Neova® Eye Therapy now combines an advanced form of DNA repair (Mitosomes) along with a blend of advanced ingredients that relieve puffiness and provide antioxidant protection. Copper Peptide Complex® technology continues to fight the signs of aging and help restore skin’s youthful texture. This new formulation still includes Haloxyl™ to help reduce the appearance of dark circles and also has the protection and regeneration properties of the advanced ceramides present in Skinmimics®.

Introduction
Wrinkles, puffiness, and dark circles under the eyes are not very desirable features for most people despite the fact that they are thought to be inevitable results of aging and environmental stress and damage. Wrinkles, of course, are caused in part by the natural slowdown of repair of the underlying extracellular matrix (ECM) of the skin. The resulting accumulation of fine lines, wrinkles, sagging skin, dark circles, and puffiness can add to an increased appearance of age.

The skin around the eyes is very delicate, thin, and susceptible to damage. Fine lines and crow’s feet are common in this area as the skin is thinner and everyday facial expressions make use of our eye area. Dark circles may be a result of any number of things: a highly pigmented skin condition inherited from family genetics, delicate blood vessels under the delicate eye skin leading to leakage of iron and other pigments.

DNA damage is a critical aftermath of UV irradiation due to sunlight exposure and contributes to many of the visible aspects of photoaging. Exposure to UVB causes the formation of thiamine dimmers. DNA damage can also come about during the normal process of cellular metabolism and respiration.

DNA repair refers to a collection of processes used by a cell to identify and correct damage to the DNA from either normal cellular processes or UV radiation. The DNA repair process is constantly active as the cells respond to damage in the DNA structure. The rate of DNA repair is dependent on many factors such as the type of cell, the age of the cell, and the cellular environment. If a cell accumulates a large amount of DNA damage with insufficient repair, it may become dormant (senescence), initiate programmed cell death (apoptosis), or start unregulated cell proliferation (cancer).

Eye Therapy now combines an advanced form of DNA repair (Mitosomes) along with a blend of botanical ingredients that relieve puffiness and provide antioxidant protection Copper Peptide Complex® technology continues to fight the signs of aging and help restore skin’s youthful texture. The formulation also continues to include the Haloxyl™ mixture to help reduce the appearance of dark circles along with the protection and regeneration properties of the advanced ceramides present in Skinmimics.

Copper Peptide Complex®
Copper is essential to vital cellular and enzyme processes required for human health, and is the third most abundant trace metal in the body, after iron and zinc. Since the 1830s, copper has been known to be an essential nutrient. It was found that copper plays a key role in several of the body’s essential enzyme systems needed for tissue repair and other biological responses. These copper-based enzyme systems allow tissue to repair itself, blood vessels to form, wounds to close and inflammation to decrease. Copper is now known to be critical to the normal repair and healing process in all tissue, including connective tissues that comprise human skin, internal organs and bones.

The Copper Peptide Complex in Eye Therapy is a tripeptide (glycyl-L-histidyl-L-lysine) complexed with copper. The tripeptide was originally isolated
from the albumin fraction of human serum\(^1\). It was subsequently shown that the peptide existed as the copper complex and enhanced the uptake of copper by cells\(^2^4\). The glycyll-histidyl-L-lysine peptide sequence is found in several proteins associated with the extracellular matrix including the large extracellular matrix protein termed SPARC and may liberated by endogenous proteolysis or cleavage of these proteins during the repair and regeneration processes\(^5^8\). These small peptides liberated from the extracellular matrix were termed matrikines.

Skin health, dermal wound healing, and general soft tissue repair requires many of the same biological processes such as reconstitution of an extracellular matrix and increased blood from (angiogenesis).

Copper is utilized by essentially every cell and organ; resulting in the formation of important copper-dependent enzymes - including cytochrome C oxidase (energy production), superoxide dismutase (antioxidation) and lysyl oxidase (cross-linking of elastin and collagen in skin)\(^9^\).\(^1\).\(^0\).

In numerous studies, copper peptides have been shown to promote new blood vessel growth, enhance the expression of growth factors, activate matrix metalloproteases, and stimulate the formation of new collagen, elastin, and glycosaminoglycan components of tissue to accelerate the repair process\(^1\).\(^5^\)-\(^1\).\(^7\).

More importantly, Copper Peptide Complex, formulated in a wide variety of cosmetic preparations, has show to both stimulate collagen production and to reduce the visible signs of aging, improve skin laxity, clarity, and appearance, reduce the appearance of fine lines and wrinkles, and to increase skin density and thickness both on the face and eye area\(^1\).\(^8^2\)-\(^2\).\(^1\).

As shown at right, the activities of copper and copper peptide are all essential to maintaining skin health and reversing the signs of aging.

<table>
<thead>
<tr>
<th>Activities of Copper and Copper Peptide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scientific Studies</td>
</tr>
<tr>
<td>Collagen</td>
</tr>
<tr>
<td>Glycosaminoglycans</td>
</tr>
<tr>
<td>Elastin</td>
</tr>
<tr>
<td>Angiogenesis</td>
</tr>
<tr>
<td>Growth Factors</td>
</tr>
<tr>
<td>Matrix Metalloproteases</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Performance Evaluations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collagen</td>
</tr>
<tr>
<td>Skin Laxity</td>
</tr>
<tr>
<td>Skin Clarity</td>
</tr>
<tr>
<td>Skin Appearance</td>
</tr>
<tr>
<td>Fine Lines &amp; Wrinkles</td>
</tr>
<tr>
<td>Skin Density</td>
</tr>
<tr>
<td>Skin Thickness</td>
</tr>
</tbody>
</table>

**Mitosomes**

Mitosomes contain a DNA repair enzyme that recognizes the most common form of oxidative damage to DNA and initiates the repair process. Mitosomes contain an enzyme (OGG1 for 8-oxoguanine DNA glycosylase 1) produced from the common plant Arabidopsis that recognizes this damaged base (8-oxo-guanine) and initiates its removal\(^2\).\(^2\)-\(^2\).\(^3\).

Mitochondrial DNA protection is also important to anti-aging activity. Damage from oxygen radicals is a main factor in aging. These reactive oxygen species come from pollutants in the environment, from UV-A induced reactions in skin, and from the body’s own stress responses. In addition, oxygen radicals are the inevitable side-effect of energy mitochondria. The accumulation of damage to mitochondria is considered an important element of aging.

These radicals damage DNA by oxidizing its nucleotide bases from to form 8-oxo-guanine. Mitosomes shorten the time for nucleus DNA repair from 24 hours to 2 hours, Figure 1 Mitosomes tested at 0.3% repair 75% of the oxidative damage on DNA. In vitro testing at 0.5% shows that Mitosomes repair DNA in the mitochondria.

In vitro testing has shown that 1% Mitosomes completely repaired 8-oxo-guanine in cells in 2 hours, while 0.3% completed repair in about 3 hours\(^2\).\(^2\).
A vital feature of the Mitosomes enzyme is that it also protects mitochondria. The enzyme has a “mitochondrial localization signal” (MLS), which is recognized by the cells transport system, and guides it into mitochondria. This ability allows Mitosomes to repair the DNA in mitochondria after oxidative damage which occurs during normal cellular respiration.

**Haloxyl™**

The dark rings under the eyes are both associated with the status of the underlying health of the vascular network which can lead to a bluish appearance to the skin if insufficient and to rings of a blackish-brown color due to local hyperpigmentation caused by cutaneous deposition of melanin or iron pigments leaked from fragile vessels. Haloxyl, a mixture of N-Hydroxysuccinimide, Chrysin, Palmitoyl Oligopeptide and Polmitoyl Tetrapeptide-7 was formulated to combat these dark rings through a combination of flushing of the pigments and strengthening of the vascular network.

Hemoglobin, released into the tissue from the red blood cells which have leaked from the fragile vessels, breaks down to form dark colored pigments in a manner similar to bruising. In the eye area, the clearing cycle for these pigments can be slow leading to accumulation and the dark rings. These hemoglobin pigments are normally eliminated by conjugation with glucuronic acid by a series of enzymes called UDP Glucuronosyl transferases (UGTs). In a similar manner, the iron component of the hemoglobin can accumulate in the tissue in large insoluble congregations.

The Haloxyl mixture contains two components to accelerate the clearance of the hemoglobin breakdown and iron associate pigments. First, Cyrysin, a common plant flavinoid, is added to activate the clearance by UGTs shown to be present in both fibroblasts and keratinocytes. Secondly, the N-Hydroxysuccinimide, a strong complexing agent for iron was added to break up the large insoluble congregations of iron compounds allowing their clearance. In in vitro studies, the addition of increasing concentrations of Haloxyl was shown to increase the activity of UGTs by up to 600%.

The other components of Haloxyl are a mixture of two matrikines. These two matrikines are Palmitoyl Oligopeptide (palmitoyl GHK or palmitoyl-glycyl-L-histidyl-L-lysine, the base peptide of GHK-Copper Peptide Complex) and Palmitoyl Oligopeptide-7 (Palmitoyl-GQPR or palmitoyl-glycyl-L-glutaminyl-L-prolyl-L-arginine, also known as Rigin). This mixture of these two matrikines is better known as Matrixyl™ 3000. The Palmitoyl Oligopeptide acts to restore collagen production while stimulating fibroblast cells in the skin, enabling them to significantly reduce the appearance of wrinkles and maintain skin’s youthful appearance. Rigin is a synthetic peptide that is a fragment of immunoglobulin G which has been combined with palmitic acid to make it more lipophobic and thus enhance its affinity towards human skin. In vitro, palmitoyl-GQPR induces a marked dose-dependent reduction in interleukin production. UV radiation is known to accelerate interleukin production. When cells are exposed to UV radiation and then Pal-GQPR, there is an 86% reduction of interleukin production which would result in less inflammation and damage. The combination
of Palmitoyl Oligopeptide and Palmitoyl Oligopeptide-7 have been shown to reduce the depth of wrinkles by 45% after 2 months.\textsuperscript{25}

**Skinmimics\textsuperscript{®}**

Skinmimics was designed to provide a combination of protection, prevention, and regeneration cosmeceutical actives in the form of ceramide technology.\textsuperscript{26} It is a mixture of long chain ceramides, cholesterol, and Sphingokines\textsuperscript{®} signaling molecules. It has been reported that the mixture of Caprooyl-Phytosphingosine and Caprooyl-Sphingosine, components of the Skinmimics mixture, trigger the expression of genes for late-stage epidermal differentiation to enhance the synthesis of key sphingolipids in cultured keratinocytes. Similar results have been reported in studies with volunteers following application of the Skinmimics formulation. A significant reduction in TEWL (Transpidermal Water Loss) and an increase in skin elasticity has been measured. These evaluations confirm that the application of Skinmimics will help mature skin be revitalized through the combination of protection, prevention, and regeneration.

**Summary**

Eye Therapy combines an advanced form of DNA repair (Mitosomes) along with a blend of advanced ingredients that relieve puffiness and provide antioxidant protection. Copper Peptide Complex technology continues to fight the signs of aging and help restore skin's youthful texture. Mitosomes contain an enzyme (OGG1 for 8-oxoguanine DNA glycosylase 1) produced from the common plant Arabidopsis that recognizes damaged DNA bases (8-oxo-guanine) and initiates its removal. This new formulation continues to include Haloxyl to help reduce the appearance of dark circles under the eyes. Eye Therapy also has the protection and regeneration properties of the advanced ceramides of Skinmimics, mixture of long chain ceramides, cholesterol, and Sphingokine signaling molecules. This mixture of Caprooyl-Phytosphingosine and Caprooyl-Sphingosine, are reported to trigger the expression of genes for late-stage epidermal differentiation to enhance the synthesis of key sphingolipids in cultured keratinocytes.

**References**


Neova and GHK Copper Peptide Complex are registered trademarks of Procyte Corporation.

Haloxyl and Matrixyl are trademarks of Sederma. Skinmimics and Sphingokines are registered trademarks of Goldschmidt GmbH/degussa.