Antioxidants: Crucial Additions to Dermal Photoprotection

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The acute and chronic effects of UV exposure have been consistently recorded for decades. Both the endogenous protective responses against this exposure as well as daily application of topical antioxidant agents offer heightened protection against a range of damaging radicals that are known to cause UV-induced photodamage and, potentially, carcinogenesis. This review will explore the different types of radicals and their effects within the skin. In addition, a variety of well-researched botanical antioxidants and their specific mechanisms of action will be outlined to assist the clinician in identifying the most advanced topicals for dermal photoprotection.

Exposure to UV radiation is a well-documented cause of immunosuppression, oxidative damage, and skin cancer.[1-3] Although the body's systems exert protective responses against this exposure, daily application of topical antioxidants offers heightened protection against a range of damaging radicals that are known to cause photodamage, skin cancer, and other deleterious effects on human skin. Identifying the primary types of UV exposure–related radicals and their negative effects within the skin will assist in the identification of efficacious ingredients for their containment. A variety of research-supported topical antioxidants are currently available, and knowledge of their specific benefits will assist the clinician in choosing the most beneficial topicals for their patients.

RADICAL REACTIVE OXYGEN SPECIES

Radicals are compounds with unpaired electrons in their outer shell. This lack of electron balance creates highly reactive species. There are many types of free radicals, yet reactive oxygen species (ROS) have been widely studied due to their damaging effects in the skin. Of the wide variety of environmental offenders, UV radiation is a primary contributor to the overproduction of ROS and its resultant oxidative stress in the skin.[1-2] ROS include hydroxyl radicals, nitric oxide, peroxynitrite, superoxide anions, peroxide, triplet oxygen, and singlet oxygen. Although widely known for their ability to cause damage to cellular proteins, lipids, and DNA, ROS can also play a beneficial role in the body.

MAINTAINING HOMEOSTASIS

As with many systems in the human body, radicals are necessary components in the maintenance of homeostasis at the cellular level.[4] Some of the beneficial roles of free radicals in the body are the generation of adenosine-5'-triphosphate from adenosine-5'-diphosphate in the mitochondria, apoptosis of defective cells, and the generation of oxygenases that perform many regulatory functions.[4] Radicals are able to perform their needed functions without causing cascading damage to surrounding cells due to the endogenous presence of enzymatic and nonenzymatic antioxidants.[4] Enzymatic antioxidants that participate in the containment of ROS include superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, and thioredoxin reductase.[5] Additionally, ascorbate, glutathione, tocopherol, and ubiquinol work against ROS as low-molecular-weight nonenzymatic antioxidants in cells.[5] In most healthy humans, these free radicals and

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their identified scavengers work symbiotically.[6] A variety of endogenous and exogenous offenders deplete the naturally available cellular antioxidants and increase the production of ROS, leading to oxidative stress.[4] UV radiation is thought to be one of the most prominent of these exogenous damaging factors.

THE NEGATIVE EFFECTS OF UV RADIATION

UV rays are divided into 3 types based on wavelength. The shortest are UVC rays (200–280 nm). Currently, filtration by the ozone layer prevents this short wave UV radiation from reaching the Earth's surface. Midrange UVB (280–320 nm) and long-wave UVA (320–400 nm) are the rays responsible for premature photoaging, immune dysfunction, and some cancers.[7] Although UVA rays are more prominent in the sunlight that reaches the Earth's surface, they play a less significant role in carcinogenesis. UVB rays are thought to be responsible for more of the UV-induced adverse effects in the skin.[8-9] UV radiation is particularly damaging to the skin as it has been shown to not only increase levels of ROS, but it also depletes the endogenous antioxidant levels.[5] In order to adequately protect patients' skin from ROS, topical antioxidant supplementation in addition to sunscreen use is becoming the standard of care.

Multiple antioxidant ingredients have demonstrated benefits for reducing the incidence of ROS-induced photocarcinogenesis and photoaging.[1,10] While there are thousands of topical antioxidants that are worthy of further study, this article's focus is botanically sourced phenolic antioxidants. The following substances have clearly demonstrated benefits for scavenging ROS within the skin.

GREEN TEA

Green tea is derived naturally from the *Camellia sinensis* plant and is the source of multiple potent polyphenol antioxidants. Epigallocatechin gallate (EGCG) is the most plentiful polyphenol found in *C sinensis*, leading many to attribute green tea's superior antioxidant, anti-inflammatory, and chemoprotective benefits to EGCG.[11] Numerous clinical studies have demonstrated a clear correction of and protection against several UV-induced cellular alterations when EGCG is applied prior to or immediately following UV exposure. EGCG is capable of reversing the immunosuppressive effects of UV rays,[12] quenching hydrogen peroxide radicals,[13] and inducing degradation of carcinogenic cutaneous cells.[14] In addition, EGCG has been shown to inhibit lipid peroxidation and prevent the formation of nitric oxide, hydroxyl radicals, and singlet oxygen.[10-11]

RESVERATROL

Resveratrol is a potent polyphenolic compound found in grapes, berries, peanuts, and cocoa.[15-17] Research evaluating the free radical–scavenging capabilities of resveratrol has been conducted for many years and its topical and internal benefits are undeniable. Topical application of resveratrol prior to UVB exposure suppresses the production of hydrogen peroxide radicals and lipid peroxidation. Furthermore, inhibition of nuclear factor κB (NF-κB) activation, which contributes to the formation of malignancies, has been demonstrated.[10,11,18] These attributes are key to resveratrol's antiproliferative and preventative effect on tumorigenesis within the skin.[19]

FERULIC ACID

Ferulic acid is a polyphenol antioxidant found naturally in many botanical sources, such as rice bran and tomatoes. Its mechanism of action includes prevention of nitric oxide production and lipid peroxidation.[20] Ferulic acid is also able to absorb UV radiation but is not considered a sunscreen agent.[21] Comparative studies suggest that while ferulic acid is beneficial in free radical repair and surpasses the popular antioxidant idebenone in photoprotection capabilities, its scavenging effects are not as potent as green tea polyphenols.[22-23]

GENISTEIN

The isoflavone genistein is a polyphenol derivative of soybeans that effectively increases the activity of the enzymatic antioxidants found naturally in the skin.[24] Genistein's ability to prevent lipid peroxidation and hydrogen peroxide production and its interference with UV-induced cellular mutation and DNA damage make it an integral part of topical protective products.[25-26] In addition, in vivo studies involving genistein demonstrate prevention of both the short- and long-term effects of UV exposure, including erythema, cutaneous carcinomas, and visible photoaging.[27]

ERGOTHIONEINE

Ergothioneine is a lesser known antioxidant found naturally in many species of plants. Although its topical use is in its infancy, ergothioneine's superior antioxidant benefits and its ability to increase the protective activity of traditional antioxidants such as ascorbic acid,[28] make it an excellent addition to cosmeceutical products. Scientific studies indicate that ergothioneine reduces several forms of ROS, including hydrogen peroxide, hydroxyl radicals, singlet oxygen, peroxynitrite, lipid peroxides, and nitric oxides.[28-31] Ergothioneine-induced chemopreventive benefits also have been demonstrated in clinical testing.[28]

COFFEA ARABICA EXTRACT

Commonly referred to as CoffeeBerry, this polyphenolic extract is derived naturally from the unripe *Coffea arabica* plant. While in vitro studies have demonstrated a clear quenching of free radicals, the exact antioxidant mechanism of action of *C arabica* extract within the skin is still not fully understood.[32,33] *C arabica* extract's antioxidant activity could be attributed to its ability to increase glutathione reductase, superoxide dismutase, and catalase content, all of which are part of the body's natural enzymatic antioxidant activity.[34]

THEOBROMA CACAO (COCOA) SEED EXTRACT

Cocoa seed extract is a source of catechin and epicatechin polyphenols, which exhibit strong free radical–scavenging capabilities. Comparative research indicates that the amount of polyphenolic compounds found in cocoa exceeds that of teas and wine extracts.[35] Studies have demonstrated a reduction of nitric oxide, superoxide anion levels, and ROS-induced NF-κB production.[36-37] Additionally, cocoa seed extract is a natural source of resveratrol,[17] and possible carcinogen-preventative properties have also been suggested.[37]

CAFFEINE

Caffeine is a natural component found in many botanical sources. Although it is not a polyphenol itself, it is believed that caffeine plays a key role in the strong antioxidant behavior of several of the aforementioned antioxidants, including *C arabica*, green tea, and cocoa seed extract.[38-40] Studies comparing caffeinated and decaffeinated beverages showed a significant increase in the antioxidant activity of those containing caffeine.[38] Caffeine is capable of reducing several UV-induced free radicals, including hydroxyl radicals, hydrogen peroxide, peroxyl radicals, and singlet oxygen.[41] Research also suggests that topical application of caffeine can reduce UV-induced skin cancers by decreasing cellular apoptosis in UV-exposed keratinocytes.[39,41]

GARCINIA MANGOSTANA PEEL EXTRACT

Commonly referred to as mangosteen, this potent fruit derivative exhibits impressive antioxidant and chemopreventive benefits. Mangosteen is a natural source of flavonoids, such as epicatechin, and studies have shown a clear inhibition of ROS production and their resultant damage; specifically, peroxynitrite and hydrogen peroxide were affected.[42,43] Research also indicates that mangosteen induces selective apoptosis on cancerous cells.[44-45]

SILYBIN MARIANUM FRUIT EXTRACT

Milk thistle–derived silymarin is a powerful flavonoid antioxidant whose most active component is silybin. Studies performed over recent decades suggest that silymarin inhibits lipid peroxidation and nitric oxide and hydrogen peroxide production.[3] Increases in the amount of endogenous glutathione have also been observed as a result of silymarin treatment.[46] Further, an inhibition of the immunosuppression and carcinogenesis caused by UV exposure and a decreased occurrence of UV-induced cellular degradation has also been attributed to topical application of silymarin.[47-49]

PROTECTING PATIENTS

As has been identified, UV radiation is responsible for increased ROS production and the depletion of endogenous radical-scavenging antioxidants. Exposure to UV radiation may also have a negative effect on many of the topical formulations designed to protect the skin from photocarcinogenesis and photoaging.[50] It has been noted that many UV-absorbing and UV-reflecting ingredients that are commonly used in most sunscreen products are susceptible to breakdown and free radical formation with extended exposure to UV radiation.[50] Ensuring patient compliance with sun protection is a constant challenge for the physician, and this new information has made some individuals unnecessarily fear using sunscreen products. Knowing the dangerous effects of UV radiation in the skin, choosing to not wear daily sun protection in the hopes of avoiding additional free radical damage would be detrimental for patients. This potential for additional free radical exposure due to sunscreen use can be avoided by providing patients with moisturizers containing broad-spectrum UVA/UVB sun protection that include antioxidants within their formulations or antioxidant serums to use with their sunscreens. This strategy removes the need for patient concern and allows for maximum defense against damaging UV radiation.

Although radicals clearly play a role in maintaining homeostasis within the body, exposure to UV radiation and other causes of ROS is virtually unavoidable. Conversely, the resultant endogenous antioxidant depletion, ROS production, and damage to cellular proteins, lipids, and DNA can be avoided by using botanically sourced phenolic antioxidants as additions to patients' daily care regimens. Due to the variety of mechanisms of action within the different extracts reviewed, utilizing topical formulations that include multiple polyphenol antioxidants will provide patients with optimal protection against a wide variety of radical species.

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