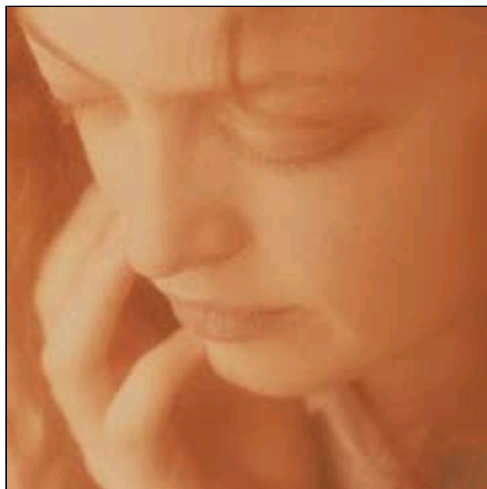


COVER STORY

Combating Skin Aging



The concept of controlling human aging remains controversial. No one disagrees, however, that individuals can significantly influence the rate at which their skin ages.

For instance, if a person wants to accelerate skin degradation, all they have to do is expose themselves to lots of ultraviolet radiation, cigarette smoke, and ethanol. Even second-hand cigarette smoke prematurely ages the skin.

Factors that induce skin damage involve the excessive production of free radicals. Protecting against these free radical insults is a proven way to slow the effects of aging.

Recently published papers confirm that a decline in natural antioxidant systems is a key factor responsible for the unsightly appearance of aged skin.

The ultimate question becomes: Can the application of topical antioxidants to the skin's surface induce a noticeable anti-aging effect? This article reveals novel findings made by research scientists working on the front lines in the battle to prevent and reverse skin aging.

The skin, as the outermost barrier of the body, is exposed to various sources of oxidative stress, in particular UV-irradiation and environmental toxins such as cigarette smoke, air pollution, etc. Internally, the skin is attacked like any other organ, through processes involving glycation (protein cross-linking), collagen-elastin degradation and free radical-induced injury.

One way of mitigating this process is to increase levels of protective antioxidants through a diet rich in fruits and vegetables or by direct topical application. Indeed, various animal and human studies have proved that topically applied antioxidants, especially vitamins C and E, as well as alpha lipoic acid exert protective effects against free radical damage (oxidative stress).¹

Free radicals form in skin upon ultraviolet exposure. Acute and chronic photo radiation damage depletes the body's natural antioxidant enzyme systems and increases oxidative protein modifications (cross-links). These pathological effects are found in the upper and lower layers of the skin. Cross-linked (glycated) proteins are classic characteristics of skin aging. Cross-linked proteins in the skin result in stiffening, wrinkling and the unsightly leathery appearance.²

New studies confirm efficacy of topical antioxidants

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 showed 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.³

Human studies have demonstrated pronounced protective effects of antioxidants when applied topically before ultraviolet radiation exposure. With respect to UVB-induced skin damage, the photoprotective effects of antioxidants are significant. Topical application of such combinations may result in a sustained antioxidant capacity of the skin, possibly due to antioxidant synergisms. Free radicals are a culprit behind UVA-induced skin alterations, thus indicating a basis for topical antioxidant administration. In a human study, topical application of antioxidants resulted in diminished severity of UVA-induced sun damage. Thus, regular application of skin care products containing antioxidants may be of the utmost benefit in efficiently preparing skin against exogenous oxidative stressors

**ORALLY INGESTED
NUTRIENTS IMPROVE SKIN
APPEARANCE**

It is well known that destructive alterations in collagen, elastin and glycosaminoglycans contribute to degenerative changes seen in aging

occurring during daily life. Sun screening agents may also benefit from combination with antioxidants resulting in increased safety and efficacy of such photoprotective products.⁴

Collagen is the chief constituent of connective tissue that supports the structure of the skin. The skin requires constant synthesis of new collagen to remain firm and youthful. Epidemiological studies strongly indicate an association between tobacco smoking and skin aging. One study showed that collagen biosynthesis was reduced by 40.1% following treatment with tobacco smoke extract. When an antioxidant mixture that included vitamins C and E were applied, the destructive alteration of collagen induced by both tobacco and UVA radiation was prevented.⁵

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, along with patient self-appraisal questionnaires. Topical vitamin C was applied to one side of each patient's face and a control vehicle on the other side for three months.

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 84.2% greater than control. Photographic assessment demonstrated significant improvement with vitamin C treatment 57.9% greater than control. This three-month study using topical vitamin C provided objective and subjective improvement in photodamaged facial skin.⁶

Considerable interest has been generated about combining antioxidants with sunscreens to provide enhanced protection against UV rays. Two of the best-known antioxidants are vitamins C and E, both of which have been shown to be effective in different models of photodamage. In a study done on swine skin, vitamin C provided additive protection against acute UVB damage (sunburn cell formation) when combined with a sunscreen. When a combination of vitamins E and C were used, very good protection from a UVB insult occurred. Vitamin C, however, was significantly better than vitamin E at protecting against a UVA-mediated phototoxic insult in this animal model.⁷

A study of vitamin C and E in young, aged and photodamaged human skin was conducted to evaluate the various levels of these antioxidants. Compared to young skin, the concentration of vitamin E in the epidermis of photodamaged skin was 44% lower, while aged skin had 39% less vitamin E. There was no difference in the dermis. Vitamin C levels were 31% lower in the epidermis of photodamaged skin and 39% lower in aged skin, while in the dermis region, vitamin C levels were 37% lower in photodamaged skin and 30% lower in aged skin. Glutathione concentrations were also lower. These results showed that the antioxidant defense system in normal aged and photoaged human skin is significantly reduced compared to young skin.⁸

Chronic inflammation is an underlying cause of common degenerative diseases. One study found that pro-oxidative factors that accelerate skin aging might activate a self-maintained micro-inflammatory process that interferes with skin elasticity and thickness. This study stated that topical antioxidants decrease this inflammatory cascade and thus afford protection to the skin structures.⁹

The effect of exposure to even ambient UV-irradiation increases the risk for long term detrimental effects characterized by wrinkles, loss of skin tone and resilience. Photoaged skin displays prominent alterations in the cellular component and the extra cellular matrix of the connective tissue. UV-exposure results in an accumulation of disorganized elastin and a severe loss of collagens, the major structural proteins of the dermal connective tissue. The unifying pathogenic agents for these changes are UV-generated free radicals. As well as causing permanent gene mutations, free radicals activate signal transduction pathways that are related to growth, differentiation, senescence and connective tissue degradation.¹⁰

Critics used to claim there was no evidence that topically based products affected skin aging. Over the past three years, a remarkable number of published studies have proven these skeptics wrong! The science clearly substantiates the role that free radicals play in causing skin aging and the fact that topically applied antioxidants confer significant protection and can even partially reverse some aspects of skin aging.

skin. A randomized, controlled study was conducted with 53 female volunteers who were supplied with an oral supplement containing glucosamine, amino acids, minerals and various antioxidant compounds. Hydration properties of the skin as well as textural analysis of the women's fine lines and wrinkles were assessed following five weeks intake of the oral supplement and results were compared with those of a control group of 12 individuals who did not take the supplement.

The results showed a statistically significant reduction in the number of visible wrinkles and a reduction in the number of fine lines in the group of women who took the supplement.

This study showed that an oral supplement containing glucosamine, minerals and various antioxidant compounds can potentially improve the appearance of visible wrinkles and fine lines. It did not, however, affect epidermal hydration. Topically applied agents are usually required to keep aging skin moist.*

* Murad H, et al. The effect of an oral supplement containing glucosamine, amino acids, minerals, and antioxidants on cutaneous aging: a preliminary study. *J Dermatolog Treat* 2001 Mar;12(1):47-51.

Vitamin A and its retinoid analogs stimulate skin cell renewal by increasing the rate of mitotic cell division.¹¹⁻¹³ One mechanism where vitamin A induces this phenomenon is to act as a signaling agent to stimulate the binding of epidermal growth factor to skin cells.¹²

**MEDICAL SCHOOL
SAYS "EVERYONE"
SHOULD APPLY
TOPICAL PHOTOPROTECTANTS**

A report released from Tulane University School of Medicine stated "every patient should topically apply photoprotectants in order to prevent photodamage to the skin."¹⁴ This report indicates the critical importance of applying a sunscreen with antioxidants every time you go out into the sun.



* Flynn TC, et al. Topical revitalization of body skin. J Eur Acad Dermatol Venereol 2000 Jul;14(4):280-4.

A characteristic of sun-damaged skin is the degradation of the supporting structure of skin caused by reduced collagen synthesis. A study involving 72 individuals of varying age groups was done to see if the topical application of natural vitamin A could improve function in both natural aged, sun-protected and photoaged skin. In one of the study groups consisting of individuals (80+ years of age), topical application of vitamin A for seven days increased fibroblast growth and collagen synthesis, while reducing levels of a collagen degrading skin enzyme (metalloproteinase). The overall findings indicated that naturally aged, sun-protected and photoaged skin share important molecular features including connective tissue damage, elevated metalloproteinase levels and reduced collagen production. Topical vitamin A treatment reduced matrix metalloproteinase expression and stimulated collagen synthesis in naturally aged and sun-protected skin, as it does in photoaged skin.¹⁴ Synthetic vitamin A drugs (Retin-A) have shown more profound acute effects in reversing both photo damaged and naturally aged skin, but some people find these drugs irritating to the skin.¹⁵

One of the most disfiguring skin diseases is the appearance of cancer. A study was done to compare the effects of dietary administration of a vitamin A drug (13-cis-retinoic acid) to the natural form of vitamin A (retinyl palmitate). Female mice were administered a chemical carcinogen to evaluate the incidence and severity on mouse skin tumor promotion. The results showed that retinyl palmitate inhibited the number and weight of tumors, whereas 13-cis-retinoic acid resulted in a decrease in weight, but not in the number of tumors promoted.¹⁶

In another study, tumors were chemically induced in a group of Swiss mice over a 23-week period. The topical application of 13-cis-retinoic acid was compared to natural vitamin A (retinyl palmitate). This study showed that both retinyl palmitate and 13-cis-retinoic acid inhibited the development of skin papillomas and also had a marked effect on skin cancers.¹⁷ Vitamin A may be one of the better-documented vitamins to protect against several types of human cancers. One of its mechanisms is to induce healthy differentiation and apoptosis of aged cells. The value of vitamin A in protecting the skin is to help facilitate cell renewal and possibly prevent skin cancers.

Studies show that the upper layer of the skin (epidermis) can be easily loaded with natural vitamin A by topical application. Besides being a precursor for retinoic acid, vitamin A also has a free radical scavenging potential. Vitamin A absorbs ultraviolet light to help protect the most delicate areas of the skin against damaging free radical attack.¹⁸ Natural vitamin A thus functions via several pathways to guard against normal and sun-induced skin aging.

Continued on Page 2 of 2

COVER STORY

Combating Skin Aging

Going beyond antioxidants

While free radicals have been implicated in much of the damage that occurs to aging skin, there are other injurious factors that result in unsightly structural and functional deterioration.

KEEPING THE SKIN WELL OILED

Nourishing the skin with topical ingredients is important, but in addition it is essential that you feed your skin nourishing food and drink. That means consuming lots of purified water and minimizing ethanol intake. Aging causes a progressive decline in our ability to internally synthesize the essential fatty acids required by the skin to maintain a youthful, moist appearance. Omega-3 fatty acids can make the skin smoother, softer and look more radiant. When skin is properly nourished, it shows less of the effects of aging. The oral ingestion of fish, flax or perilla oil provides abundant quantities of the omega-3 fatty acids that are so beneficial to the health and appearance of the skin.



(dimethylaminoethanol) was shown to produce a firming effect on the skin. This mechanism may be due to the fact that DMAE functions as a cell membrane stabilizer. Based on clinical reports, DMAE may be the first topical agent that can help firm sagging skin.

Keeping the skin moist

Replacing moisture lost to aging is a prime reason why women use face creams. Most commercial face creams are oil-based and work by blocking the release of water from the skin.

For instance, aging skin cells suffer from metabolic imbalances that preclude them from performing youthful repair functions. The groundbreaking work of Benjamin S. Frank, M.D. showed that RNA improved cellular energy and the ability of the skin's cells to use oxygen. This improved metabolism enhances the movement of young cells to the surface of the skin where they replace old cells.

Another benefit from topically applied RNA is to repair early skin cell damage. Clinical trials by Dr. S.J. Jellinek in the 1970s demonstrated how creams containing RNA/DNA caused a visible lifting/tightening of the skin, and the wrinkles appeared to be less visible in a three-week period. Although the study was a small-scale study, it was nonetheless a double blind test. Very few commercial products provide the potency of RNA and DNA used in these studies.

Glycolic acid is a potent alpha-hydroxy acid that has been shown to erase fine wrinkles in aging human skin. The mechanism of action of glycolic acid is to break down old cells at the skin's surface so they can be replaced with more youthful cells underneath. A 22-week, double-blind, randomized clinical trial at Massachusetts General Hospital in 74 women over age 40 showed that topically applied alpha-glycolic acid significantly reduced wrinkling and other types of damage caused by chronic sun exposure. An alpha-hydroxy acid should be included as a constituent of any anti-aging topical program.

A study in the *Journal of Pharmacology and Biophysical Research* showed that ginkgo biloba extract signals fibroblast activity in the skin to increase the synthesis of collagen, while serving as an anti-inflammatory agent. Topical application of ginkgo extract has been found to reduce the irritation that some people experience when using products like Retin-A and highly concentrated fruit acid compounds.

One of the major problems of advanced aging is the sagging of tissues caused by the destruction of the skin's underlying support structure (primarily collagen and elastin). While much of this structural deterioration may be preventable by lifestyle changes and proper use of oral and topical agents, it is difficult to reverse this unsightly collapse of facial tissues. In a study published in *Skin Research Technologies*,¹⁹ DMAE

THE IMPORTANCE OF MAINTAINING HEALTHY SKIN

Our skin is the largest organ in the human body weighing approximately ten pounds and covering an area of about 16 sq. ft. People often take skin for granted and tend not to take optimal care of it. Our skin is responsible for protecting our internal organs from the toxic external world. Our skin protects us from heat, cold and physical injuries. It also provides us with sensory information about the nature of the external world, and is our first defense against invasion by bacteria, viruses and other toxic elements. The skin is also an excretory organ, removing toxins from the body via perspiration.

As people grow older, however, they cannot rely on oil-based preparations to block the release of moisture. That is because aged skin loses the ability to attract moisture in the first place and fundamentally becomes dehydrated. At this point, aged skin needs to be replenished with its natural moisturizer complex in order to attract and retain water.

The most advanced moisturizer is Ceraphyl® NGA, which functions by reducing the excessive drying in the upper-layers of the skin. Drs. Stig E. Friberg and David W. Osborne showed that Ceraphyl® NGA inhibits trans epidermal water loss by preventing the lipids (fats) from crystallizing. This mechanism is central to preventing dry, thin, leathery, dull, wrinkled skin. Ceraphyl® NGA also seems to increase the effectiveness of sunscreens and enhance the receptiveness of skin cells to antioxidants such as vitamins A, C and E.



THYROID FUNCTION AND SKIN APPEARANCE

People who are deficient in thyroid hormone are often overweight, easily fatigued and mentally depressed. Thyroid deficient individuals also have dry, flaky, sluggish skin. A blood thyroid profile or two-week basal temperature charting can reveal low or borderline low thyroid function. Refer to the Thyroid Replacement Therapy protocol at www.lef.org for information about diagnosing and treating thyroid deficiency.

Hyaluronic acid helps the skin retain its youthful moisture via a different mechanism than Ceraphyl® NGA. Hyaluronic acid maintains the integrity of the connective tissue because it is a source of manganese and glucosamine. Injectable hyaluronic acid may one day replace injectable collagen, but this important skin-preserving nutrient is available without a prescription today in over-the-counter skin creams.

The ability of skin to hold moisture is directly related to its NaPCA (sodium pyrrolidone carboxylic acid) content. NaPCA is one of the skin's most important natural moisturizers. Old skin, however, contains only about half the NaPCA as young skin. NaPCA facilitates the moistening by pulling water in out of the air. Optimal protection against age-accelerating dehydration is best obtained by the topical application of NaPCA, hyaluronic acid, lactic acid, urea, Ceraphyl® NGA and squalane every day.

Delivering nutrients to the skin

A concern amongst dermatologists is whether agents that are proven effective in fighting skin aging can be consistently delivered to the specific layers of the skin where they are known to induce their biological effect. The advent of liposome delivery technology has enabled scientists to increase the efficacy of topical anti-aging agents by delivering them into the inner layers of the skin.

A patented liposome delivery system trademarked QuSomes® (meaning "quick liposomes") was discovered in late 2000. This technology represents a substantial enhancement in conventional liposome vehicles. QuSomes® not only delivers active skin protecting ingredients faster into the lower layers of the skin, but these liposomes are also designed to protect the active ingredient from deterioration. With the unique QuSome® delivery system, the solubility of the active anti-aging agents is preserved, thereby enabling them to reside longer in the areas of the skin where they exert their greatest biological effects.

The availability of QuSomes® enables nutrients like alpha lipoic acid to be reliably delivered to the inner layers of the skin. Alpha lipoic acid is a super-potent fat and water-soluble antioxidant. What has scientists so excited about alpha lipoic acid is its role in maintaining the health of the mitochondria, the powerhouses of the cell itself. When the mitochondria are metabolically compromised, skin cells cannot perform youthful repair functions.

In addition, alpha lipoic acid helps turn off an inflammatory messenger known as nuclear factor kappa B (NFkB). The expression of NFkB induces inflammation at an early stage. Factors that suppress NFkB inhibit skin damaging inflammatory processes.²⁰ (Editor's Note: NFk-B is a transcription factor. Transcription factors are messengers found inside the cell, which carry information from the cytoplasm to the nucleus. There they may activate or inhibit the production of certain proteins or enzymes, which then carry out a particular cell function. Such a function might be increased inflammatory factors.)

Another benefit to having abundant quantities of alpha lipoic acid in the skin is its ability to regulate a collagen-regulating factor known as AP-1. When alpha lipoic acid activates AP-1, it turns on enzymes that digest only glycation-damaged collagen. As we age, proteins become glycated, resulting in the formation of non-functioning cross-linked tissues (advanced glycated end products, AGEs). The accumulation of these cross-links is a hallmark molecular characteristic of visible skin aging.

QuSomes® can deliver alpha lipoic acid deeper into the lower epidermis (top layer) and upper dermis (lower layer) of skin. This makes alpha lipoic acid an exciting new weapon in

THE SKIN'S TWO LAYERS

Our skin consists of two main layers-the dermis and epidermis. The dermis is the inner layer of skin that contains nerve fibers, fat cells, blood vessels, sweat and oil glands, and hair follicles. The

the battle against the ravages of time.

Summary

Recently published findings indicate that one may have more control over the rate at which their skin ages than any other organ of the body.

To slow skin aging and partially reverse it, an individual must take a comprehensive approach to gain control over all of the factors that have been identified in the skin degeneration process.

For many years, a debate raged in the dermatological community as to whether topically applied anti-aging preparations could slow skin aging. The scientific literature now indicates that the daily application of a variety of agents can have a profound effect on both the health and appearance of the skin.

The next article describes the pioneering work of a medical doctor who developed the first topical preparation that contained ingredients that have now been shown to both protect and restore skin that has been damaged by irradiation and/or normal aging.

dermis also contains collagen and elastin, two proteins that are responsible for the structure and elasticity of the skin itself. It is these proteins that are subject to the process of aging. The sweat and oil glands in the dermis protect the outer layer of skin with a thin coating of oil and perspiration.

The epidermis is the very outer layer of our skin. New cells generated by the dermis continually replace this layer. Removal of the epidermis, as in a scrape or burn, reveals an unprotected sensitive dermis underneath.

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