

LE Magazine January 2007

## On The COVER

### Scientifically Advanced Skin Care

#### Innovative Nutrients to Revitalize Your Skin

By Dave Tuttle



Your face is one of your most precious assets. Sadly, as we age, most people will display a face ravaged by time, free-radical damage, and excessive sun exposure. While you may feel young and vibrant, your face can communicate a very different state of affairs.

Each year, billions of dollars are spent on skin creams that make wild promises unsupported by scientific research. New skin care products trumpet “anti-aging, anti-wrinkle ingredients,” but in most cases, few if any of these ingredients have undergone rigorous testing and validation.

However, in laboratories around the world, scientists are testing new ingredients that reinforce the skin’s underlying architecture, limit the destructive impact of photoaging, and even activate genes that encourage nourishment and repair of the skin’s vital matrix. By reducing oxidative stress, restoring moisture, repairing signs of photoaging, and promoting healthy supportive tissues, these

topical agents can literally turn back the clock on skin aging.

Daily use of topical creams that incorporate clinically proven ingredients—complemented by a program of regular exercise, restful sleep, nourishing diet, and supplementation with powerful natural antioxidants—can reverse unsightly skin aging and help restore healthy, vibrant, youthful-looking skin.

#### **MATRIXYL™ 3000, CERAMIDES REDUCE SKIN WRINKLING**

To help aging baby boomers actively restore the youthful look of their skin, researchers have developed powerful new ingredients that take the science of skin care to a new level. Two of these promising new agents are Matrixyl™ 3000 and ceramides.

Matrixyl™ 3000 is a unique ingredient that consists of peptides, or short amino acid chains. It helps to lift the skin, thus minimizing the appearance of wrinkles. Matrixyl™ 3000 contains two different peptides, known as matrikines, that act as cellular messengers to promote skin restructuring and repair. These biochemicals interact with specific receptors to activate genes that are involved in cell proliferation and renewal of the collagen-rich extracellular matrix (the connective tissue between cells that provides crucial support to the skin). Both healthy cells and the extracellular matrix are essential to firm, healthy skin.<sup>1</sup> The components of Matrixyl™ 3000 work synergistically to help restore and maintain the skin’s youthful appearance.



When cells that produce collagen and elastin were incubated for 72 hours with Matrixyl™ 3000, they synthesized significantly greater amounts of extracellular matrix, the protein-rich skeleton that provides structural support to skin. Enhancing the extracellular matrix helps “plump up” the skin, minimizing the appearance of wrinkles and creases. A clinical trial with 46 volunteers, aged 39-74, demonstrated the visible effects of Matrixyl™ 3000. After eight weeks of two daily applications of Matrixyl™ 3000, the participants had average reductions of 14% in skin roughness and 15% in wrinkle depth, while the surface occupied by deep wrinkles declined by 45%. An assessment of skin tone showed a 20% improvement during the same time frame.<sup>2</sup>

Another innovative ingredient for restoring youthful skin is a high concentration of ceramides, or lipids similar to those found in cell membranes and brain tissues. These lipids are essential in maintaining the protective functions of the skin’s outermost layer, known as the stratum corneum.<sup>3</sup> Ceramides play an important role in generating and sustaining the water permeability barrier in the skin.<sup>4</sup> As such, they are important for improving skin hydration, reducing susceptibility to irritation, and restoring skin

integrity.<sup>5</sup> Youthful skin is noticeably bright and glowing largely because it is well hydrated. Unfortunately, ceramide concentrations in the skin decline with age, leading to dry, rough skin.<sup>6</sup> Topical application of ceramides has been shown to capture and bind water, which is required for the skin to remain supple, smooth, and hydrated.

Matrixyl™ 3000 and ceramides are innovative new compounds that work in synergy with the skin's known physiology to help maintain and restore smooth, supple skin.<sup>7</sup>

## THE ANATOMY OF SKIN AGING

The skin is the body's largest organ and one of its most complex, comprising multiple layers of epithelial tissues that protect underlying muscles and organs. The skin protects against pathogens, provides insulation, temperature regulation, and sensation, and helps synthesize vitamin D.

The skin's outermost layer, known as the epidermis, provides a waterproof barrier against the external environment. The epidermis largely comprises keratin, a fibrous protein made by keratinocyte cells, and melanin, the skin's main pigment, which is produced by melanocyte cells.

Below the epidermis is the dermis, which provides essential support to the epidermis. In addition to nerves and glands, the dermis contains essential proteins called collagen and elastin. Collagen is the skin's main supportive protein, while elastin provides the skin with flexible elasticity. Helping to provide moisture to the skin are essential lipids and glycosaminoglycans, which are large, sugar-like molecules that bind with water.

Years of cumulative free-radical damage can induce dramatic changes in the skin's health and appearance. The epidermis becomes less capable of tissue repair and renewal.<sup>13</sup> Collagen becomes sparser and less soluble.<sup>13-15</sup> Elastin fibers are slowly degraded and damaged, and areas of sun-damaged skin accrue abnormally structured elastin.<sup>15,16</sup> Glycosaminoglycans can no longer properly interact with water, while lipid content decreases with age.<sup>15,16</sup>

The end result of these many age-related changes is skin prone to wrinkling, dryness, sagging, decreased flexibility, dullness, and poor healing responses.

## IDEBENONE FIGHTS PHOTOAGING, IMPROVES SKIN HEALTH

As adults age, their skin is more likely to exhibit the effects of photoaging, which produces negative changes in skin color, texture, and health caused by cumulative exposure to ultraviolet light. New findings suggest that antioxidant-rich, high-energy compounds may help defend against the effects of photoaging.

Free radicals damage not only proteins and DNA, but also the skin's surface lipids. Made up of a complex mixture of sebum (an oily substance produced by the sebaceous glands) and small amounts of epidermal lipids, these surface lipids provide the body's outermost protection against oxidative damage.<sup>8,9</sup>

Coenzyme Q10 (CoQ10) is a fat-soluble antioxidant that helps prevent free-radical damage to the skin's surface lipids. However, CoQ10 concentrations in skin decline significantly in older people.<sup>9</sup> The loss of this protective nutrient is a likely cause of the increased incidences of skin diseases and photoaging seen in aging adults.

In fact, an eight-year Italian study found a direct link between CoQ10 levels and the progression of melanoma, the deadliest of skin cancers.<sup>10</sup> Not only were CoQ10 concentrations in people with melanoma lower than in healthy subjects, but patients whose cancer spread (metastasized) to other tissues had CoQ10 levels below those of the metastasis-free subgroup. Clearly, CoQ10 is an important protective nutrient for aging skin.

Recognizing the importance of CoQ10 in skin health, scientists searched for related compounds that can confer even greater benefits to the skin. This search led to idebenone, a nutritional cousin, or analogue, of CoQ10. Since idebenone is a smaller molecule than CoQ10, it is better suited to penetrating the skin, where it can confer important protective effects.<sup>11</sup>

Idebenone has been shown to produce clinically visible improvements in photodamaged skin. In a study of 41 female subjects aged 30-65, applying idebenone to the face in the morning and evening for six weeks reduced skin roughness and dryness by 26%, and decreased fine lines and wrinkles by 29%.<sup>12</sup> The subjects also exhibited a 37% increase in skin hydration and a 33% overall improvement in assessment for photodamaged skin. These improvements were primarily seen in the epidermis, though there was some increase in dermal collagen as well. Skin biopsies revealed decreased levels of an inflammatory protein, a change associated with the stimulation of collagen production. Topically applied idebenone thus improves numerous markers of skin health while reducing the visible signs of aging.

Idebenone may protect the skin through its potent antioxidant effects.<sup>12</sup> One research team studied various antioxidants to gauge their protective effects against oxidative stress. They found that idebenone was the most effective antioxidant studied, providing more protection than CoQ10, vitamin E, kinetin, vitamin C, or lipoic acid.<sup>17</sup> This antioxidant quality allows idebenone to inhibit lipid peroxidation, thus protecting skin cell lipids and membranes.<sup>18</sup>

Topical use of idebenone represents an important step forward in scientifically based skin care. Through its antioxidant effects, idebenone helps protect skin from the effects of oxidative stress and photoaging, restoring moisture, refining texture, reducing fine lines and wrinkles, and promoting a more youthful appearance.



### POMEGRANATE NATURALLY ENHANCES SKIN RENEWAL

An ancient fruit with many modern health-promoting applications, pomegranate is best known for its strong antioxidant properties.<sup>19</sup> This is due to its high concentration of phenolic compounds, such as ellagic acid.<sup>20</sup> In addition to its applications in supporting cardiovascular health and protecting against cancer, pomegranate has now demonstrated multiple benefits as a topical skin treatment.

Pomegranate may help reverse visible signs of aging by promoting a moderate thickening of the epidermis, while maintaining healthy epidermal cell differentiation.<sup>21</sup> The fruit extract also prolonged the life of cells in the dermis known as fibroblasts. Fibroblasts produce the skin's essential structural fibers, including collagen and elastin. Pomegranate thus promotes regeneration of cells in the two most important layers of healthy skin, the epidermis and dermis.

### REVERSE SKIN AGING NATURALLY: WHAT YOU NEED TO KNOW

- The skin is highly susceptible to free-radical-induced damage due to aging and exposure to environmental stressors. Skin damage that occurs from excessive exposure to ultraviolet light is known as photoaging.
- Skin aging manifests as wrinkles, sagging skin, rough texture, decreased moisture content, impaired wound healing, and discoloration.
- Restoring the skin's youthful appearance requires repairing free-radical-induced damage, providing antioxidant protection, restoring moisture content, supporting production of collagen, elastin, and keratin, and enhancing the skin's healing mechanisms.
- Matrixyl 3000™ and ceramides are innovative new ingredients that hydrate and plump the skin to reduce wrinkles and restore smooth, youthful skin.
- Glycolic acid helps reduce wrinkles, eliminate discoloration, and speed the healing of sun damage. Hyaluronic acid helps ensure adequate skin moisture content and enhances the skin's healing capacity.
- Research has validated that topical antioxidants—including idebenone, pomegranate, green tea, and vitamins E and C—fight photoaging, lessen fine lines, and may protect against skin cancer.

As the skin ages, its ability to quickly heal cuts, abrasions, and other wounds is dramatically diminished. A study from India discovered that the high content of phenolic compounds in pomegranate greatly improves wound-healing activity, significantly reducing the number of days required for complete healing of skin wounds.<sup>22</sup>

A Japanese study found that ellagic acid potently suppresses lipid peroxidation in the skin, thus helping to guard against damage from ultraviolet radiation.<sup>20</sup> An Israeli research team noted that pomegranate's antioxidant activity was similar to that of green tea and much greater than that of red wine.<sup>23</sup> The researchers also found that pomegranate demonstrates robust anti-inflammatory effects by inhibiting a biochemical pathway that fuels inflammatory changes.<sup>23</sup>

Pomegranate may also help to protect against skin cancers. Numerous studies have found that topically applied pomegranate seed and fruit extracts significantly reduce the incidence and number of skin tumors that form in experimental models of skin cancer.<sup>24,25</sup>

By protecting against photoaging, supporting skin cell regeneration, promoting wound healing, and preventing cancerous changes, pomegranate provides broad-spectrum support for aging skin.





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#### **GREEN TEA POLYPHENOLS: POWERFUL ANTIOXIDANT PROTECTION**

Green tea is one of the world's most popular beverages, particularly in Asian countries like China, Korea, Japan, and India. Green tea is valued for its many contributions to whole-body health, and emerging research demonstrates that green tea benefits the skin as well as the rest of the body.

Green tea leaves contain polyphenols that are recognized as potent antioxidants and effective scavengers of free radicals. These include a variety of catechins, the most important of which is epigallocatechin-3-gallate (EGCG).<sup>26</sup>

Numerous studies have shown that topical application of green tea confers broad-spectrum protection against photodamage, one of the leading causes of visibly aged skin. Polyphenols from green tea leaves have been found to protect against the adverse effects of overexposure to ultraviolet light.

#### **MITOCHONDRIAL DYSFUNCTION CONTRIBUTES TO SKIN AGING**

Scientists have long known that aging is associated with declining function of the mitochondria, the cellular power plants that produce energy to fuel the body.<sup>43</sup> Mitochondrial dysfunction has been linked with diverse conditions such as neurodegenerative diseases and cancer.<sup>44</sup> Emerging research suggests that impaired mitochondrial energy production plays an important role in another condition associated with advancing years: aging of the skin.<sup>45</sup>

Essential to youthful, healthy skin are cells called fibroblasts. Fibroblasts produce the essential proteins known as collagen and elastin, which provide structural support and elasticity to the skin. In aging adults, however, fibroblast cells demonstrate dramatic mitochondrial dysfunction.<sup>45</sup> As a result, fibroblasts are less able to produce the energy required to carry out their essential skin-supporting functions. Scientists believe that this energy deficit of essential skin cells contributes to the visible signs of skin aging.<sup>8,9</sup>

The fat-soluble antioxidant coenzyme Q10 is widely used to counteract the decline in mitochondrial energy production that accompanies aging.<sup>45</sup> Scientists have discovered that both oral and topical use of CoQ10 restores deficient CoQ10 levels in skin cells.<sup>46</sup> Oral and topical CoQ10 may thus help to counteract one of the underlying contributors to skin aging: impaired mitochondrial energy production. CoQ10's nutritional cousin, idebenone, also supports mitochondrial energy production,<sup>18</sup> while demonstrating enhanced absorption through the skin.<sup>11</sup> Idebenone may thus play an essential role in counteracting skin aging due to impaired cellular energy production.

For example, in a study at Case Western Reserve University, volunteers had areas of their skin treated with a green tea extract.<sup>27</sup> Thirty minutes later, they were exposed to simulated solar radiation at a dose high enough to produce inflammatory redness, or erythema. The portions of the skin treated with green tea extracts had a reduced number of sunburn cells, and immune cells just below the skin surface were protected from the effects of the radiation. Green tea extract also protected against radiation-induced DNA damage. The researchers concluded that green tea polyphenols are effective in averting many of the detrimental effects of sunlight, and may thus serve as natural photoprotective agents.<sup>27</sup> The photoprotective benefits of topical green tea have also been reported in other studies as well.<sup>28-30</sup>

A study from Korea found that when EGCG is topically applied to aged human skin, it stimulates the proliferation of epidermal keratinocytes, which increased the thickness of the epidermis.<sup>26</sup> EGCG also inhibited the death of the keratinocytes after a period of exposure to ultraviolet radiation, thus conferring important photoprotection.

When topically applied or consumed orally, green tea polyphenols enhance cells' protective responses to inflammation and various chemicals that promote tumor growth. At the same time, these phytochemicals prevent ultraviolet B-induced oxidative stress and immune system suppression.<sup>31</sup>

By countering the effects of ultraviolet light and other cancer-inducing agents, green tea provides crucial protection to delicate skin tissues.

## GLYCOLIC, HYALURONIC ACIDS AID SKIN TEXTURE, APPEARANCE

As people grow older, they often notice that their skin becomes dry and discolored. Glycolic acid and hyaluronic acid may help to alleviate these signs of skin aging.

Derived from sugar cane, glycolic acid is considered the most powerful of the skin-rejuvenating fruit acids called alpha-hydroxy acids. Glycolic acids helps trap moisture in the skin, promote collagen formation, and release the buildup of dead skin cells to reveal brighter, younger-looking skin. Widely used as an anti-aging agent for the skin, glycolic acid has demonstrated its efficacy in numerous studies.

In a three-month study, people who applied topical glycolic acid to the face and neck demonstrated improvements in all assessments of photoaging, including statistically significant gains in general skin texture, color, and wrinkle reduction.<sup>32</sup> A six-month study with 65 participants noted an average 27% increase in epidermal thickness in those who used a daily topical glycolic acid cream.<sup>33</sup>



A study at Yale Medical School also found that applying a glycolic acid cream before exposure to ultraviolet B light helped protect the skin against inflammation and redness (erythema) from sunburn. Daily application of glycolic acid for seven days after sun exposure reduced redness and inflammation by 16%.<sup>34</sup> This effect suggests that glycolic acid confers antioxidant effects in the skin.

Another important and innovative ingredient in skin care is hyaluronic acid. A large sugar-like molecule found in every tissue of the body, hyaluronic acid is particularly important to the skin's extracellular matrix, where it attracts and binds with water and its gel-like structure provides volume and fullness for the skin. Hyaluronic acid is thus crucial for maintaining smoothness and moisture in the skin.<sup>35</sup>

Hyaluronic acid also stimulates wound healing and helps protect wounds from free-radical damage. A study at the Wound Healing Center in Brescia, Italy, revealed that topically administered hyaluronic acid permeates the skin and provides powerful antioxidant protection against free radicals.<sup>36</sup> This bolsters the skin's ability to heal from cuts and abrasions.

Glycolic and hyaluronic acids thus provide crucial antioxidant protection to the skin, restoring healthy texture, color, and moisture content.

## VITAMINS C AND E DEFEND AGAINST FREE RADICALS

Since the skin can easily be overwhelmed by free-radical-induced oxidative stress, ensuring broad-spectrum antioxidant protection is crucial in fighting skin aging. Decades of research have shown that vitamin E and vitamin C are especially important in preserving and restoring skin health.

Vitamin E is the primary naturally occurring antioxidant in the stratum corneum, the outermost layer of the epidermis. Composed primarily of alpha-tocopherol, this vitamin provides the bulk of our first-line defense against free radicals.<sup>37</sup> As a result, tocopherol depletion is a very early and sensitive biomarker of environmentally induced oxidative stress. Under such conditions, topical application of antioxidants can support the physiological mechanisms that maintain or restore a healthy skin surface.<sup>38</sup>

An experiment at the University of California, Berkeley, found that ultraviolet radiation significantly decreases concentrations of vitamin E in the skin.<sup>39</sup> However, when vitamin E-rich oil was applied before the skin was subjected to radiation, much higher concentrations of vitamin E were preserved. This suggests that topical use of vitamin E can help maximize its concentration in the skin, helping to fight free radicals generated by solar radiation and other environmental stressors.

In a double-blind study, a topical vitamin C complex was applied to one half of the face and a placebo gel to the opposite side. Clinical evaluation of wrinkling, pigmentation, inflammation, and hydration was performed prior to the study and at weeks 4, 8, and 12. The results showed a statistically significant improvement of the vitamin C-treated side, with decreased photoaging scores of the cheeks and the peri-oral area. The overall facial improvement of the vitamin C side was statistically significant. Biopsies showed increased collagen formation in the vitamin C group. This study demonstrated that topically applied vitamin C results in clinically visible and statistically significant improvement in wrinkling when used for 12 weeks. This clinical improvement correlated with biopsy evidence of new collagen formation.<sup>40</sup>

A randomized, double-blind, controlled study was conducted on human volunteers to determine the efficacy of topical vitamin C application in treating mild-to-moderate photodamage of facial skin. Methods of evaluating efficacy included an objective, computer-assisted image analysis of the skin surface, subjective clinical photographic analysis, and a patient self-appraisal questionnaire. Topical vitamin C was applied to one side of each patient's face and a control vehicle on the other side for three months.<sup>41</sup>

The results using the optical image analysis demonstrated that compared to the placebo vehicle, the vitamin C-treated side of the face showed a statistically significant 71% combined score improvement. Clinical assessment parameters demonstrated significant improvement with vitamin C treatment compared to the placebo vehicle for fine wrinkling, tactile roughness, skin laxity/tone, sallowness/yellowing, and overall features. Patient questionnaire results demonstrated statistically significant improvement overall with the vitamin C treatment (84% greater than control). Photographic assessment demonstrated significant improvement with vitamin C treatment (58% greater than control). This three-month study using topical vitamin C provided objective and subjective improvements in photodamaged facial skin.<sup>41</sup>



A study of vitamins C and E in young, aged, and photodamaged human skin sought to ascertain the various levels of these antioxidants in each skin type. The findings showed that the concentration of vitamin E was significantly lower in the epidermis (upper layer) of photoaged skin (56% lower than in young skin) and aged skin (61% lower than in young skin). There was no difference in vitamin E levels in the dermis of each skin type. In photoaged skin, vitamin C levels were 69% lower in the epidermis and 63% lower in the dermis; in naturally aged skin, vitamin C levels were 61% lower in the epidermis and 70% lower in the dermis. Glutathione concentrations were also lower compared to young skin. These results show that the antioxidant defense systems in normal aged and photoaged human skin are significantly diminished compared to young skin.<sup>42</sup>

Vitamin E and vitamin C thus work together to provide antioxidant protection, support collagen synthesis, and reduce wrinkling of the skin.

## CONCLUSION

The skin's complex structure is vulnerable to free-radical-induced stress that manifests over time as wrinkles, dryness, thinning, and discoloration. Fortunately, innovative topical skin care agents help fight the signs of photoaging while restoring moisture, minimizing wrinkles, and improving the overall texture, health, and appearance of the skin.

Diligent daily use of topical nutritional and botanical agents such as Matrixyl™ 3000, ceramides, glycolic acid, hyaluronic acid, idebenone, pomegranate, green tea, and vitamins E and C can help preserve and enhance skin quality. Advanced topical skin care should thus be considered an important component of a comprehensive anti-aging strategy, with the added benefit of producing highly visible results in a matter of only weeks or months.

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