

Innovative Cosmeceuticals: Sirtuin Activators and Anti-Glycation Compounds

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Skin aging is a combination of natural aging with superimposed photoaging. Naturally aged skin is thin, fragile and finely wrinkled whereas photoaged skin is rough and thickened with deep coarse wrinkles. In addition photoaging is characterized by mottled pigmentation, solar lentigines, telangectasias and a loss of elasticity. The science behind skin aging has exploded in the past decade. Skin aging has now been defined on both a cellular and molecular level. The study of genomics in aging skin provides us with potential targets as points for intervention. In this regard, the science behind skin aging becomes a platform for the development of new anti-aging strategies and products. In this paper two new and emerging approaches to treat aging skin will be discussed. Sirtuin activating and anti-glycation products are already being marketed by cosmetic and pharmaceutical companies. These anti-aging approaches are backed by basic science research and the ingredients used are supported by proof of concept studies although clinical trials are often lacking. It is this bench to beauty counter approach to cosmeceuticals that remains an industry standard today.

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The study of aging elucidates that the process is complicated and multifactorial. The role of oxidative stress in aging has been well defined and is supported by significant scientific research.¹⁻³ Antioxidants are known to neutralize damaging free radicals and have diverse biological effects.⁴⁻⁶ They are extremely popular among consumers who ingest them as supplements in an attempt to mitigate signs of aging and apply them topically to improve the skin's appearance.

The authors of recent studies^{7,8} have demonstrated that genomic factors are important in regulating skin aging. The genetic changes that characterize skin aging have been delineated by comparing young skin to naturally aged and photoaged skin.⁸ Through these studies, we know that skin aging is associated with a down-regulation of genes associated with lipid biosynthesis, formation of keratin filaments, and the cornified envelope. This explains the compromise in barrier function and dryness observed in elderly patients. In photoaged skin there is an up-regulation of the transcription factor

activator protein 1 that produces collagen degrading matrix metalloproteinases (MMPs). Procollagen 1 genes are down-regulated, resulting in a net loss of dermal collagen, leaving skin thin and wrinkled. Photoaged skin is characterized by an up-regulation in inflammation that is mediated by transcription factor nuclear factor kappa beta and an up-regulation in genes responsible for elastin degradation. This accounts for the accumulation of elastotic material that is the hallmark of photoaging.

Dietary Restriction and Aging

The observation that dietary restriction (DR) extends life span and reduces age-related illnesses led to the discovery of a family of enzymes called sirtuins.⁹ Sirtuins mediate the effects of DR and have been identified in a variety of species, including drosophila, worms, rodents, and most recently humans.¹⁰ There are 7 mammalian sirtuins, named SIRT 1 through SIRT 7, with SIRT1 being the most important in humans.

Research has demonstrated that sirtuins are nicotinamide adenine dinucleotide-dependent enzymes that deacetylate histone.¹⁰ When histone is deacetylated, transcription does not occur; thus, sirtuins function primarily as gene silencers.¹¹⁻¹³ As such, sirtuins regulate many biological processes,

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Table 1 Physiological Processes Modulated by Sirtuins

Enhance longevity
Cell-cycle regulation
Gene silencing
Stress response
Insulin sensitivity
Gluconeogenesis
Lipid metabolism
Axonal degeneration
Apoptosis

particularly those that occur in response to stressful stimuli.¹⁴ Sirtuins mediate DNA repair, energy homeostasis, axonal degeneration, apoptosis, gluconeogenesis, lipid metabolism, the stress response, and aging (Table 1).^{15,16}

Because DR is not a practical antiaging strategy, there is a great deal of interest in identifying compounds that can mimic this effect.¹⁷ The screening of multiple small molecules as potential sirtuin-activating compounds found that resveratrol was the most potent of those evaluated.¹⁸ Resveratrol is a polyphenolic antioxidant with diverse biological effects that is found in high concentrations in grapes and red wine. Investigators have shown that resveratrol prevents insulin resistance, improves cardiovascular health, protects neurons from degeneration, reduces inflammation and arthritis, prevents cancer, and increases longevity (lifespan).¹⁹⁻²³ Resveratrol deacetylates targets of SIRT1, supporting its mechanism of action as a DR mimetic.^{20,21}

Resveratrol has been shown to have chemopreventative and antiproliferative effects. Resveratrol acts as an antitumor agent by affecting all 3 pathways of carcinogenesis, including initiation, promotion, and progression.²⁴ Topical resveratrol was evaluated for chemopreventative effects by the use of a photocarcinogenesis model.²⁵ Mice were subjected to chronic ultraviolet B exposure, and test groups received either pretreatment or posttreatment with topical resveratrol. After 28 weeks, both pre- and posttreatment groups had a highly significant inhibition in tumor incidence compared with control. Both groups also demonstrated a delay in onset of tumorigenesis. Because posttreatment imparted equal protection to pretreatment, the authors suggest that the benefits of resveratrol were not attributable to sunscreen effects. Their data also suggest that resveratrol exerts its antitumor activity at least in part via modulation of expression and function of survivin, a member of the inhibitor of apoptosis gene family. Resveratrol has been shown to stimulate apoptosis in a variety of cell lines and is associated with an increase in expression of tumor suppressor genes.^{26,27}

Resveratrol has significant potential as a topical antiaging ingredient in view of its antioxidant and sirtuin activating properties. Resveratrol down-regulates important transcription factors involved in photoaging, including activator protein 1 and nuclear factor kappa beta.²⁸ Resveratrol has been shown to suppress expression of MMP-1 and MMP-3 in dermal fibroblasts indicating it may be of value in preserving dermal collagen.²⁹

In a comparative study in which the authors assessed the antioxidant capacity of commercially available skin care products, when oxygen radical absorbance capacity testing was used, they found that 1% resveratrol (FAMAR, Athens, Greece) was more potent than 1% idebenone (Prevage MD; Allergan, Inc, Irvine, CA).³⁰ The oxygen radical absorbance capacity test is an industry standard for assessing the antioxidant capacity of cosmetics. The resveratrol product had a 17-fold greater antioxidant capacity indicating a significant potential as a preventive for photoaging. Additional studies have demonstrated that antioxidant capabilities of resveratrol in human fibroblasts are dose dependent.³¹

In addition, resveratrol is known to be a phytoestrogen with potential to attenuate the symptoms of menopause.³² Resveratrol binds to estrogen receptors and has been shown to protect against bone loss without the risk of breast cancer.^{33,34} Estrogen enhances glycosaminoglycans, increases collagen content, and hydrates the skin. It is possible that resveratrol may have similar benefits on aging skin.³⁵ Further studies on the use of phytoestrogens to treat aging skin are warranted.

The science behind resveratrol is plentiful and promising. In view of its diverse biological properties, it is likely that this botanical will augment the therapeutic armamentarium of many fields of medicine, including dermatology. Although there are numerous nutraceuticals and cosmeceuticals in the market that tout resveratrol, objective clinical studies confirming their benefits are by in large lacking. It is of interest to note that studies are underway evaluating synthetic derivatives of resveratrol and other small molecule sirtuin activators.³⁶ Many of these molecules appear to be more potent than resveratrol and produce a signaling profile that is similar to DR. There is a great deal of interest in these innovative sirtuin activators although they are not commercially available at this time.

A unique ingredient that has been shown to increase sirtuin expression are biopeptides from the yeast *Kluoveromyces*.³⁷ These biopeptides activate SIRT1 in human epidermal cells and dermal fibroblasts and decrease ultraviolet B-mediated cell senescence and DNA fragmentation.³⁷ An oil-water emulsion containing 1% yeast biopeptides, an extract of *Aframomum angustifolium* seeds, and 9 other antiaging ingredients was tested on 33 female subjects.³⁷ The subjects applied the product once daily to the face and neck for 4 weeks. Skin hydration was improved after the first application, and there was a significant improvement in a variety of parameters of photoaging, including fine lines and wrinkles, pigmentation, radiance, and texture after 4 weeks of use. This product containing yeast biopeptides in combination with multiple beneficial ingredients offers a complementary approach to treating aging skin.

Glycation and Skin Aging

The observation that diets with high sugar content elevate levels of sugar in the blood and skin dates back to 1945.³⁸ Most sugar deposited in skin is protein bound and by lowering dietary sugars one can effectively lower skin sugar con-

Table 2 Botanicals with Anti-glycation Activity

Blueberry
Quercetin
Silymarin
Cloves
Ginger
Cinnamon
Allspice
Sage
Marjoram
Tarragon
Rosemary

tent. In diabetics, circulating glucose interacts with proteins, lipids and nucleic acids resulting in the formation of advanced glycation end products (AGE).³⁹ Advanced glycation end products are directly implicated in many of the complications seen in diabetics, including vascular disease, nephropathy, retinopathy, and neuropathy.

In the skin the primary AGE is glycated collagen.⁴⁰ Glycated collagen is crosslinked through covalent bonds rendering collagen stiff and interfering with collagen repair mechanisms. It is postulated that glycated collagen may be responsible for vascular changes, poor wound healing and skin stiffness seen in diabetics.⁴¹ It is of interest that glycation of collagen also occurs as part of the normal aging process.⁴² Glycated collagen begins to appear in patients who are in their late 20s and accumulates at a rate of approximately 3.7% per year. The percentage of glycated collagen varies according to diet and is increased with sun exposure.⁴³

In addition to sugar, preformed AGE consumed through dietary sources can also glycate collagen and other proteins.⁴⁴ Cooking techniques, such as grilling, frying, and roasting, produce AGEs that can be absorbed through dietary ingestion. To avoid dietary AGE consumption, cooking food by poaching, boiling, or steaming is preferable. In addition to affecting proteins, AGE consumed through diet appear to interfere with normal intestinal flora.⁴⁵ This alteration in gut flora reduces absorption of nutrients and chemicals that may inhibit AGE formation and thus further contributes to an inflammatory response.

The importance of controlling AGE has led to studies attempting to identify compounds that may inhibit their production. Chelating agents and antioxidants that are scavengers of hydroxyl radicals block the glycation process.⁴⁶ In a comparative study, extracts of 24 herbs and spices were tested for their ability to inhibit glycation of albumin.⁴⁷ In general, spice extracts were more potent inhibitors of glycation than herb extracts, with ginger, cinnamon, allspice, and cloves, being among the most potent. Herbs such as sage, marjoram, tarragon, and rosemary were also effective. Other botanicals, such as silymarin, blueberry extract, and quercetin, have also demonstrated potent antiglycation activity (Table 2).^{48,49} Finally, studies have demonstrated that carnosine, carnitine, taurine, and α -lipoic acid are also effective.⁵⁰ It is important to note that to date no diet-related compounds

have been shown to remove already-formed AGE, so prevention appears to be key.^{51,52}

The use of antiglycation ingredients in antiaging cosmetics has gained favor with cosmetic companies, although clinical studies are few. In an interesting study, authors evaluated the antiglycation and antiaging effects of a topical product containing blueberry extract and C-xyloside on diabetic skin.⁵³ Blueberry extract has known antiglycation properties whereas C-xyloside stimulates glycosaminoglycan production. Twenty type II diabetic females 55+ years in age with moderate aging applied the cosmeceutical product to their faces, hands, and inner forearm twice daily for 12 weeks. Clinical grading, digital photography, skin caliper measurements, corneometry, and skin AGE measurements were performed at baseline, 4, 8, and 12 weeks. After 12 weeks, the investigators found statistically significant improvement in skin caliper measurements, skin hydration, and parameters of skin aging, including fine lines, firmness, radiance, skin tone, smoothness, creping, and overall appearance when compared with baseline. Of interest was the fact that skin AGE as measured by skin autofluorescence remained unchanged throughout the study. The authors suggest that small sample size and limited time frame of the study may have been insufficient to produce a statistically significant change in skin AGE. Studies like this highlight the need for further research on the use of topically applied anti-glycation products.

The use of cosmeceuticals containing antioxidants, alpha hydroxy acids, and retinoids remain the gold standard for dermatologists. The plethora of science, clinical studies and long-term clinical use substantiate their benefits. As the science behind aging continues to evolve, there will undoubtedly be new approaches and ingredients marketed to treat aging skin. Although there is new and exciting science to support the potential of sirtuin activators and anti-glycation products further investigation is warranted to confirm their clinical efficacy.

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