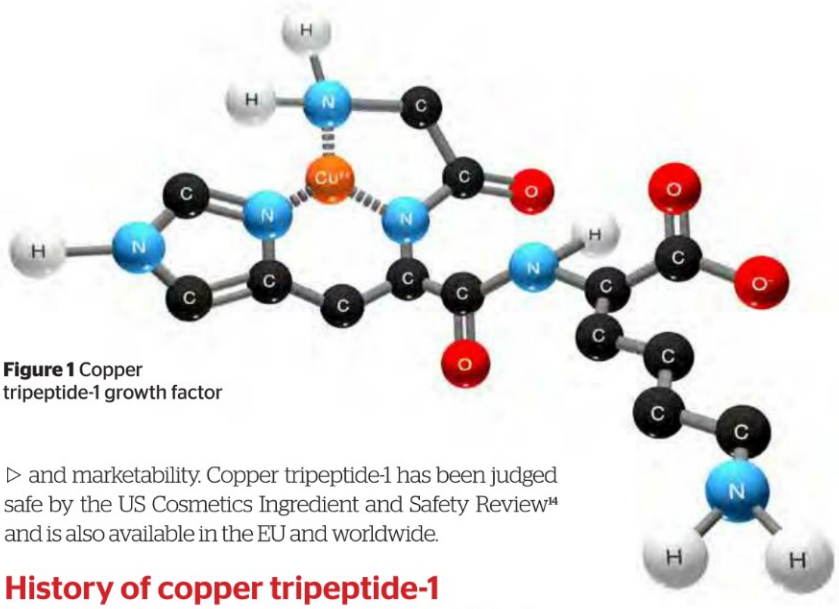

Figure 1 Copper tripeptide-1 growth factor

▷ and marketability. Copper tripeptide-1 has been judged safe by the US Cosmetics Ingredient and Safety Review[14] and is also available in the EU and worldwide.

History of copper tripeptide-1

Information about this compound was first published by Loren Pickart in 1975[15]. In the many subsequent papers by Pickart and others, the compound was described as a growth factor with actions like hepatocyte growth factor (HGF)[16]. HGF is like other molecules in the family of growth factors in that it is a very long peptide chain with a large molecular weight and size. It is therefore more correct to describe copper tripeptide-1 as a growth factor analogue since it is composed of only three amino acids (a tripeptide). It is now known to fit into the family of cytokines. Because it is such an important messenger molecule with a wide range of properties and functions, it has sometimes been termed a 'matrikine'[17]. However, in the literature it may still be referred to as a growth factor.

The molecular structure of copper tripeptide-1 is indicated by its name, i.e. a tripeptide chain consisting of glycine, histidine, and lysine (GHK) complexed with copper (*Figure 1*).

Natural role in the human body

Copper tripeptide-1 exists naturally within human tissue and is therefore bio-identical. It exhibits a surprisingly diverse array of repair functions. Injured tissues contain large amounts of this compound where it acts as a signalling agent for repair and regeneration[18]. In these repair processes, it signals the synthesis of collagen, elastin, and glycosaminoglycan (GAG) ground substances[19]. Early in its discovery, its regenerative effects were realized for hepatocytes. These involved the anti-senescence of aged liver cells into physiologically younger cells and protection from, as well as reversal of, toxin-mediated hepatic damage[20-22].

> "As long as compatibility with other actives is considered in the formulation technology, its ease of penetration makes copper tripeptide-1 a good choice for inclusion in cosmeceutical products."

As well as being present in wounded tissue, copper tripeptide-1 was also found to be a normal inhabitant of saliva, urine, and all collagenated tissue, as well as discovered to have important effects in maintaining and repairing all tissue types[23].

Copper tripeptide-1 exists in forms both complexed with and without copper. It has a high affinity with copper, a metal associated with many enzymes in the human body that benefit tissue repair, inflammation, metabolism, and synthesis of vital molecular structures[24]. Copper metal ions themselves are also found in high concentrations around healing wounds and are therefore implicated in wound healing and inflammatory processes. Much of the benefit of copper tripeptide-1 relates to its ability to efficiently bind and transfer copper ions, a quality also related to its mitigation of oxidative stress[25].

Skin penetration

The design of the skin serves as an effective physiochemical barrier. Penetration of long-chain peptides is problematic in spite of recent advances in drug delivery, which are not available for cosmeceuticals. In general, compounds greater than 500 Daltons in size are unable to penetrate the skin barrier[26]. Yet the majority of biologic processes are modulated by specific amino acid sequences. Short chain peptides with good barrier penetration that do not require advanced penetration enhancers or drug delivery systems are of great interest to the cosmetics industry[27].

Copper tripeptide-1 easily penetrates the stratum corneum barrier[28]. As long as compatibility with other actives is considered in the formulation technology, its ease of penetration makes copper tripeptide-1 a good choice for inclusion in cosmeceutical products.

Actions and benefits for aesthetics

Copper tripeptide-1 may be considered one of the body's emergency response molecules. It is released during injury and comes to the body's aid when the processes below are activated.

Wound healing

Any tissue injury signals the release of copper tripeptide-1, which signals repair processes to begin. A huge body of scientific evidence supports the essential role of copper tripeptide-1 in the acceleration of wound healing in many human and animal wound types[29-32], including surgical[33,34], post-laser[35], Mohs[36], ischemic[37], burns, large skin grafts[38], hair transplants[39], refractory venous stasis ulcers[40], diabetic ulcers[41], and others. Diabetic wounds healed three times faster in the presence of copper tripeptide-1 and time to re-epithelialization was shortened[42,43].

Figure 2 and *Table 1* below illustrate the ability of copper tripeptide-1 to improve wound healing in skin for surgical wounds. The digital photographs shown in *Figure 2* are of two identical full-thickness skin wounds made with a ▷

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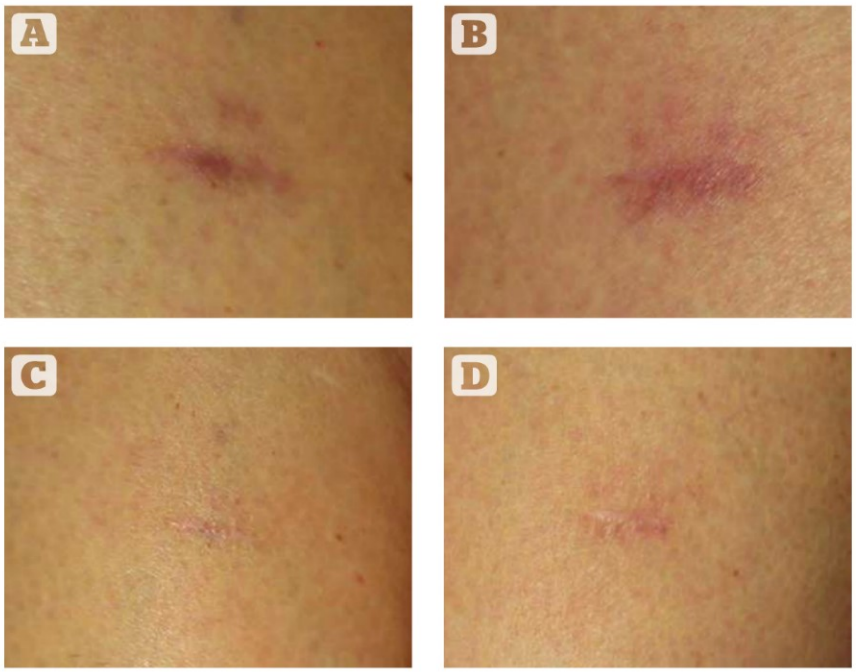


Figure 2 Photographs are of a full-thickness surgical wound made with a #15 scalpel and sutured with interrupted 6-0 nylon. (A) 3 month treated, (B) 3 month control. (C) 6 month treated, (D) 6 month control. Sutures removed at 7 days and product application begun with a serum containing copper tripeptide-1 plus other actives. Control and treated photographs taken at 3 months and 6 months post-wounding. For the treated side, product was applied twice daily for 3 months and then once daily for the ensuing 3 months. Improved scar appearance noted for the two treated photographs.

▷ scalpel penetrating to the hypodermis. Both wounds were one centimeter in length. Sutures were removed at one week post-incision and application of a cosmeceutical product[44] containing copper tripeptide-1 was initiated on the treated side. The photographs illustrate a much more cosmetically acceptable wound on the treated side at time periods of both 3 months and 6 months post-incision. These are compared to the control incision without product application that shows adequate wound healing but an inferior cosmetic result. These results substantiate the ability of cosmeceutical products containing copper tripeptide-1 to improve post-procedure scarring.

The incisional wounds of *Figure 2* were then punch biopsied and sent to a fully blinded dermatopathologist for microscopy. The dermatopathologist's description of the two wounds, both control and treated, are given in *Table 1*. With application of the cosmeceutical product containing copper tripeptide-1 to the treated incision, fewer inflammatory cells were seen and the stratum corneum exhibited a normal appearance. The stratum corneum was described as fully 'basket-weaved' and having the same appearance as the adjacent non-scarred area. Collagen bundles were regular and in orderly parallel bundles. These light microscopic findings further explain the improved cosmetic results seen with the treated scar in *Figure 2*.

Tissue remodelling and skin renewal

Furthermore, copper tripeptide-1 is active not only in wound healing but also for normal tissue remodelling. Studies have documented these regenerative effects in both human and animal studies. Animal studies have included rats, mice, pigs, rabbits, horses, dogs, and guinea pigs. The types of wounds studied in humans and animals have included gastrointestinal ulcers, liver injury from toxins, surgical wounds, burn wounds, ischemic wounds, bone fractures, punch biopsies, skin transplants, hair transplants, and tissue wounds evaluated in wound chambers. In skin, the specific effects of copper tripeptide-1 include increasing keratinocyte proliferation and normal collagen synthesis[45,46], improving skin thickness[47], skin elasticity and firmness[48], improving wrinkles[49], photodamage[50] and glycation[51], uneven pigmentation, skin clarity and tightening, and upregulating protective barrier proteins[52,53].

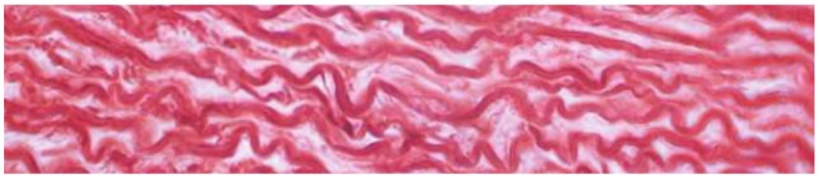
> "In skin, the specific effects of copper tripeptide-1 include increasing keratinocyte proliferation and normal collagen synthesis."

Copper tripeptide-1 has decreased chemotherapeutic hair loss in both animals and humans and improved hair transplant survival and 'take'. Furthermore, through effects on decorin[54], new collagen made under the direction of copper tripeptide-1 assumes the correct anatomical configuration rather than a disorganized scar[55]. Matrix support structures of the dermis including collagen I, collagen III, and glycosaminoglycans[56] increase as normal tissue configuration is restored in the presence of this growth factor. Thus it may be said that the properties of tissue remodelling and renewal associated with copper tripeptide-1 are ubiquitous throughout the human body and not unique to skin. The compound's properties make it an attractive addition to cosmeceuticals both for anti- ▷

Table 1 Histology report

PARAMETER	CONTROL	TREATED
Inflammation	55–65 chronic inflammatory cells per perivascular space	Less than 50 chronic inflammatory cells per perivascular space
Collagen	Collagen bundles in disarray, gaps between bundles	Collagen bundles regular and orderly, parallel bundle
Skin surface	Scar surface more elevated above skin surface orthohyperkeratosis present	Stratum corneum fully basket-weaved, with adjacent non-scarred area

At 6 months, both the control and treated scars shown in *Figure 2* were punch biopsied and sent to a blinded dermatopathologist for sectioning. Improved inflammation scores and improved collagen architecture were described on the treated side.



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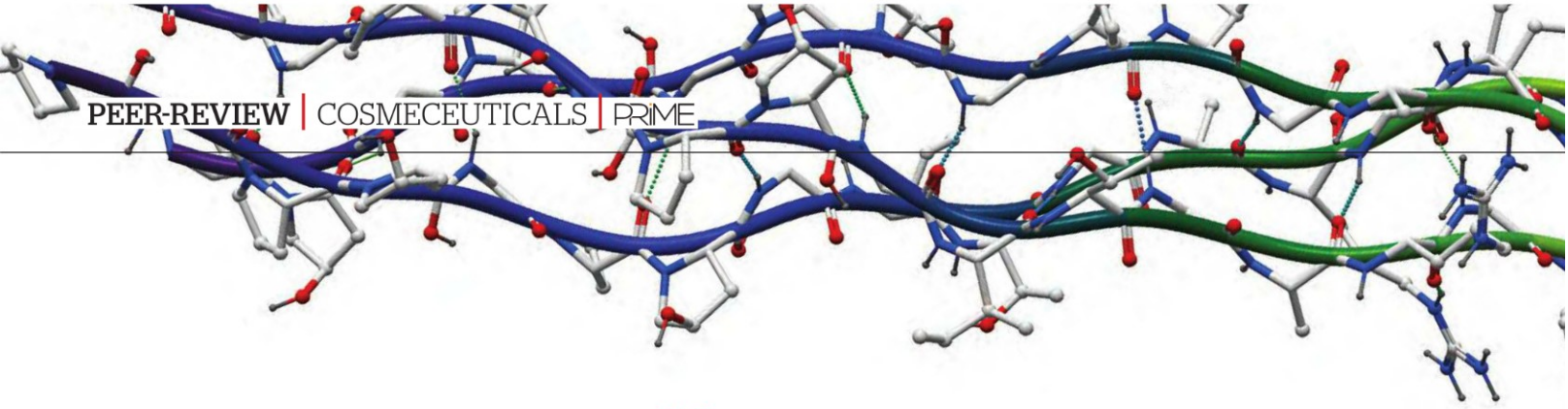
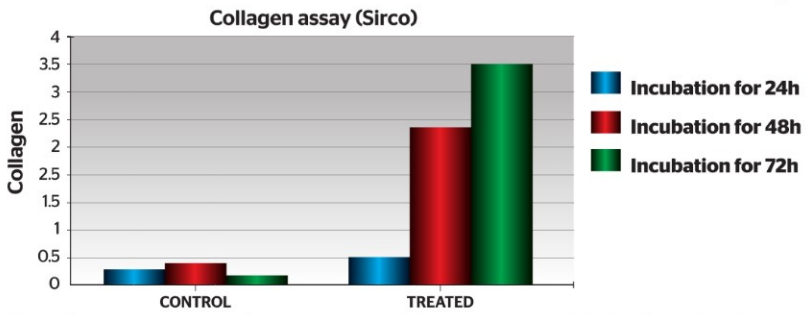


▷ ageing effects and for optimizing post-procedure results.

Figure 3 illustrates the ability of a cosmeceutical product[57] to improve collagen synthesis in aged fibroblasts. Fibroblasts from a 55 year-old patient were specified in the experiment to give a truer test of product. Metabolism slows with ageing and protein synthesis declines. Specifically, collagen synthesis decreases by about 1% per year after the age of twenty, and from the age of sixty years humans synthesize about one-half of the collagen they were able to make at the age of twenty years. Each of the three bars for the control and the treated fibroblasts exposed to product were measured at 24 hours, 48 hours, and 72 hours, respectively. The fibroblasts exposed to the cosmeceutical product containing copper tripeptide-1 showed collagen synthesis increasing through each time period. This is more remarkable when considering that, per experimental protocol, the cosmeceutical product was rinsed off the cells after application. Thus the experiment further substantiates that the copper tripeptide-1-containing product achieved delivery to the site of action inside the aged fibroblasts to initiate steps in the process of collagen synthesis. These results have application both for post-procedural results as well as in the mitigation of ageing where architecturally correct collagen synthesis is impaired and declines.

> “Collagen synthesis decreases by about 1% per year after the age of twenty, and from the age of sixty humans synthesize about one-half of the collagen they were able to make at the age of twenty.”

Figure 3 Collagen assay perfomed on a 55 year old patient's fibroblasts



Treated areas were exposed to a cream containing copper tripeptide-1 and rinsed, without reapplication. Improved and increasing collagen synthesis during each day's measurement.

Likelihood of keloid formation is reduced and scar surface area is decreased[59]. Collagen production with this active was superior to creams containing vitamin C or retinoic acid[60].

Anti-tumor effect and DNA repair

Copper tripeptide-1 has a strong anti-tumor effect[61] on both primary tumor growth and metastases mediated

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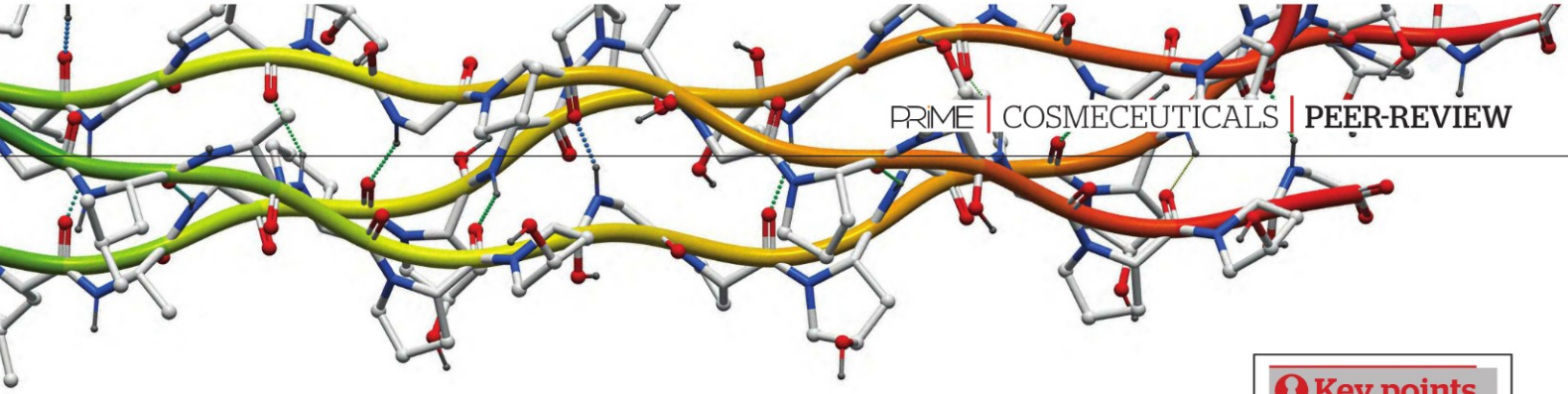

by multiple possible mechanisms[62] including decorin[63,64], apoptosis[65], and biologic chelation of the potentially pro-oxidant metals—iron[66] and copper[67,68]. It protects DNA from the damaging effects of radiation during cancer treatments and photoaging. Radiated fibroblasts showed restoration of intact functioning after exposure to copper tripeptide-1. A variety of tumor cell lines have been shown to be suppressed or die in the presence of this compound while healthy cell lines continued to grow normally. This and other evidence implies that copper tripeptide-1 may be used in topical products to enhance normal tissue repair without fear of neoplastic transformation.

Stem cell anti-senescence

Survival of stem cells in the basal epidermis and other epithelial cells is promoted by tripeptide-1[69,70]. This suggests it could have an important anti-ageing effect[71,72] and, in fact, its anti-senescent effects[73] have been demonstrated on a number of tissue types including skin[74]. Keratinocyte proliferation is encouraged through stem cell maintenance encouraged via copper tripeptide-1[75].

Antioxidant and anti-inflammatory effects

Many of the body's intrinsic antioxidant systems, including superoxide dismutase, are induced by copper tripeptide-1 as demonstrated in healing wounds[76].

Conclusion

Copper tripeptide-1 is a novel compound of great interest to aesthetics. This is related to its ubiquitous abilities not only in skin but also in other tissues to initiate tissue regeneration and wound repair for all types of wounds, increase collagen synthesis, effect DNA repair, quiet excess inflammatory processes, and act as an antioxidant. Its potential for improving post-procedure results and decreasing the velocity of ageing is obvious. Its safety profile is also quite remarkable and increases the level of interest. No adverse effects or issues have been found for copper-tripeptide-1 in spite of extensive research involving the compound since the early 1980s. As well as acting as a growth factor, it also has attractive anti-neoplastic effects that substantiate its safety profile for the ageing patient.

▶ ***Declaration of interest*** *The author serves as Clinical Director for INNOVATIVE SKINCARE®, an international cosmeceutical company based in the United States and manufacturer of iS CLINICAL® products.*

▶ ***Figure 2-3*** © *INNOVATIVE SKINCARE®*

▶ ***Table 1*** © *INNOVATIVE SKINCARE®*

Key points

- Copper tripeptide-1 is a short-chain peptide complexed with copper that acts as a growth factor in human skin and that is bio-identical to a compound found throughout human tissue
- This molecule belongs to the group of emergency response molecules used for tissue repair and regeneration including properly directed collagen synthesis
- There is a long history of research from the 1980s using this compound for many medical applications including wound healing and aesthetics
- The mechanism of copper tripeptide-1 as well as its extensively documented safety profile and anti-neoplastic properties make it an ideal molecule for topical regeneration of ageing skin

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