



A SUPPLEMENT TO

JOURNAL OF DRUGS IN DERMATOLOGY

JDD

DRUGS • DEVICES • METHODS

SKIN GLYCATION UNVEILED: NAVIGATING
THE SCIENCE OF SUGAR'S IMPACT ON SKIN

This educational supplement to the *Journal of Drugs in Dermatology* was supported by an independent educational grant from SkinCeuticals.

Sugar Sag: What Is Skin Glycation and How Do You Combat It?

Based on a Medscape Education Online Activity

Release Date: April 1, 2024

Expiration: April 1, 2025

Target Audience

This activity is intended for plastic surgery and aesthetic medicine specialists, dermatologists, and other clinicians who treat skin conditions or specialize in skin care.

Goal Statement

The goal of this activity is for learners to be better able to have increased knowledge on the effect of sugars on aging skin, and how advanced glycation end-products (AGEs) impact the skin, as well as greater competence in recommending skincare regimens for patients that take into account the processes of glycation and oxidative stress.

Learning Objectives

Upon completion of this activity, learners will have:

- **Increased knowledge** regarding the
 - Factors that contribute to glycation of the skin
 - Mechanism of action of cosmeceuticals targeting glycation of the skin
- **Greater competence** regarding the
 - Recommendation of appropriate skincare regimens for patients that encompass multiple aspects of the oxidative stress cascade

Disclosures

Medscape, LLC requires every individual in a position to control educational content to disclose all financial relationships with ineligible companies that have occurred in the past 24 months. Ineligible companies are organizations whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients. All relevant financial relationships for anyone with the ability to control the content of this educational activity have been mitigated. Others involved in the planning of this activity have no relevant financial relationships.

Author

Zoe Diana Draelos MD

President, Dermatology Consulting Services, PLLC
High Point, North Carolina

Zoe Diana Draelos MD has the following relevant financial relationships: Contracted researcher and consultant for: Aclaris Therapeutics, Inc.; Aesthetics Biomedical; Allergan, Almirall; Amderma; Amgen, Inc.; AOBiome; Arcutis Biotherapeutics, Inc.; Bausch Health; Bayer AG; Biopelle; Boehringer Ingelheim Pharmaceuticals, Inc.; Boots; Botanix Pharmaceuticals; Brickell Biotech, Inc.; Burt's Bees; Carpe; Chattem Chemicals Inc.; The Chlorox Company; Clarke Pharmaceuticals, Inc.; Colgate-Palmolive Company; Coloplast Corp.; Combe; DelArrivo, Inc.;

Dermavant Sciences, Inc.; Dermira, Inc.; Dial; Dr. Reddy's Laboratories Ltd.; Estée Lauder Inc.; E.T. Browne Drug Co., Inc.; Evolus, Inc.; Ferndale Laboratories, Inc.; Foamix Pharmaceuticals Ltd.; Galderma Laboratories, LP; Genentech, Inc.; General Mills, Inc.; GlaxoSmithKline; Helix Biomedix, Inc.; Henkel; International Specialty Products, Inc.; Johnson & Johnson Services, Inc.; Kamedis; Kao Corporation; La Roche-Posay; LEO Pharma Inc.; Lilly; L'Oréal; Maruho Co., Ltd.; Merck; Nice-Pak Products, Inc.; Novartis; Nu Skin; Perricone MD; Perrigo Company plc; Pfizer Inc.; PharmaNet, Inc.; Proctor & Gamble; Reckitt Benckiser Group plc; Revance Therapeutics, Inc.; Rodan & Fields, LLC; Roivant Sciences Ltd; Sanofi; SkinCeuticals; Symrise; Taro Pharmaceuticals Industries Ltd.; Teoxane; TEVA Pharmaceuticals USA, Inc.; Topix Pharmaceuticals, Inc.; Vanda Pharmaceuticals Inc.; Verrica Pharmaceuticals; Warner-Chilcott; WellSpring Pharmaceutical Corporation; YA-MAN Ltd; ZO Skin Health, Inc.

Editor

Briana Betz PhD

Senior Medical Education Director, Medscape, LLC

Briana Betz PhD has no relevant financial relationships.

Writer

Jason Luis Quiñones PhD

Associate Medical Writer, Medscape, LLC

Jason Luis Quiñones PhD has no relevant financial relationships.

Compliance Reviewer

Leigh Schmidt, MSN, RN, CNE, CHCP

Associate Director, Accreditation and Compliance, Medscape, LLC

Leigh Schmidt, MSN, RN, CNE, CHCP, has no relevant financial relationships.

Accreditation Statement



In support of improving patient care, Medscape, LLC is jointly accredited with commendation 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(s)*[™]. Physicians should claim only the credit commensurate with the extent of their participation in the activity. Aggregate participant data will be shared with commercial supporters of this activity.

Contact This Provider: cme@medscape.net

For Nurses

Awarded 0.25 contact hour(s) of nursing continuing professional development for RNs and APNs; 0.00 contact hours are in the area of pharmacology.

Contact This Provider: cme@medscape.net

For Pharmacists

Medscape designates this continuing education activity for 0.25 contact hour(s) (0.025 CEUs) (Universal Activity Number: JA0007105-0000-24-005-H01-P).

IPCE



IPCE CREDIT[™]

This activity was planned by and for the healthcare team, and learners will receive 0.25 Interprofessional Continuing Education (IPCE) credit for learning and change.

Supporter

This educational supplement to the *Journal of Drugs in Dermatology* was supported by an independent educational grant from SkinCeuticals.

Instructions For Participation and Credit

There are no fees for participating in or receiving credit for this educational activity. For information on applicability and acceptance of continuing education credit for this activity, please consult your professional licensing board. 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 via the URL or by scanning the QR code.
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/CETracker. 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.



www.medscape.org/journal/skin-glycation

Medscape Education © 2024 Medscape, LLC

Sugar Sag: What Is Skin Glycation and How Do You Combat It?

Zoe Diana Draelos MD

President, Dermatology Consulting Services, PLLC, High Point, NC

ABSTRACT

Skin aging is influenced by various exogenous and endogenous factors, ranging from ultraviolet (UV) light exposure and environmental toxins to biological sources, such as those that arise from normal metabolic processes (eg, free radicals). Glycation is the normal process by which glucose and other reducing sugars react with proteins to form an array of heterogeneous biomolecular structures known as advanced glycation end-products (AGEs) over time. However, AGEs are toxic to human cells and are implicated in the acceleration of inflammatory and oxidative processes, with their accumulation in the skin being associated with increased skin dulling and yellowing, fine lines, wrinkles, and skin laxity. Clinicians should become cognizant of how AGEs develop, what their biological consequences are, and familiarize themselves with available strategies to mitigate their formation.

J Drugs Dermatol. 2024;23:4(Suppl 1):s5-10.

A Biological Definition of Advanced Glycation End-Products (AGEs)

As time goes on and our bodies change, alterations in the texture and color of our skin serve as a constant reminder of aging. Skin aging is a multifactorial process, reflecting the sum effects of genetic, endogenous, and environmental factors.¹ Exogenous sources include exposure to ultraviolet (UV) light and environmental toxins, such as tobacco products and heavy metals, while endogenous sources derived from normal cellular metabolism can also contribute to aging. This includes processes such as glycation, which significantly promotes unwanted changes in human skin.¹⁻³

Factors and Sources Contributing to the Development of AGEs

Skin glycation is the biological process by which glucose and other reducing sugars react with and modify biomolecular entities, such as lipids, nucleic acids, and proteins, to form many complex heterogeneous molecules potentially toxic to cells and tissues. These products of nonenzymatic sugar reactivity with other biological molecules are collectively known as advanced glycation end-products (AGEs).¹⁻³ To date, more than

20 species of AGEs have been identified in human skin and are primarily classified based on differences in their biochemical properties.^{2,3} The principal mechanism by which these AGEs are created endogenously is known as the Maillard reaction. This nonenzymatic reaction was discovered initially in the 1900s and was shown to give rise to yellowish-to-brown-colored products that develop following the heating of a mixture of amino acids with reducing sugars.^{2,4} Other mechanisms that can form AGEs and their associated intermediates include sugar autoxidation, lipid peroxidation, and the polyol pathway. Along with the formation of AGEs, these pathways can produce additional reactive compounds (eg, Amadori products, dicarbonyls, Schiff bases, and oxidized compounds) that can disrupt normal cellular physiology (Figure 1).^{1-3,5}

Exogenous sources linked to the production and accumulation of AGEs include eating refined and simple carbohydrates, as well as foods that are cooked at high temperatures (eg, grilling, frying, and baking) that have a brown/crunchy consistency (eg, cookies, chicken), which acquires its characteristic color and texture from the Maillard reaction.^{1-3,6} Excessive alcohol consumption, smoking, and living a sedentary lifestyle can also contribute to the production of AGEs. Other external factors that can increase the content of AGEs in the skin include exposure to pollution, metabolites in tobacco smoke, and UV light.¹⁻³ Individuals should also be aware that self-tanning products contain compounds

(eg, dihydroxyacetone [DHA], the active tanning ingredient in sunless tanning lotions) capable of increasing levels of AGEs in the skin.^{7,8} While most AGEs appear to arise from Maillard reactions occurring at the stratum corneum of the skin, studies suggest that self-tanning components (from sunless/chemical tanners) such as DHA (~12%, according to a US Food and Drug Administration [FDA] investigator-led study) may also slightly penetrate the epidermis and dermis layers where they can then promote some glycation.⁹⁻¹¹ However, the use of self-tanners is generally considered a safe alternative to UV-induced tanning.

Consequences of Skin Glycation

Due to their ability to negatively alter skin biology, the accumulation of AGEs is tied to several adverse effects in both the extracellular and intracellular compartments (Figure 1). One particularly problematic effect of AGEs is their ability to diminish protein function by altering their structure through cross-linking mechanisms.¹⁻³ This impacts several protein factors that comprise the architectural framework of the extracellular matrix (ECM). For example, ECM proteins, such as collagen and elastin, can be captured and cross-linked by various AGEs, resulting in the loss of their native conformation (ie, normal structure). This compromises the integrity and biomechanical properties of the skin, ultimately causing reduced skin elasticity and increased stiffness.¹⁻³ These processes are further exacerbated by the fact that, as humans age, skin fibroblasts exhibit a reduced capacity to secrete elastin and collagen fibers, further decreasing the quality of the ECM in the dermis.^{1,12} In addition to the deepening and lengthening of skin wrinkles, these molecular events contribute to several manifestations of skin aging, such as yellowing, pigmentation changes (browning), and autofluorescence.^{1,3}

Another important biological effect of AGEs and their intermediates is their capacity to independently react with molecular oxygen and metals to generate reactive oxygen species (ROS), furthering their toxic potential.¹⁻³ Additionally, AGEs can promote an inflammatory phenotype in cells by stimulating the production and release of pro-inflammatory cytokines and ROS.¹⁻³ The ROS and cytokine-inducing phenotypes observed in cells with elevated levels of AGEs may also be partly mediated by the binding of AGEs to the receptor for advanced glycation end-products (RAGE), the activation of which results in oxidative stress and upregulation of pro-inflammatory cytokines.^{13,14} Lastly, AGEs can impair the signal transduction properties of cell growth and survival pathways, impinging upon important cellular cascades, including those required for normal proliferation, differentiation, motility, and cell death.^{2,3,15}

Given the pleiotropic effects of AGEs in the cell, it is no surprise that their presence and persistence are linked to several disease pathologies (Figure 1).^{1-3,5} The role of AGEs in patients with chronic metabolic disorders, such as diabetes, has garnered much attention, being a condition marked by a hyperglycemic state where patients may eventually suffer from skin complications (eg, ulcers, wound healing issues).^{2,3,16,17} The high glucose levels in patients with diabetes can serve as a reservoir for accelerating AGE-related metabolism.^{2,3,18} Indeed, patients with diabetes display higher levels of AGEs in their skin than healthy individuals.^{19,20} Studies have also shown a correlation between high sugar levels and skin aging among patients with diabetes, and it has been revealed that patients with diabetes have impaired structural and mechanical properties in dermal collagen.^{2,3,21,22} These observations point to a possible role of AGEs in mediating some aspects of diabetic disease. However, the exact mechanisms are poorly understood and likely involve other biological factors.

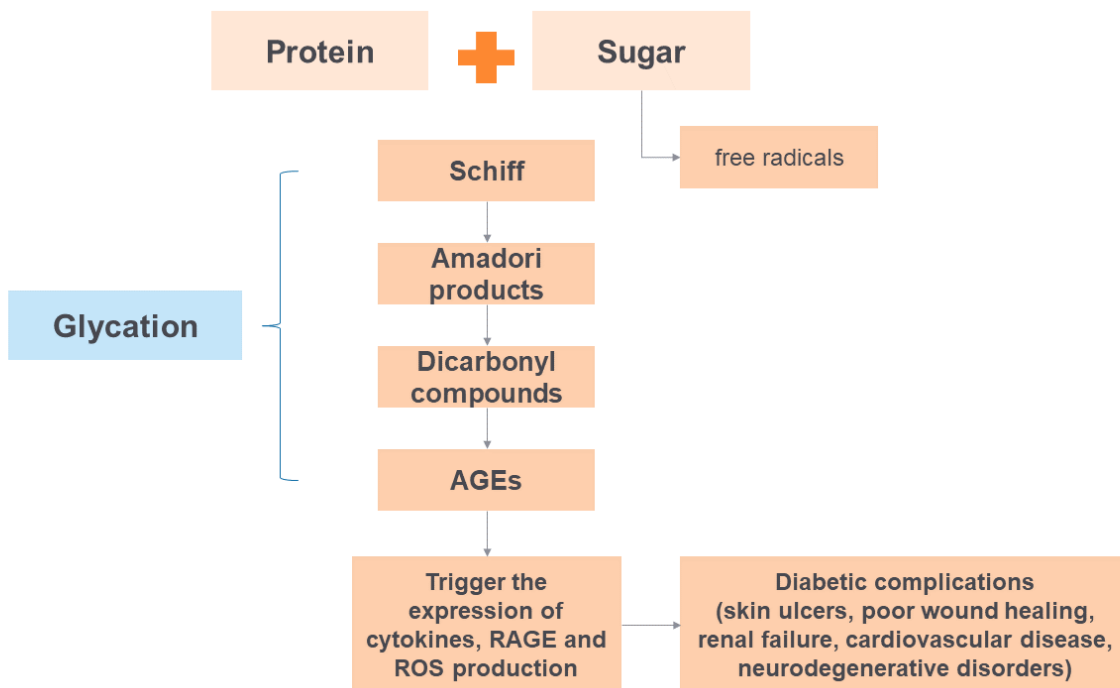
The formation of AGEs and activation of AGE pathways are also implicated in other chronic illnesses and conditions marked by an underlying inflammatory element, such as cardiovascular disease, neurodegenerative processes, and kidney disorders (Figure 1).^{1-5,23} Whether AGEs are involved in initiating or driving the progression of such diseases remains unclear. Still, research scholars theorize that AGEs may help elicit cellular responses and pathways that involve pro-inflammatory signals and promote oxidative stress, leading to age-related disease and metabolic disorders (see Figure 1 for a summary of key biological effects and consequences of AGEs in humans).²

Recommendations for Preventing Skin Glycation and Reducing AGEs

Lifestyle Modification

Clinicians should emphasize to their patients that the most direct strategy to mitigate the accumulation of AGEs is to restrict the intake of exogenous sources of sugar and heat-treated foods (eg, fried and baked foods) (Figure 2). This aligns with the observation that patients with diabetes and renal failure who receive a diet low in AGEs have reduced circulating levels of AGEs and inflammatory biomarkers.^{15,24,25} Therefore, it is recommended that patients are educated on how to modify their lifestyle by regularly exercising and changing their diet to consume healthier foods. Consuming fruits and vegetables may be beneficial since they contain antioxidants, such as phytochemicals, phenolic acids, and polyphenols, that can contend with AGE-related free radical stress.¹⁻⁵ Additional lifestyle modifications include limiting the use of cigarettes,

FIGURE 1. AGEs: Biological effects and involvement in human disease.⁵



Creative Commons Attribution Licenses 4.0 Adapted from Kang Q, et al. Advanced glycation end products in diabetic retinopathy and phytochemical therapy. *Front Nutr.* 2022;9:1037186.

reducing consumption of alcoholic beverages, and lessening exposure to environmental pollutants and UV light, as these are all exogenous sources of AGEs.¹⁻⁵

Emerging Investigative Agents and the Role of Nutraceuticals

Several promising pharmacologic approaches are being studied, all aimed at processes that target AGEs and the chemical steps that lead to their formation. Current classes of agents under study include carbonyl-trapping agents, which aim to reduce carbonyl stress; metal ion chelators or free radical scavengers, which work to block sugar oxidation; crosslinking reversal agents, which undo cross-linked AGEs; and the use of RAGE antagonists (eg, anti-RAGE antibodies, soluble decoy RAGE, and small molecule inhibitors) to lessen the effects of free radical-mediated stress and inflammation in tissues.¹⁻⁵ However, these approaches are still in their early development phases, and much work remains to establish their place as emerging treatments to target AGEs.

Topical formulations containing plant-based compounds have been studied for their antioxidant and antiglycation properties in the skin.^{1-3,5} Such compounds may be derived from licorice root (eg, glycyrrhetic acid) and wild fruits (eg, anthocyanins, flavonoids).^{26,27} Blueberry extract is another organic source rich in antioxidants and has been studied for its potential beneficial role in several diseases, including type 2 diabetes (T2D).²⁸ In one small study of 20 female patients with T2D, a topical formulation containing blueberry extract and C-xyloside (a glycosaminoglycan stimulator) significantly improved several parameters of skin aesthetics including fine lines ($P=.01$), firmness ($P=.0011$), radiance ($P<.001$), tone ($P=.014$), smoothness ($P<.001$), creping ($P<.004$), and overall appearance ($P<.001$).²⁹ However, researchers were unable to measure changes in AGEs due to the short duration of the study (12 weeks).²⁹ Further trials are needed to analyze this topical formulation over extended periods and capture potential meaningful changes in skin AGEs.

Another emerging strategy to prevent excessive skin glycation due to AGEs includes the use of exogenous collagen. In a recent study of 31 Japanese patients aged 47 to 87 years old,

FIGURE 2. Strategies for reducing AGEs: Lifestyle recommendations.³³⁻³⁶



the investigators showed that consumption of exogenous collagen (5 g, derived from fish) containing high concentrations of prolyl-hydroxyproline and hydroxyprolyl-glycine or placebo for 12 weeks resulted in significantly lower levels of skin AGEs ($P < .05$) and a slightly lower insulin resistance index (correlation between the rate of change in levels of AGEs and the rate of change in the homeostasis model assessment ratio, [HOMA-R values, an indicator of insulin resistance]). The study formulation was well tolerated, with no significant safety signals reported.³⁰ Although larger trials in a broader study population are needed, these data suggest that consumable collagen peptides should be further studied as a possible intervention to manage illnesses related to the accumulation of AGEs.

Lastly, vitamin supplements (eg, vitamins B₆, C, D, E) can also target the process of glycation since they can scavenge free radicals, preventing the generation of reactive intermediates involved in forming AGEs.^{1,15,31,32}

Clinical Pearls From the Physician

Remember, it is important to counsel your patients on how to make their skin look healthier and protect it from external factors that may enhance the metabolism of AGEs and their toxic accumulation. Important lifestyle modifications include increasing the consumption of fruits and vegetables that are enriched with antioxidants and refraining from eating foods that are high in sugar, baked, fried, or roasted.³⁷ Patients should also refrain from smoking and excess alcohol consumption.^{36,37} Incorporating a daily supplement that contains vitamins C, D, and E into one's daily regimen may also help maintain skin health, as these nutrients can aid in building a line of defense against AGEs and associated oxidative stress.³² Patients may also consider applying a daily moisturizer cream, sunscreen, or facial foundation to shield them from the unwanted effects of UV rays and pollutants (eg, aerosolized nanoparticles).³⁸ Lastly, for patients who use makeup, using colored cosmetics that contain talc, kaolin, or oxide-based compounds (eg, titanium oxide, iron oxide) is advised.^{39,40} This is important as it can provide an additional layer of skin protection against the effects of environmental insults that cause glycation and speed up the aging process.

DISCLOSURES

Zoe Diana Draelos MD has the following relevant financial relationships: Contracted researcher and consultant for: Aclaris Therapeutics, Inc.; Aesthetics Biomedical; Allergan, Almirall; Amderma; Amgen, Inc.; AOBiome; Arcutis Biotherapeutics, Inc.; Bausch Heath; Bayer AG; Biopelle; Boehringer Ingelheim Pharmaceuticals, Inc.; Boots; Botanix Pharmaceuticals; Brickell Biotech, Inc.; Burt's Bees; Carpe; Chattem Chemicals Inc.; The Chlorox Company; Clarke Pharmaceuticals, Inc.; Colgate-Palmolive Company; Coloplast Corp.; Combe; DelArrivo, Inc.; Dermavant Sciences, Inc.; Dermira, Inc.; Dial; Dr. Reddy's Laboratories Ltd.; Estée Lauder Inc.; E.T. Browne Drug Co., Inc.; Evolus, Inc.; Ferndale Laboratories, Inc.; Foamix Pharmaceuticals Ltd.; Galderma Laboratories, LP; Genentech, Inc.; General Mills, Inc.; GlaxoSmithKline; Helix Biomedix, Inc.; Henkel; International Specialty Products, Inc.; Johnson & Johnson Services, Inc.; Kamedis; Kao Corporation; La Roche-Posay; LEO Pharma Inc.; Lilly; L'Oréal; Maruho Co., Ltd.; Merck; Nice-Pak Products, Inc.; Novartis; Nu Skin; Perricone MD; Perrigo Company plc; Pfizer Inc.; PharmaNet, Inc.; Proctor & Gamble; Reckitt Benckiser Group plc; Revance Therapeutics, Inc.; Rodan & Fields, LLC; Roivant Sciences Ltd; Sanofi; SkinCeuticals; Symrise; Taro Pharmaceuticals Industries Ltd.; Teoxane; TEVA Pharmaceuticals USA, Inc.; Topix Pharmaceuticals, Inc.; Vanda Pharmaceuticals Inc.; Verrica Pharmaceuticals; Warner-Chilcott; WellSpring Pharmaceutical Corporation; YA-MAN Ltd; ZO Skin Health, Inc.

Compensation: Zoe Diana Draelos MD received an honorarium from Medscape Education for authorship of this manuscript.

Commercial Supporter: Supported by an independent educational grant from SkinCeuticals.

ACKNOWLEDGMENT

The author would like to thank Briana Betz PhD and Jason Luis Quiñones PhD for their assistance in drafting the manuscript, Joel Vega for his editorial assistance, and Trudy Grenon Stoddert ELS for her editorial assistance and for preparing the manuscript for submission.

REFERENCES

- Zheng W, Li H, Go Y, et al. Research advances on the damage mechanism of skin glycation and related inhibitors. *Nutrients*. 2022;14:4588.
- Zgutka K, Tkacz M, Tomasiak P, et al. A role for advanced glycation end products in molecular ageing. *Int J Mol Sci*. 2023;24:9881.
- Chen C-Y, Zhang J-Q, Li L, et al. Advanced glycation end products in the skin: Molecular mechanisms, methods of measurement, and inhibitory pathways. *Front Med (Lausanne)*. 2022;9:837222.
- Twarda-Clapa A, Olezak A, Bialkowska AM, et al. Advanced glycation end-products (AGEs): Formation, chemistry, classification, receptors, and diseases related to AGEs. *Cells*. 2022;11:1312.
- Kang Q, Dai H, Jiang S, et al. Advanced glycation end products in diabetic retinopathy and phytochemical therapy. *Front Nutr*. 2022;9:1037186.
- Inan-Eroglu E, Ayaz A, Buyuktuncer Z, et al. Formation of advanced glycation endproducts in foods during cooking process and underlying mechanisms: a comprehensive review of experimental studies. *Nutr Res Rev*. 2020;33:77-89.
- Garone M, Howard J, Fabrikant J. A review of common tanning methods. *J Clin Aesthet Dermatol*. 2015;8:43-47.
- Smith KR, Granberry M, Tan MC, et al. Dihydroxyacetone induces G2/M arrest and apoptotic cell death in A375P melanoma cells. *Environ Toxicol*. 2018;33:333-342.
- Perer J, Jandova J, Fimbres J, et al. The sunless tanning agent dihydroxyacetone induces stress response gene expression and signaling in cultured human keratinocytes and reconstructed epidermis. *Redox Biol*. 2020;36:101594.
- Petersen AB, Wulf HX, Gniadecki R, et al. Dihydroxyacetone, the active browning ingredient in sunless tanning lotions, induces DNA damage, cell-cycle block and apoptosis in cultured HaCaT keratinocytes. *Mutat Res*. 2004;560:173-186.
- Yourick JJ, Koenig ML, Yourick DL, et al. Fate of chemicals in skin after dermal application: does the in vitro skin reservoir affect the estimate of systemic absorption? *Toxicol Appl Pharmacol*. 2004;195:309-320.
- de Araújo R, Lôbo M, Trindade K, et al. Fibroblast growth factors: A controlling mechanism of skin aging. *Skin Pharmacol Physiol*. 2019;32:275-282.
- Basta G, Lazzerini G, Turco SD, et al. At least 2 distinct pathways generating reactive oxygen species mediate vascular cell adhesion molecule-1 induction by advanced glycation end products. *Arterioscler Thromb Vasc Biol*. 2005;25:1401-1407.

14. Yeh CH, Sturgis L, Haidacher J, et al. Requirement for p38 and p44/p42 mitogen-activated protein kinases in RAGE-mediated nuclear factor-kappaB transcriptional activation and cytokine secretion. *Diabetes*. 2001;50:1495-1504.
15. Gkogkolou P, Böhm M. Advanced glycation end products (AGEs): Emerging mediators of skin aging. In: Farage M, Miller K, Maibach H, eds. *Textbook of Aging Skin*. Berlin, Germany: Springer-Verlag. 2016;1-12.
16. Gkogkolou P, Böhm M. Advanced glycation end products: Key players in skin aging? *Dermatoendocrinol*. 2012;4:259-270.
17. Qing C. The molecular biology in wound healing & non-healing wound. *Chin J Traumatol*. 2017;20:189-193.
18. Jud P, Sourij H. Therapeutic options to reduce advanced glycation end products in patients with diabetes mellitus: A review. *Diabetes Res Clin Pract*. 2019;148:54-63.
19. Uruska A, Gandecka A, Araszkiwicz A, et al. Accumulation of advanced glycation end products in the skin is accelerated in relation to insulin resistance in people with type 1 diabetes mellitus. *Diabet Med*. 2019;36:620-625.
20. Yu Y, Thorpe SR, Jenkins AJ, et al. Advanced glycation end-products and methionine sulphoxide in skin collagen of patients with type 1 diabetes. *Diabetologia*. 2006;49:2488-2498.
21. Quondamatteo F. Skin and diabetes mellitus: what do we know? *Cell Tissue Res*. 2014;355:1-21.
22. Argyropoulos AJ, Robichaud P, Balimunkwe RM, et al. Alterations of dermal connective tissue collagen in diabetes: Molecular basis of aged-appearing skin. *PLoS One*. 2016;11:e0153806.
23. Cepas V, Collino M, Mayo JC, et al. Redox signaling and advanced glycation endproducts (AGEs) in diet-related diseases. *Antioxidants (Basel)*. 2020;9:142.
24. Uribarri J, Peppas M, Xai W, et al. Dietary glycotoxins correlate with circulating advanced glycation end product levels in renal failure patients. *Am J Kidney Dis*. 2003;42:532-538.
25. Chao P-C, Huang C-N, Hsu C-C, et al. Association of dietary AGEs with circulating AGEs, glycated LDL, IL-1 α and MCP-1 levels in type 2 diabetic patients. *Eur J Nutr*. 2010;49:429-434.
26. Rehman MU, Farooq A, Ali R, et al. Preclinical evidence for the pharmacological actions of glycyrrhizic acid: A comprehensive review. *Curr Drug Metab*. 2020;21:436-465.
27. Li Y, Zhang J-J, Xu D-P, et al. Bioactivities and health benefits of wild fruits. *Int J Mol Sci*. 2016;17:1258.
28. Kalt W, Cassidy A, Howard LR, et al. Recent research on the health benefits of blueberries and their anthocyanins. *Adv Nutr*. 2020;11:224-236.
29. Draelos ZD, Yatskayer M, Raab S, et al. An evaluation of the effect of a topical product containing C-xyloside and blueberry extract on the appearance of type II diabetic skin. *J Cosmet Dermatol*. 2009;8:147-151.
30. Koizumi S, Okada Y, Miura S, et al. Ingestion of a collagen peptide containing high concentrations of prolyl-hydroxyproline and hydroxyprolyl-glycine reduces advanced glycation end products levels in the skin and subcutaneous blood vessel walls: a randomized, double-blind, placebo-controlled study. *Biosci Biotechnol Biochem*. 2023;87:883-889.
31. Anwar S, Khan S, Almatroudi A, et al. A review on mechanism of inhibition of advanced glycation end products formation by plant derived polyphenolic compounds. *Mol Biol Rep*. 2021;48:787-805.
32. Draelos ZD. Aging skin: the role of diet: facts and controversies. *Clin Dermatol*. 2013;31:701-706.
33. Zawada A, Machowiak A, Rychter AM, et al. Accumulation of advanced glycation end-products in the body and dietary habits. *Nutrients*. 2022;14:3982.
34. Zheng W, Li H, Go Y, et al. Research advances on the damage mechanism of skin glycation and related inhibitors. *Nutrients*. 2022;14:4588.
35. Ruiz HH, Ramasamy R, Schmidt AM. Advanced glycation end products: Building on the concept of the "common soil" in metabolic disease. *Endocrinology*. 2020;161:bqz006.
36. Rungratanawanich W, Qu Y, Wang Z, et al. Advanced glycation end products (AGEs) and other adducts in aging-related diseases and alcohol-mediated tissue injury. *Exp Mol Med*. 2021;53:168-188.
37. Prasad C, Imrhan V, Marotta F, et al. Lifestyle and advanced glycation end products (AGEs) burden: Its relevance to healthy aging. *Aging Dis*. 2014;5:212-217.
38. Draelos ZD. Revisiting the skin health and beauty pyramid: A Clinically Based Guide to Selecting Topical Skincare Products. *J Drugs Dermatol*. 2021;20:695-699.
39. Draelos ZD. The multifunctional value of sunscreen-containing cosmetics. *Skin Therapy Lett*. 2011;16:1-3.
40. Lim HW, Draelos ZD, eds. *Clinical Guide to Sunscreens and Photoprotection*. 1st ed. CRC Press;2009.

AUTHOR CORRESPONDENCE

Zoe Diana Draelos MD

E-mail:..... zdraelos@northstate.net

