This supplement was supported by an independent educational grant from
SkinCeuticals

A SUPPLEMENT TO
cutis®
CUTANEOUS MEDICINE FOR THE PRACTITIONER

REFERENCED IN *INDEX MEDICUS*

VOL. 107 | NO. 3S | MARCH 2021 | mdedge.com/dermatology

The Why, What, When, and How of Topical Antioxidants in Cosmeceuticals

Patricia Farris, MD

The Why, What, When, and How of Topical Antioxidants in Cosmeceuticals

Patricia Farris, MD

doi:10.12788/cutis.0179

CONTINUING MEDICAL EDUCATION

MEDSCAPE DISCLAIMER STATEMENT

As an organization accredited by the ACCME, Medscape, LLC, requires everyone who is in a position to control the content of an education activity to disclose all relevant financial relationships with any commercial interest. The ACCME defines "relevant financial relationships" as financial relationships in any amount, occurring within the past 12 months, including financial relationships of a spouse or life partner, that could create a conflict of interest.

Medscape, LLC, encourages authors to identify investigational products or off-label uses of products regulated by the US Food and Drug Administration, at first mention and where appropriate in the content.

CME INFORMATION

CME / ABIM MOC / CE
Release Date: 2/1/2021
Expiration Date: 2/2/2022

Target Audience: This activity is intended for dermatologists, plastic surgery and aesthetic specialists, primary care physicians, and nurses.

Goal Statement: The goal of this activity is to improve the understanding of the mechanisms of oxidative stress in the skin and therapeutic approaches to minimize these effects.

Learning Objectives: After participating in the activity, the dermatologists, plastic surgery and aesthetic specialists, primary care physicians, and nurses should be able to:

Have increased knowledge regarding
- The role of oxidative stress in skin aging
- Clinical data associated with various classes of antioxidants

Demonstrate greater confidence in their ability to:
- Tailor topical antioxidants to patients to protect against oxidative stress

Disclosures:

Faculty

Patricia Farris, MD
Clinical Associate Professor
Tulane University
Private Practice at Sanova Dermatology
Metairie, Louisiana

Disclosure: Patricia Farris, MD, has disclosed the following relevant financial relationships: Served as an advisor or consultant for: CeraVe; La Roche Posay; Nutraceutical Wellness, LLC; SkinCeuticals; U.SK Under Skin; co-founder or RegimenMD

Editors

Briana Betz, PhD
Medical Education Director,
WebMD Global, LLC

Disclosure: Briana Betz, PhD, has disclosed no relevant financial relationships.

Frances McFarland, PhD, MA
Medical Writer, Medscape, LLC

Disclosure: Frances McFarland, PhD, MA, has disclosed no relevant financial relationships.

CME, CE Reviewer / Nurse Planner

Hazel Dennison, DNP, RN, FNP, CHCP, CPHQ, CNE
Associate Director, Accreditation and Compliance, Medscape, LLC

Disclosure: Hazel Dennison, DNP, RN, FNP, CHCP, CPHQ, CNE, has disclosed no relevant financial relationships.

ACCREDITATION STATEMENTS

In support of improving patient care, Medscape, LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

FOR PHYSICIANS

Medscape, LLC designates this enduring material for a maximum of 0.25 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

- PARS ID: 201579721

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 0.25 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit. Aggregate participant data will be shared with commercial supporters of this activity.

FOR NURSES

Awarded 0.25 contact hours of nursing continuing professional development for RNs and APNs; 0.25 contact hours are in the area of pharmacology.

Supported by an independent educational grant from
SkinCeuticals

CONTINUING MEDICAL EDUCATION

Instructions for Participation and Credit There are no fees for participating in or receiving credit for this online educational activity. For information on applicability and acceptance of continuing education credit for this activity, please consult your professional licensing board.

This activity is designed to be completed within the time designated on the title page; physicians should claim only those credits that reflect the time actually spent in the activity. To successfully earn credit, participants must complete the activity online during the valid credit period that is noted on the title page. To receive *AMA PRA Category 1 Credit*™, you must receive a minimum score of 75% on the post-test.

Follow these steps to earn CME/CE credit*:

1. Read the target audience, learning objectives, and author disclosures.
2. Study the educational content.
3. Access the post-test webpage at www.medscape.org/interview/cosmeceutical-antioxidants
4. Online, choose the best answer to each test question. To receive a certificate, you must receive a passing score as designated at the top of the test. We encourage you to complete the Activity Evaluation to provide feedback for future programming.

You may now view or print the certificate from your CME/CE Tracker. You may print the certificate, but you cannot alter it. Credits will be tallied in your CME/CE Tracker and archived for 6 years; at any point within this time period you can print out the tally as well as the certificates from the CME/CE Tracker.

**The credit that you receive is based on your user profile.*

The Why, What, When, and How of Topical Antioxidants in Cosmeceuticals

INTRODUCTION

The free radical theory of aging asserts that aging arises from an accumulation of reactive oxygen species (ROS).[1] In the skin, these ROS are also produced primarily by keratinocytes and fibroblasts.[2] ROS are also produced in mitochondria as a byproduct of cellular respiration and can cause DNA damage and mitochondrial dysfunction.[2] Additionally, ROS are generated as a result of various environmental exposures. The exposome is defined as the sum of all of the exposures to which an individual is subjected to throughout a lifetime. (Figure 1).[3] Of paramount importance among these exposures are solar radiation, pollution, poor nutrition, stress, body temperature, and even lack of sleep.[3] As we age, antioxidant levels are diminished, leading to an accumulation of ROS, oxidative stress, and accelerated skin aging.[3,4]

This article describes environmental impacts on the skin, the clinical effects of these impacts, our natural defenses, and topical antioxidants to combat aging. The article concludes with recommendations on topical antioxidant use.

ENVIRONMENTAL IMPACTS AND THEIR CLINICAL EFFECTS IN THE SKIN

Light and Radiation

Dermatologists have long focused on the dangers of ultraviolet (UV) light, which is carcinogenic and accelerates skin aging. UVA and UVB act differently on the skin. UVB light is the shortest wavelength of light to affect the skin. It penetrates primarily to the level of the epidermis, where it is absorbed by chromophores and particularly by DNA, leading to DNA damage and carcinogenesis.[2,5] UVB exposure causes sunburn through the

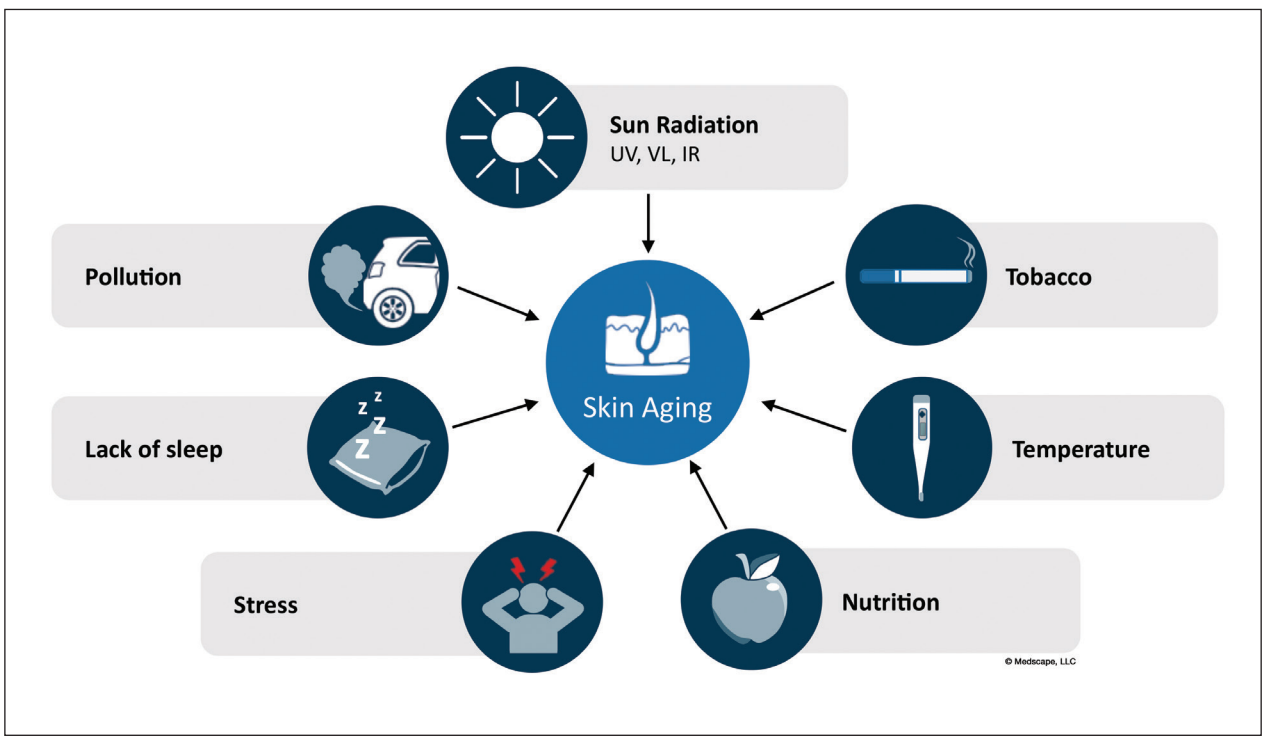

FIGURE 1. The Exposome.[3]
The exposome is the sum of all the exposures to which an individual is subjected over their lifetime.
Abbreviations: IR = infrared; UV = ultraviolet; VL = visible light.

release of proinflammatory mediators that induce redness and swelling in the skin, and it drives delayed tanning by activating melanocytes and melanogenesis within the epidermis.[2,5]

UVA light is less energetic than UVB, but at a longer wavelength, it penetrates more deeply into the dermis, where it can damage the extracellular matrix.[2] UVA light upregulates melanin production and induces immediate pigment darkening through melanin photo-oxidation and redistribution within keratinocytes.[5] It also drives ROS production and oxidative stress, affecting various transcription factors that contribute to skin aging. Among these is activator protein 1 (AP-1), which increases production of the metalloproteinase enzymes that break down collagen. Further, AP-1 inhibits collagen production by downregulating transforming growth factor-β and reducing procollagen gene expression.[2,6] UVA-induced oxidative stress also affects the expression of nuclear factor κB (NF-κB), increasing inflammation and creating even more oxidative stress.[3,4]

Increasing evidence demonstrates that visible light, near-infrared, and infrared wavelengths also contribute to the appearance of photo-aged skin (Figure 2).[2,5,6] At longer wavelengths, these forms of light penetrate even more deeply into the lower layers of the dermis, upregulating oxidative stress, metalloproteinases, and the release of proinflammatory mediators similarly to UVA.[5,6] Visible light is known to induce pigmentation among patients with darker skin types, but not among those with lighter skin.[5] Infrared exposure contributes to skin aging by promoting angiogenesis, inflammation, and matrix metalloproteinase (MMP) production.[6]

Pollutants

Air pollutants that affect the skin include ozone, small particulate matter, and cigarette smoke.[7,8] Ozone does not penetrate the skin, but it induces damage through oxidation of lipids and proteins in the stratum corneum.[8,9] Chronic ozone exposure depletes the stratum corneum of antioxidants leaving it more vulnerable to oxidative stress.[7-10] Ozone also induces inflammation by upregulating NF-κB and COX-2.[8,9,11] Particulate matter and smog do penetrate the skin, and like ozone, they induce oxidative stress and inflammation.[7,8,12] Thus, ozone and particulate matter induce effects similar to those seen with UV light.

Cigarette smoke is a complex pollutant comprising a large number of toxic and carcinogenic compounds, along with ROS, reactive nitrogen species, and carbon monoxide.[7,13] Because it contains particulates and a gas phase, it can act on different targets and layers of the skin.[7] Like other pollutants, cigarette smoke increases oxidative

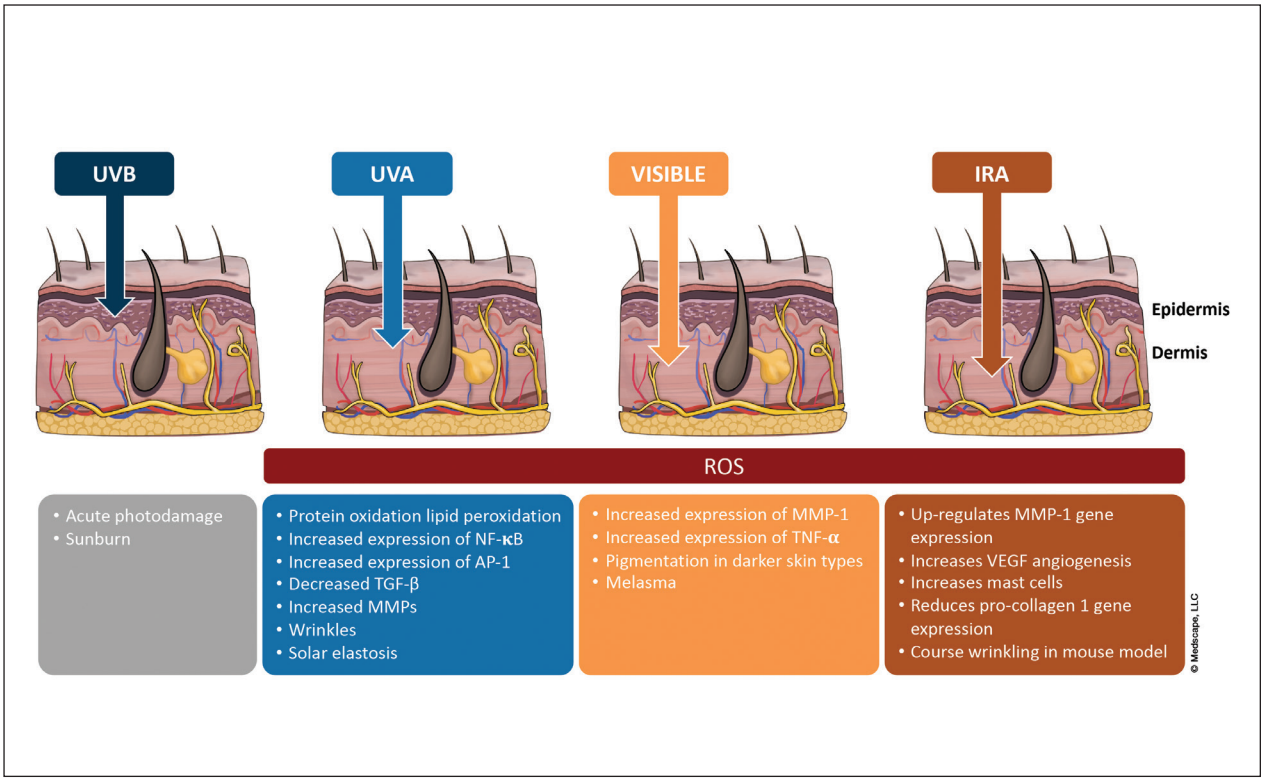

FIGURE 2. Effects of Different Wavelengths of the Electromagnetic Spectrum on the Skin[2,5,6]
Abbreviations: AP-1 = activator protein 1; IRA = infrared radiation; MMP = matrix metalloproteinase; NF-κB = nuclear factor-kappa B; TGF-β = transforming growth factor beta; TNF-α = tumor necrosis factor alpha; VEGF = vascular endothelial growth factor.

stress, but it also contributes independently to skin wrinkling though a cascade of molecular events (Figure 3).[7,13]

Summary of Clinical Effects of Environmental Factors

Environmental skin aging is referred to as extrinsic aging. Whereas intrinsically aged skin is thin and pale, with fine wrinkles and no spots, extrinsically aged skin is dry and flaky, and has deeper, coarser wrinkles; telangiectasia formation; and hyperpigmentation and discoloration, brown spots, lentigines, and sallowness.[2,8] Patients who smoke show exaggerated wrinkling and uneven skin tone with gray and yellowish discoloration and prominent telangectasia.[7,13] One study has shown that patients who live closer to traffic smog and particulate matter from vehicles show exaggerated pigmented spots and wrinkling.[14] Thus, environmental factors contribute largely to what concerns patients most about the appearance of aging skin.

COMBATING OXIDATIVE STRESS IN THE SKIN

Endogenous Defenses

The skin contains an efficient array of antioxidants that offer protection against both external and internal assaults.[15] Nonenzymatic antioxidants, which include vitamin A, vitamin C, vitamin E, coenzyme Q10, alpha-lipoic acid, and urocanic acid, are used to neutralize free radicals.[4,16] Enzymatic antioxidants such as glutathione peroxidase, glutathione S-transferase, superoxide dismutase, catalase, and heme oxygenase, neutralize free radicals and aid in regenerating antioxidants that have already been used.[4,16] The interplay between nonenzymatic and enzymatic antioxidants neutralizes and fends off oxidative stress.[15]

Topical Antioxidants

Although many effective treatments are available to combat the visible signs of aging, prevention is key. Sunscreens, protective clothing, and sun avoidance helps minimize UV damage.[17] However, sunscreens do not protect adequately against UV-induced oxidative stress, nor do they protect against the longer wavelengths of light, such as visible and infrared.[8] Topical antioxidants can, therefore, be used to provide an additional layer of environmental protection against solar radiation and against other environmental aggressors, such as pollution.[8,17,18] Topical antioxidants contain a variety of ingredients, including vitamin C, vitamin E, and botanical antioxidants such as resveratrol, ferulic acid, genistein, curcuminoids, green tea and grape seed extract.[10,16,19-21] Enzymatic antioxidants such as superoxide dismutase have also been touted.[22]

Early studies by Pinnell and colleagues laid the groundwork for the use of topical antioxidants as photoprotectors. Pinnell demonstrated that properly formulated

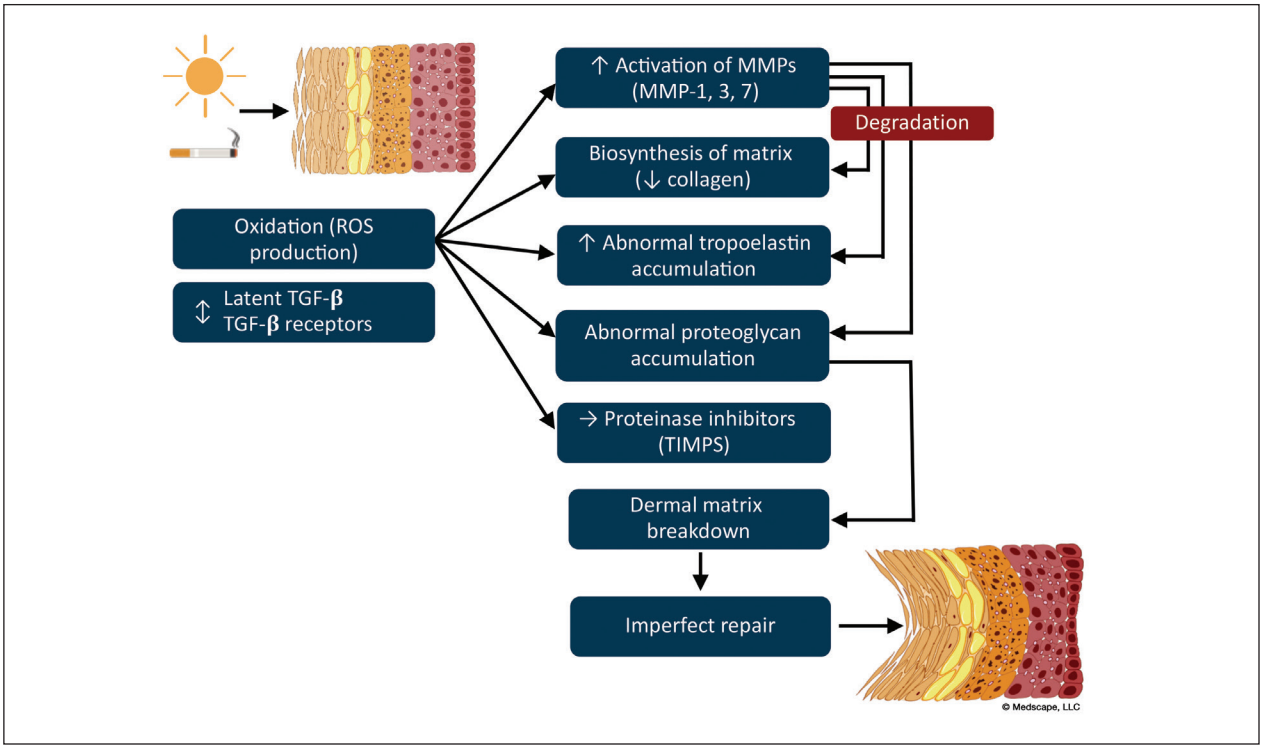

FIGURE 3. Molecular Mechanisms Underlying Tobacco Smoke-Induced Aging[13]
Abbreviations: MMP = matrix metalloproteinase; ROS = reactive oxygen species; TGF-β = transforming growth factor beta; TIMP = tissue inhibitor of metalloproteinase.

vitamin C in the form of L-ascorbic acid could protect skin from UVB-induced sunburn.[23,24] They also demonstrated that when vitamins C and E were used together, it conferred additional photoprotection compared to vitamin C alone.[25] And finally, they showed that a triple combination of vitamin C, vitamin E, and ferulic acid could provide eight times the photoprotection of vitamin C alone.[26,27] More recently, studies have also shown that vitamin C combined with vitamin E and ferulic acid and pholretin combined with vitamin C and ferulic acid offer protection against ozone and that a combination of vitamin C, ferulic acid, and *Deschampia antartica* extract improves skin barrier function and reduces the effects of air pollutants on the skin.[10,28]

RECOMMENDATIONS

To prevent extrinsic aging, dermatologists should recommend a combination of topical antioxidants and sunscreen. Antioxidants are generally applied directly to the skin in the morning, followed by a broad-spectrum sunscreen. Some sunscreens are formulated with antioxidants, allowing for ease of application. DNA repair enzymes, such as photolyase, can curb the development of actinic keratoses and skin cancer and may be of value to prevent skin aging.[29,30] Reparative products should be used at night and include ingredients such as retinoids, growth factors and peptides. This protect and repair treatment paradigm helps patients keep skin healthy and attractive.

REFERENCES

1. Gladyshev VN. The free radical theory of aging is dead. Long live the damage theory! *Antioxid Redox Signal.* 2014;20:727-731.
2. Kammeyer A, Luiten RM. Oxidation events and skin aging. *Ageing Res Rev.* 2015;21:16-29.
3. Krutmann J, Bouloc A, Sore G, et al. The skin aging exposome. *J Dermatol Sci.* 2017;85:152-161.
4. Rinnerthaler M, Bischof J, Streubel MK, et al. Oxidative stress in aging human skin. *Biomolecules.* 2015;5:545-589.
5. Mahmoud BH, Hexsel CL, Hamzavi IH, et al. Effects of visible light on the skin. *Photochem Photobiol.* 2008;84:450-462.
6. Schieke SM, Schroeder P, Krutmann J. Cutaneous effects of infrared radiation: from clinical observations to molecular response mechanisms. *Photodermatol Photoimmunol Photomed.* 2003;19:228-234.
7. Pecorelli A, Woodby B, Prieux R, et al. Involvement of 4-hydroxy-2-nonenal in pollution-induced skin damage. *Biofactors.* 2019;45:536-547.
8. McDaniel D, Farris P, Valacchi G. Atmospheric skin aging—contributors and inhibitors. *J Cosmet Dermatol.* 2018;17:124-137.
9. Valacchi G, Fortino V, Bocci V. The dual action of ozone on the skin. *Br J Dermatol.* 2005;153:1096-1100.
10. Valacchi G, Muresan XM, Sticozzi C, et al. Ozone-induced damage in 3D-skin model is prevented by topical vitamin C and vitamin E compound mixtures application. *J Dermatol Sci.* 2016; 82:209-212.
11. Cotovio J, Onno L, Justine P, et al. Generation of oxidative stress in human cutaneous models following in vitro ozone exposure. *Toxicol In Vitro.* 2001;15:357-362.
12. Magnani ND, Muresan XM, Belmonte G, et al. Skin damage mechanisms related to airborne particulate matter exposure. *Toxicol Sci.* 2016;149:227-236.
13. Morita A. Tobacco smoke causes premature skin aging. *J Dermatol Sci.* 2007;48:169-175.
14. Vierkötter A, Schikowski T, Ranft U, et al. Airborne particle exposure and extrinsic skin aging. *J Invest Dermatol.* 2010;130:2719-2726.
15. Sant'anna Addor FA. Antioxidants in dermatology. *An Bras Dermatol.* 2017;92:356-362.
16. Pandel R, Poljšak B, Godic A, et al. Skin photoaging and the role of antioxidants in its prevention. *ISRN Dermatol.* 2013; 2013:930164.
17. Matsui MS, Hsia A, Miller JD, et al. Non-sunscreen photoprotection: antioxidants add value to a sunscreen. *J Investig Dermatol Symp Proc.* 2009;14:56-59.
18. Rai R, Shanmuga SC, Srinivas C. Update on photoprotection. *Indian J Dermatol.* 2012;57:335-342.
19. Ratz-Łyko A, Arct J. Resveratrol as an active ingredient for cosmetic and dermatological applications: a review. *J Cosmet Laser Ther.* 2019;21:84-90
20. Zduńska K, Dana A, Kolodziejczak A, et al. Antioxidant properties of ferulic acid and its possible application. *Skin Pharmacol Physiol.* 2018;31:332-33
21. Dunaway S, Odin R, Zhou L, et al. Natural antioxidants: multiple mechanisms to protect skin from solar radiation. *Front Pharmacol.* 2018;9:392.3.
22. Altobelli GG, Van Noorden S, Balato A, et al. Copper/zinc superoxide dismutase in human skin: current knowledge. *Front Med (Lausanne).* 2020;7:183.
23. Pinnell SR, Yang H, Omar M, et al. Topical L-ascorbic acid: percutaneous absorption studies. *Dermatol Surg.* 2001;27:137-142.
24. Daar D, Combs S, Dunston S, et al. Topical vitamin C protects porcine skin from ultraviolet radiation-induced damage. *Br J Dermatol.* 1992;127:247-253.
25. Lin J-Y, Selin A, Shea CR, et al. UV photoprotection by combination topical antioxidants vitamin C and vitamin E. *J Am Acad Dermatol.* 2003;48:866-874.
26. Murray JC, Burch JA, Streilein RD, et al. A topical antioxidant solution containing vitamins C and E stabilized by ferulic acid provides protection for human skin against damage caused by ultraviolet irradiation. *J Am Acad Dermatol.* 2008;59:418-425.
27. Lin FH, Lin JY, Gupta RD, et al. Ferulic acid stabilizes a solution of vitamins C and E and doubles its photoprotection of skin. *J Invest Dermatol.* 2005;125:826-832.
28. Milani M, Hashtroody B, Piacentini M, et al. Skin protective effects of an antipollution, antioxidant serum containing Deschampsia antartica extract, ferulic acid and vitamin C: a controlled single-blind, prospective trial in women living in urbanized, high air pollution area. *Clin Cosmet Investig Dermatol.* 2019;12:393-399.
29. Yarosh DB, Rosenthal A, Moy R. Six critical questions for DNA repair enzymes in skincare products: a review in dialog. *Clin Cosmet Investig Dermatol.* 2019;12:617-624.
30. Sondenheimer K, Krutmann J. Novel means for photoprotection. *Front Med (Lausanne).* 2018;5:162.

A SUPPLEMENT TO

cutis®

CUTANEOUS MEDICINE FOR THE PRACTITIONER