

# Skin Photoprotection by Polyphenols

Subjects: Chemistry, Medicinal

Contributor: Farid Mena

Polyphenols are phytochemicals with proven antioxidant and antiinflammatory properties. Premature aging and UV-induced skin conditions could be better overcome by topical polyphenols nanoformulations. Further, polyphenols nanoformulations can be of great interest for the cosmetic industries and any individuals who want to improve their skin appearance. Examples in this regard are provided and the potential toxicity issues related to the use of nanomaterials are highlighted.

Keywords: Nanomaterials ; Nanoparticles ; Nanomedicine ; Bioactive molecules ; Antioxidants ; Antiinflammatory ; Dermatology ; Polyphenols ; Cosmetics ; Topical application ; Skin conditions

---

## 1. Introduction

For over a decade, reports from animal models and humans have increasingly provided evidence that polyphenols have potential benefits on skin (e.g., photoprotection, anti-aging features), due to their antiinflammatory, antioxidant and deoxyribonucleic acid (DNA) repair properties. <sup>[1][2][3][4][5][6][7]</sup>

Polyphenols are represented by a superfamily of various naturally occurring phytochemicals (> 4000) that are abundant in our diet (e.g., vegetables, fruits, nuts, seeds). <sup>[8][9]</sup> These compounds are divided into three main classes (i.e., flavonoids, stilbenes and lignans), which are further subdivided according to their structural similarities (e.g., number of phenol rings). <sup>[1][8][9]</sup>

Their chemical structures, molecular mechanisms, metabolism, relative systemic bioavailability, plant source and content of various dietary polyphenols have been reviewed elsewhere. <sup>[8][9][10][11][12][13]</sup>

Interestingly, a controlled transdermal application of certain polyphenols (e.g., resveratrol and EGCG) for treating skin conditions (e.g., photo-damaged skin), in their bulk- or, preferentially, their nano-forms, usually present the following advantages compared to that of oral or intravenous intake: (1) maximization of local exposure, (2) an increase in the efficacy, (3) improvement of the stability (e.g., decrease of photo-induced polyphenols degradation), (4) minimization of the administered dose, (5) enhancement of the bioavailability at the targeted site (e.g., skin), and (6) reduction of the systemic toxicity (i.e., contribution to the individual's safety). <sup>[14][15][16][17][18][19][20]</sup>

Chronic exposure or acute high doses of UV, such as solar ultraviolet irradiation (UVR)—especially UV-type A radiation (UVA, 315-400 nm), which constitutes about 95% of the UVR in natural sunlight reaching the earth's surface—is known to induce a series of damage to the skin (e.g., direct molecular damage such as DNA strand breaks and/or oxidative stress-mediated damage such as lipid peroxidation). This, subsequently, can lead to photoaging (aka UV-induced premature/accelerated skin aging) or photo-carcinogenesis (aka skin UV-induced cancers). <sup>[21][22][23][24][25]</sup> For instance, it is known that after UVR-induced reactive oxygen species (ROS), the metalloproteinases (MMP)-1, -3, -9 levels are increased, causing collagen and elastin degradation before forming coarse wrinkles and sagging skin. <sup>[26]</sup> However, these overall effects can be reduced by polyphenols (e.g., tea-derived catechins), which consequently contribute to a slow-down of the aging process and reduce the incidence of skin cancers (e.g., melanomas or nonmelanomas such as squamous cell carcinoma (SCC) or basal cell carcinoma (BCC)). <sup>[1][26][27][28][29][30][31][32][33][34][35][36][37][38]</sup>

Therefore, the evaluation of skin polyphenol-based products (e.g., polyphenol-rich sunscreens), <sup>[6][29][39][40][41][42][43]</sup> as well as the potential benefit of dietary polyphenols, <sup>[31][44][45][46][47][48]</sup> is promising and remains a challenging field of research.

Nevertheless, one should still keep in mind that some polyphenols could be a double-edged sword for the human skin, exerting not only protective (i.e., antioxidation) but also possible damaging actions (e.g., allergic reactions, contact dermatitis, phytodermatoses, and photo-phytodermatoses, enhanced UV-induced apoptosis of "normal" cells) depending on their physico-chemical parameters. <sup>[13][14]</sup>

## 2. Skin PhotoProtective Effects of Polyphenols: An Overview

A number of scientific studies with certain phytochemicals such as tea-, grape-, or soy-derived polyphenols, performed in animal models and humans/human cells exposed to UV-induced DNA damage, have provided a molecular basis to mechanistically explain the anti-skin photoaging (e.g., anti-accelerated signs of aging such as reduced wrinkles, improvement in elastic tissue content) as well as the skin photo-chemopreventive effect (e.g., DNA repair and antioxidant activities, anti-photo-induced immune suppression such as anti-depletion of antigen-presenting cells (APC)), suggesting that these natural compounds can serve as alternatives or enhancers to sunscreens or as dietary supplements.

EGCG is a green-tea derived catechin polyphenol (i.e., flavanol). Several studies [27][28][30][32][33][34][35][36][37][38][49][50][51][52][53][54][55] have reported potential benefits of oral administration or topical applications of EGCG for preventing or treating skin conditions (e.g., skin photo-damage) in animals (e.g., usually mice) and humans. Indeed, EGCG displays a number of features such as anti-inflammatory, antioxidant and DNA repair activities. [4]

Resveratrol is a phytoalexin antioxidant derived from natural products such as the skin of red grapes, peanuts, blueberries and cranberries. [8][9] Resveratrol has received extensive attention through the link with the "French paradox," and later with its chemopreventive activity demonstrated in animal cancer models and in humans. [45][56][57][58][59][60][61][62][63][64][65][66][67]

Silymarin consists of a family of flavonoids (silibinin (a major member [68]), isosilybin, silychristin, silydianin, and taxifoline) commonly found in the dried fruit of the milk thistle plant *Silybum marianum* (L. Gaertner). Silymarin was recently shown to display chemopreventive effects, antioxidant, anti-inflammatory, and immune-modulatory properties. Studies have also revealed that it can be valuable against photo-induced carcinogenesis and premature aging, [68][69][70][71] in various animal tumor models [72][73][74][75][76] and humans. [77][78][79][80] Moreover, silymarin may favorably supplement sunscreen protection. [68][69][70][74]

The soybean isoflavone genistein (aglycone) is a potent antioxidant, a specific inhibitor of protein tyrosine kinase, and a phytoestrogen with photoprotective properties. [81] During the past decade, a series of studies and reports have demonstrated that genistein (as topical, oral or systemic agent) has significant antiphotocarcinogenic and anti-photoaging effects in animal models (e.g., mice, pigs) [82][83] and human cells (e.g., fibroblasts, keratinocytes). [84][85][86][87][88]

Ellagic acid (EA) is a phenolic acid found in a wide variety of fruits and nuts such as raspberries, strawberries, pomegranate, walnuts, grapes, and blackcurrants. [89][90] These molecules are receiving particular attention as agents that may have potential bioactivities preventing skin photo-damage in human cells due to their potent ability to scavenge ROS and reactive nitrogen species (RNS), [90][91][92] decreasing the expression of pro-MMP-2 and pro-MMP-9, precursors of two elastolytic enzymes, [93] and inhibiting cell proliferation. [93]

## 3. Conclusion

Most of the polyphenols presented in this chapter are emerging as efficient skin photoprotectors. Indeed, the overall studies performed in animal models and/or in humans show that these phytochemicals exert skin photoprotective properties, especially through their antioxidant (i.e., as scavengers of free radicals), anti-inflammatory, and antitumoral activities. It is becoming clear that topical/transdermal application of polyphenols (i.e., as cosmeceutics) presents certain advantages (e.g., lower systemic toxicity usually associated with required increased doses to reach a specific tissue) over oral or intravenous administration (e.g., as nutraceuticals) of these phytochemicals. Further, polyphenol nano-formulations are proving to have advanced pharmacological effects (e.g., efficacy, safety, selectivity) compared to the therapeutic entities they contain. Evidently, although it appears that the prospects are very bright for the possible use of polyphenols in skin photoprotection, more clinical trials are needed with pure bulk- or nano-polyphenols formulations.

---

## References

1. Menaa F., Menaa A., Tréton J.. Polyphenols against skin aging; Watson R.R., Preedy V.R., Zibadi S., Eds.; Academic Press: Sandiego, CA, USA, 2014; pp. 819-830.
2. Farrukh Afaq; Polyphenols: Skin Photoprotection and Inhibition of Photocarcinogenesis. *Mini-Reviews in Medicinal Chemistry* **2011**, 11, 1200-1215, [10.2174/13895575111091200](#).
3. Stéphane Quideau; Denis Deffieux; Céline Douat-Casassus; Laurent Pouységu; Plant Polyphenols: Chemical Properties, Biological Activities, and Synthesis. *Angewandte Chemie International Edition* **2011**, 50, 586-621, [10.1002/anie.201000044](#).

4. Joi A. Nichols; Santosh K. Katiyar; Skin photoprotection by natural polyphenols: anti-inflammatory, antioxidant and DNA repair mechanisms. *Archives of Dermatological Research* **2009**, 302, 71-83, [10.1007/s00403-009-1001-3](https://doi.org/10.1007/s00403-009-1001-3).
5. Felipe Jiménez; Thomas F. Mitts; Kela Liu; Yanting Wang; Aleksander Hinek; Ellagic and Tannic Acids Protect Newly Synthesized Elastic Fibers from Premature Enzymatic Degradation in Dermal Fibroblast Cultures. *Journal of Investigative Dermatology* **2006**, 126, 1272-1280, [10.1038/sj.jid.5700285](https://doi.org/10.1038/sj.jid.5700285).
6. Sheldon R. Pinnell; Cutaneous photodamage, oxidative stress, and topical antioxidant protection. *Journal of the American Academy of Dermatology* **2003**, 48, 1-22, [10.1067/mjd.2003.16](https://doi.org/10.1067/mjd.2003.16).
7. P. Morganti; C. Bruno; F. Guarneri; A. Cardillo; P. Del Ciotto; F. Valenzano; Role of topical and nutritional supplement to modify the oxidative stress\*. *International Journal of Cosmetic Science* **2002**, 24, 331-339, [10.1046/j.1467-2494.2002.00159.x](https://doi.org/10.1046/j.1467-2494.2002.00159.x).
8. Massimo D'archivio; Carmela Filesi; Roberta Di Benedetto; Raffaella Gargiulo; Claudio Giovannini; Roberta Masella; Polyphenols, dietary sources and bioavailability.. *Annali dell'Istituto Superiore di Sanità* **2007**, 43, 348-361, .
9. Claudine Manach; Augustin Scalbert; Christine Morand; Christian Rémésy; Liliana Jiménez; Polyphenols: food sources and bioavailability. *The American Journal of Clinical Nutrition* **2004**, 79, 727-747, [10.1093/ajcn/79.5.727](https://doi.org/10.1093/ajcn/79.5.727).
10. Scholz; Gary Williamson; Interactions Affecting the Bioavailability of Dietary Polyphenols in Vivo. *International Journal for Vitamin and Nutrition Research* **2007**, 77, 224-235, [10.1024/0300-9831.77.3.224](https://doi.org/10.1024/0300-9831.77.3.224).
11. Claudine Manach; Gary Williamson; Christine Morand; Augustin Scalbert; Christian Rémésy; Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. *The American Journal of Clinical Nutrition* **2005**, 81, 230S-242S, [10.1093/ajcn/81.1.230s](https://doi.org/10.1093/ajcn/81.1.230s).
12. G. Williamson; Claudine Manach; Bioavailability and bioefficacy of polyphenols in humans. II. Review of 93 intervention studies. *The American Journal of Clinical Nutrition* **2005**, 81, 243S-255S, [10.1093/ajcn/81.1.243s](https://doi.org/10.1093/ajcn/81.1.243s).
13. Liudmila Korkina; Saveria Pastore; Chiara De Luca; Vladimir A. Kostyuk; Metabolism of Plant Polyphenols in the Skin: Beneficial Versus Deleterious Effects. *Current Drug Metabolism* **2008**, 9, 710-729, [10.2174/138920008786049267](https://doi.org/10.2174/138920008786049267).
14. Menaa F., Menaa A., Menaa B.. Polyphenols nano-formulations for topical delivery and skin tissue engineering; Watson R.R., Preedy V.R., Zibadi S., Eds.; Academic Press: Sandiego, CA, USA, 2014; pp. 839-848.
15. Charles-Henry Cottart; Valérie Nivet-Antoine; Christelle Laguillier-Morizot; Jean-Louis Beaudeux; Resveratrol bioavailability and toxicity in humans. *Molecular Nutrition & Food Research* **2009**, 54, 7-16, [10.1002/mnfr.200900437](https://doi.org/10.1002/mnfr.200900437).
16. Howard Epstein; Cosmeceuticals and polyphenols. *Clinics in Dermatology* **2009**, 27, 475-478, [10.1016/j.clindermatol.2009.05.011](https://doi.org/10.1016/j.clindermatol.2009.05.011).
17. Tatsiana G. Shutava; Shantanu S. Balkundi; Pranitha Vangala; Joshua J. Steffan; Rebecca L. Bigelow; James A. Cardelli; D. Patrick O'Neal; Yuri Lvov; Layer-by-Layer-Coated Gelatin Nanoparticles as a Vehicle for Delivery of Natural Polyphenols. *ACS Nano* **2009**, 3, 1877-1885, [10.1021/nn900451a](https://doi.org/10.1021/nn900451a).
18. A. Barras; A. Mezzetti; A. Richard; S. Lazzaroni; S. Roux; P. Melnyk; D. Betbeder; N. Monfiliette-Dupont; Formulation and characterization of polyphenol-loaded lipid nanocapsules. *International Journal of Pharmaceutics* **2009**, 379, 270-277, [10.1016/j.ijpharm.2009.05.054](https://doi.org/10.1016/j.ijpharm.2009.05.054).
19. Chow H.H., Cai Y., Hakim I.A., Crowell J.A., Shahi F., Brooks C.A., et al.; Pharmacokinetics and safety of green tea polyphenols after multiple-dose administration of epigallocatechingallate and polyphenon E in healthy individuals. *Clin. Cancer Res.* **2003**, 9, 3312-3319, .
20. A. Scalbert; Christine Morand; Claudine Manach; Christian Rémésy; Absorption and metabolism of polyphenols in the gut and impact on health. *Biomedicine & Pharmacotherapy* **2002**, 56, 276-282, [10.1016/s0753-3322\(02\)00205-6](https://doi.org/10.1016/s0753-3322(02)00205-6).
21. Kozina L.S., Borzova I.V., Arutiunov V.A., Ryzhak G.A.; The role of oxidative stress in skin aging. *Adv. Gerontol.* **2012**, 25, 217-222, .
22. P.S. Peres; V.A. Terra; F.A. Guarneri; R. Cecchini; A.L. Cecchini; Photoaging and chronological aging profile: Understanding oxidation of the skin. *Journal of Photochemistry and Photobiology B: Biology* **2011**, 103, 93-97, [10.1016/j.jphotobiol.2011.01.019](https://doi.org/10.1016/j.jphotobiol.2011.01.019).
23. Ichihashi M., Ueda M., Budyanto A.; UV-induced skin damage. *Toxicology* **2003**, 189, 21-39, .
24. Christel Masson; Farid Menaa; Ghislaine Pinon-Lataillade; Yveline Frobert; Sylvie Chevillard; J. Pablo Radicella; Alain Sarasin; Jaime F. Angulo; Global genome repair is required to activate KIN17, a UVC-responsive gene involved in DNA replication. *Proceedings of the National Academy of Sciences* **2003**, 100, 616-621, [10.1073/pnas.0236176100](https://doi.org/10.1073/pnas.0236176100).
25. Mukhtar H., Elmetts C.A.; Photocarcinogenesis: Mechanisms, Models and Human Health Implications. *Photochemistry and Photobiology* **1996**, 63, 355-355, [10.1111/j.1751-1097.1996.tb03039.x](https://doi.org/10.1111/j.1751-1097.1996.tb03039.x).

26. Hsiu-Mei Chiang; Tsen-Jung Lin; Chen-Yuan Chiu; Chiung-Wen Chang; Kuo-Chiu Hsu; Pei-Ching Fan; Kuo-Ching Wen; Coffea arabica extract and its constituents prevent photoaging by suppressing MMPs expression and MAP kinase pathway. *Food and Chemical Toxicology* **2011**, 49, 309-318, [10.1016/j.fct.2010.10.034](#).
27. Santosh K. Katiyar; Green tea prevents non-melanoma skin cancer by enhancing DNA repair. *Archives of Biochemistry and Biophysics* **2011**, 508, 152-158, [10.1016/j.abb.2010.11.015](#).
28. Murat Turkoglu; T Uğurlu; G Gedik; A M Yılmaz; A. Süha Yalçın; In vivo evaluation of black and green tea dermal products against UV radiation.. *Drug Discoveries & Therapeutics* **2010**, 4, 362-367, .
29. S. Saraf; Chanchal Deep Kaur; Phytoconstituents as photoprotective novel cosmetic formulations. *Pharmacognosy Reviews* **2010**, 4, 1-11, [10.4103/0973-7847.65319](#).
30. Melissa M. Camouse; Diana Santo Domingo; Freddie R. Swain; Edward P. Conrad; Mary S. Matsui; Daniel Maes; Lieve Declercq; Kevin D. Cooper; Seth R. Stevens; Elma D. Baron; et al. Topical application of green and white tea extracts provides protection from solar-simulated ultraviolet light in human skin. *Experimental Dermatology* **2009**, 18, 522-526, [10.1111/j.1600-0625.2008.00818.x](#).
31. Eve Bralley; Phillip Greenspan; James L. Hargrove; Diane K. Hartle; Inhibition of Hyaluronidase Activity by Select Sorghum Brans. *Journal of Medicinal Food* **2008**, 11, 307-312, [10.1089/jmf.2007.547](#).
32. Annie E. Chiu; Joanna L. Chan Ab; Dale G. Kern; Sabine Kohler; Wingfield E. Rehms; Alexa B. Kimball; Double-Blinded, Placebo-Controlled Trial of Green Tea Extracts in the Clinical and Histologic Appearance of Photoaging Skin. *Dermatologic Surgery* **2006**, 31, 855-860, [10.1111/j.1524-4725.2005.31731](#).
33. Farrukh Afaq; Nihal Ahmad; Hasan Mukhtar; Suppression of UVB-induced phosphorylation of mitogen-activated protein kinases and nuclear factor kappa B by green tea polyphenol in SKH-1 hairless mice. *Oncogene* **2003**, 22, 9254-9264, [10.1038/sj.onc.1207035](#).
34. Praveen K Vayalil; Craig A Elmets; Santosh K. Katiyar; Treatment of green tea polyphenols in hydrophilic cream prevents UVB-induced oxidation of lipids and proteins, depletion of antioxidant enzymes and phosphorylation of MAPK proteins in SKH-1 hairless mouse skin.. *Carcinogenesis* **2003**, 24, 927-936, [10.1093/carcin/bgg025](#).
35. Santosh K. Katiyar; H Mukhtar; Green tea polyphenol (-)-epigallocatechin-3-gallate treatment to mouse skin prevents UVB-induced infiltration of leukocytes, depletion of antigen-presenting cells, and oxidative stress.. *Journal of Leukocyte Biology* **2001**, 69, 719-726, .
36. Santosh Katiyar; Craig Elmets; Green tea polyphenolic antioxidants and skin photoprotection (Review). *International Journal of Oncology* **2001**, 18, 1307-1313, [10.3892/ijo.18.6.1307](#).
37. Craig A. Elmets; Divya Singh; Karen Tubesing; Mary Matsui; Santosh Katiyar; Hasan Mukhtar; Cutaneous photoprotection from ultraviolet injury by green tea polyphenols. *Journal of the American Academy of Dermatology* **2001**, 44, 425-432, [10.1067/mjd.2001.112919](#).
38. Santosh K. Katiyar; Craig A. Elmets; Rajesh Agarwal; Hasan Mukhtar; PROTECTION AGAINST ULTRAVIOLET-B RADIATION-INDUCED LOCAL and SYSTEMIC SUPPRESSION OF CONTACT HYPERSENSITIVITY and EDEMA RESPONSES IN C3H/HeN MICE BY GREEN TEA POLYPHENOLS. *Photochemistry and Photobiology* **2008**, 62, 855-861, [10.1111/j.1751-1097.1995.tb09147.x](#).
39. Talita Pizza Anunciato; Pedro Alves Da Rocha Filho; Carotenoids and polyphenols in nutricosmetics, nutraceuticals, and cosmeceuticals. *Journal of Cosmetic Dermatology* **2012**, 11, 51-54, [10.1111/j.1473-2165.2011.00600.x](#).
40. Lucy Chen; Judy Y. Hu; Steven Q. Wang; The role of antioxidants in photoprotection: A critical review. *Journal of the American Academy of Dermatology* **2012**, 67, 1013-1024, [10.1016/j.jaad.2012.02.009](#).
41. Nevla Delalle-Lozica; Local therapy as basic anti-aging prevention.. *Acta Clinica Croatica* **2010**, 49, 529-536, .
42. Bruce M. Freedman; Topical antioxidant application enhances the effects of facial microdermabrasion. *Journal of Dermatological Treatment* **2009**, 20, 82-87, [10.1080/09546630802301818](#).
43. Mary S. Matsui; Andrew Hsia; Janine D. Miller; Kaija Hanneman; Heather Scull; Kevin D. Cooper; Elma Baron; Non-Sunscreen Photoprotection: Antioxidants Add Value to a Sunscreen. *Journal of Investigative Dermatology Symposium Proceedings* **2009**, 14, 56-59, [10.1038/jidsymp.2009.14](#).
44. Patricia OyetakinWhite; Heather Tribout; Elma D. Baron; Protective Mechanisms of Green Tea Polyphenols in Skin. *Oxidative Medicine and Cellular Longevity* **2012**, 2012, 1-8, [10.1155/2012/560682](#).
45. Veronique S. Chachay; Carl M. J. Kirkpatrick; Ingrid J. Hickman; Maree Ferguson; Johannes B. Prins; Jennifer H. Martin; Resveratrol - pills to replace a healthy diet?. *British Journal of Clinical Pharmacology* **2011**, 72, 27-38, [10.1111/j.1365-2125.2011.03966.x](#).

46. Mary Ndiaye; Carol Philippe; Hasan Mukhtar; Nihal Ahmad; The grape antioxidant resveratrol for skin disorders: Promise, prospects, and challenges. *Archives of Biochemistry and Biophysics* **2011**, 508, 164-170, [10.1016/j.abb.2010.12.030](https://doi.org/10.1016/j.abb.2010.12.030).
47. Zoe Diana Draelos; Nutrition and enhancing youthful-appearing skin. *Clinics in Dermatology* **2010**, 28, 400-408, [10.1016/j.clindermatol.2010.03.019](https://doi.org/10.1016/j.clindermatol.2010.03.019).
48. Nick Morley; Tim Clifford; Leo Salter; Sandra Campbell; David Gould; Alison Curnow; The green tea polyphenol (-)-epigallocatechin gallate and green tea can protect human cellular DNA from ultraviolet and visible radiation-induced damage. *Photodermatology, Photoimmunology & Photomedicine* **2005**, 21, 15-22, [10.1111/j.1600-0781.2005.00119.x](https://doi.org/10.1111/j.1600-0781.2005.00119.x).
49. Santosh K. Katiyar; Mudit Vaid; Harry Van Steeg; Syed M. Meeran; Green tea polyphenols prevent UV-induced immunosuppression by rapid repair of DNA damage and enhancement of nucleotide excision repair genes.. *Cancer Prevention Research* **2010**, 3, 179-89, [10.1158/1940-6207.CAPR-09-0044](https://doi.org/10.1158/1940-6207.CAPR-09-0044).
50. Syed M. Meeran; Sudheer K. Mantena; Craig A. Elmet; Santosh K. Katiyar; (-)-Epigallocatechin-3-Gallate Prevents Photocarcinogenesis in Mice through Interleukin-12–Dependent DNA Repair. *Cancer Research* **2006**, 66, 5512-5520, [10.1158/0008-5472.can-06-0218](https://doi.org/10.1158/0008-5472.can-06-0218).
51. Praveen K. Vayalil; Anshu Mittal; Yukihiko Hara; Craig A. Elmet; Santosh K. Katiyar; Green Tea Polyphenols Prevent Ultraviolet Light-Induced Oxidative Damage and Matrix Metalloproteinases Expression in Mouse Skin. *Journal of Investigative Dermatology* **2004**, 122, 1480-1487, [10.1111/j.0022-202x.2004.22622.x](https://doi.org/10.1111/j.0022-202x.2004.22622.x).
52. Anshu Mittal; Chandrika Piyathilake; Yukihiko Hara; Santosh K. Katiyar; Exceptionally High Protection of Photocarcinogenesis by Topical Application of (-)-Epi gal locatechin-3-Gal late in Hydrophilic Cream in SKH-1 Hairless Mouse Model: Relationship to Inhibition of UVB-Induced Global DNA Hypomethylation. *Neoplasia* **2003**, 5, 555-565, [10.1016/s1476-5586\(03\)80039-8](https://doi.org/10.1016/s1476-5586(03)80039-8).
53. Jongll Kim; Jae-Sung Hwang; Youn-Ki Cho; Yongku Han; Young-Jin Jeon; K H Yang; Protective Effects of (-)-Epigallocatechin-3-Gallate on UVA- and UVB-Induced Skin Damage. *Skin Pharmacology and Physiology* **2001**, 14, 11-19, [10.1159/000056329](https://doi.org/10.1159/000056329).
54. Santosh K. Katiyar; Farrukh Afaq; Kashif Azizuddin; Hasan Mukhtar; Inhibition of UVB-Induced Oxidative Stress-Mediated Phosphorylation of Mitogen-Activated Protein Kinase Signaling Pathways in Cultured Human Epidermal Keratinocytes by Green Tea Polyphenol (-)-Epigallocatechin-3-gallate. *Toxicology and Applied Pharmacology* **2001**, 176, 110-117, [10.1006/taap.2001.9276](https://doi.org/10.1006/taap.2001.9276).
55. Santosh K. Katiyar; Mary S. Matsui; Craig A. Elmet; Hasan Mukhtar; Polyphenolic Antioxidant (-)-Epigallocatechin-3-Gallate from Green Tea Reduces UVB-Induced Inflammatory Responses and Infiltration of Leukocytes in Human Skin. *Photochemistry and Photobiology* **1999**, 69, 148-53, [10.1562/0031-8655\(1999\)069<0148:paegfg>2.3.co;2](https://doi.org/10.1562/0031-8655(1999)069<0148:paegfg>2.3.co;2).
56. Zhen Yang; Sun Yang; Bobbye J. Misner; Rita Chiu; Feng Liu; Frank L. Meyskens; Nitric oxide initiates progression of human melanoma via a feedback loop mediated by apurinic/aprimidinic endonuclease-1/redox factor-1, which is inhibited by resveratrol. *Molecular Cancer Therapeutics* **2008**, 7, 3751-3760, [10.1158/1535-7163.mct-08-0562](https://doi.org/10.1158/1535-7163.mct-08-0562).
57. Sharmila Shankar; Chemoprevention by resveratrol: molecular mechanisms and therapeutic potential. *Frontiers in Bioscience* **2007**, 12, 4839, [10.2741/2432](https://doi.org/10.2741/2432).
58. Meishiang Jang; Lining Cai; George O. Udeani; Karla V. Slowing; Cathy F. Thomas; Christopher W. W. Beecher; Harry H. S. Fong; Norman R. Farnsworth; A. Douglas Kinghorn; Rajendra G. Mehta; et al. Cancer Chemopreventive Activity of Resveratrol, a Natural Product Derived from Grapes. *Science* **1997**, 275, 218-220, [10.1126/science.275.5297.218](https://doi.org/10.1126/science.275.5297.218).
59. S. Renaud; M. De Lorgeril; Wine, alcohol, platelets, and the French paradox for coronary heart disease. *The Lancet* **1992**, 339, 1523-1526, [10.1016/0140-6736\(92\)91277-f](https://doi.org/10.1016/0140-6736(92)91277-f).
60. Kwang Ho Kim; Jung Ho Back; Yucui Zhu; Josh Arbesman; Mohammad Athar; Levy Kopelovich; Arianna L. Kim; David R. Bickers; Resveratrol Targets Transforming Growth Factor-β2 Signaling to Block UV-Induced Tumor Progression. *Journal of Investigative Dermatology* **2011**, 131, 195-202, [10.1038/jid.2010.250](https://doi.org/10.1038/jid.2010.250).
61. Moammir Hasan Aziz; Shannon Reagan-Shaw; Jianqiang Wu; B. Jack Longley; Nihal Ahmad; Chemoprevention of skin cancer by grape constituent resveratrol: relevance to human disease?. *The FASEB Journal* **2005**, 19, 1193-1195, [10.1096/fj.04-3582fje](https://doi.org/10.1096/fj.04-3582fje).
62. Moammir Hasan Aziz; Farrukh Afaq; Nihal Ahmad; Prevention of Ultraviolet-B Radiation Damage by Resveratrol in Mouse Skin Is Mediated via Modulation in Survivin. *Photochemistry and Photobiology* **2005**, 81, 25, [10.1562/2004-08-13-ra-274.1](https://doi.org/10.1562/2004-08-13-ra-274.1).
63. Shannon Reagan-Shaw; Farrukh Afaq; Moammir Hasan Aziz; Nihal Ahmad; Modulations of critical cell cycle regulatory events during chemoprevention of ultraviolet B-mediated responses by resveratrol in SKH-1 hairless mouse skin. *Oncogene* **2004**, 23, 5151-5160, [10.1038/sj.onc.1207666](https://doi.org/10.1038/sj.onc.1207666).

64. Farrukh Afaq; Vaqar Mustafa Adhami; Nihal Ahmad; Prevention of short-term ultraviolet B radiation-mediated damages by resveratrol in SKH-1 hairless mice.. *Toxicology and Applied Pharmacology* **2003**, 186, 28-37, .
65. Yong Liu; Fangxiao Chan; Haimei Sun; Jihong Yan; Dongying Fan; Dongzhi Zhao; Jing An; De-Shan Zhou; Resveratrol protects human keratinocytes HaCaT cells from UVA-induced oxidative stress damage by downregulating Keap1 expression. *European Journal of Pharmacology* **2011**, 650, 130-137, [10.1016/j.ejphar.2010.10.009](#).
66. Vaqar Mustafa Adhami; Farrukh Afaq; Nihal Ahmad; Suppression of Ultraviolet B Exposure-Mediated Activation of NF- $\kappa$ B in Normal Human Keratinocytes by Resveratrol1. *Neoplasia* **2003**, 5, 74-82, .
67. Sreekanth Narayanapillai; Chapla Agarwal; Cynthia Tilley; Rajesh Agarwal; Silibinin Is a Potent Sensitizer of UVA Radiation-induced Oxidative Stress and Apoptosis in Human Keratinocyte HaCaT Cells†. *Photochemistry and Photobiology* **2011**, 88, 1135-1140, [10.1111/j.1751-1097.2011.01050.x](#).
68. Santosh K. Katiyar; Silymarin and skin cancer prevention: anti-inflammatory, antioxidant and immunomodulatory effects (Review).. *International Journal of Oncology* **2005**, 26, 169-176, [10.3892/ijo.26.1.169](#).
69. Santosh K. Katiyar; Mudit Vaid; Molecular mechanisms of inhibition of photocarcinogenesis by silymarin, a phytochemical from milk thistle (*Silybum marianum* L. Gaertn). *International Journal of Oncology* **2010**, 36, 1053-1060, [10.3892/ijo.00000586](#).
70. Céline Couteau; Clotilde Cheignon; Eva Paparis; Laurence J M Coiffard; Silymarin, a molecule of interest for topical photoprotection. *Natural Product Research* **2012**, 26, 2211-2214, [10.1080/14786419.2011.637219](#).
71. Rajesh Agarwal; Charu Agarwal; Haruyo Ichikawa; Rana P Singh; Bharat B. Aggarwal; Anticancer potential of silymarin: from bench to bed side.. *Anticancer Research* **2007**, 26, 4457-4498, .
72. Mudit Vaid; Ram Prasad; Tripti Singh; Craig A. Elmet; Hui Xu; Santosh K. Katiyar; Silymarin inhibits ultraviolet radiation-induced immune suppression through DNA repair-dependent activation of dendritic cells and stimulation of effector T cells. *Biochemical Pharmacology* **2013**, 85, 1066-1076, [10.1016/j.bcp.2013.01.026](#).
73. Katiyar S.K., Meleth S., Sharma S.D.; Silymarin, a flavonoid from milk thistle (*Silybum marianum* L.), inhibits UV-induced oxidative stress through targeting infiltrating CD11b1 cells in mouse skin. *Photochem. Photobiol.* **2008**, 84, 266-271, .
74. S. M. Meeran; Silymarin inhibits UV radiation-induced immunosuppression through augmentation of interleukin-12 in mice. *Molecular Cancer Therapeutics* **2006**, 5, 1660-1668, [10.1158/1535-7163.mct-06-0095](#).
75. Santosh K. Katiyar; Treatment of silymarin, a plant flavonoid, prevents ultraviolet light-induced immune suppression and oxidative stress in mouse skin.. *International Journal of Oncology* **2002**, 21, 1213-1222, [10.3892/ijo.21.6.1213](#).
76. Santosh K. Katiyar; Neil J. Korman; Hasan Mukhtar; Rajesh Agarwal; Protective effects of silymarin against photocarcinogenesis in a mouse skin model.. *JNCI: Journal of the National Cancer Institute* **1997**, 89, 556-565, [10.1093/jnci/89.8.556](#).
77. Santosh K. Katiyar; Sudheer K. Mantena; Syed M. Meeran; Silymarin Protects Epidermal Keratinocytes from Ultraviolet Radiation-Induced Apoptosis and DNA Damage by Nucleotide Excision Repair Mechanism. *PLOS ONE* **2011**, 6, e21410, [10.1371/journal.pone.0021410](#).
78. Alena Rajnochová Svobodová; Adela Zdarilova; Jana Mališková; Hana Mikulková; Daniela Walterova; Jitka Vostálová; Attenuation of UVA-induced damage to human keratinocytes by silymarin. *Journal of Dermatological Science* **2007**, 46, 21-30, [10.1016/j.jdermsci.2006.12.009](#).
79. L.-H. Li; L.-J. Wu; S.-I. Tashiro; S. Onodera; F. Uchiumi; Takashi Ikejima; Activation of the SIRT1 pathway and modulation of the cell cycle were involved in silymarin's protection against UV-induced A375-S2 cell apoptosis. *Journal of Asian Natural Products Research* **2007**, 9, 245-252, [10.1080/10286020600604260](#).
80. Lin-Hao Li; Li-Jun Wu; Bei Zhou; Zhen Wu; Shin-Ichi Tashiro; Satoshi Onodera; Fumiaki Uchiumi; Takashi Ikejima; Silymarin Prevents UV Irradiation-Induced A375-S2 Cell Apoptosis. *Biological & Pharmaceutical Bulletin* **2004**, 27, 1031-1036, [10.1248/bpb.27.1031](#).
81. Huachen Wei; Rao Saladi; Yuhun Lu; Yan Wang; Sapna R. Palep; Julian Moore; Robert Phelps; Eileen Shyong; Mark G. Lebwohl; Isoflavone Genistein: Photoprotection and Clinical Implications in Dermatology. *The Journal of Nutrition* **2003**, 133, 3811S-3819S, [10.1093/jn/133.11.3811s](#).
82. Jing-Yi Lin; Joshua A. Tournas; James A. Burch; Nancy A. Monteiro-Riviere; Jan Zielinski; Topical isoflavones provide effective photoprotection to skin. *Photodermatology, Photoimmunology & Photomedicine* **2008**, 24, 61-66, [10.1111/j.1600-0781.2008.00329.x](#).
83. Y Wang; X Zhang; M Lebwohl; V DeLeo; H Wei; Inhibition of ultraviolet B (UVB)-induced c-fos and c-jun expression in vivo by a tyrosine kinase inhibitor genistein. *Carcinogenesis* **1998**, 19, 649-654, [10.1093/carcin/19.4.649](#).

84. Yi Na Wang; Wei Wu; Hong Chao Chen; Hong Fang; Genistein protects against UVB-induced senescence-like characteristics in human dermal fibroblast by p66Shc down-regulation. *Journal of Dermatological Science* **2010**, 58, 19-27, [10.1016/j.jdermsci.2010.02.002](#).
85. Julian O. Moore; Yongyin Wang; William G. Stebbins; Dayuan Gao; Xueyan Zhou; Robert Phelps; Mark Lebwohl; Huachen Wei; Photoprotective effect of isoflavone genistein on ultraviolet B-induced pyrimidine dimer formation and PCNA expression in human reconstituted skin and its implications in dermatology and prevention of cutaneous carcinogenesis. *Carcinogenesis* **2006**, 27, 1627-1635, [10.1093/carcin/bgj367](#).
86. Cécile Mazière; Françoise Dantin; Françoise Dubois; René Santus; Jean-Claude Mazière; Biphasic effect of UVA radiation on STAT1 activity and tyrosine phosphorylation in cultured human keratinocytes. *Free Radical Biology and Medicine* **2000**, 28, 1430-1437, [10.1016/s0891-5849\(00\)00264-1](#).
87. Paulo Filipe; João N. Silva; Josiane Haigle; João P. Freitas; Afonso Fernandes; René Santus; Patrice Morlière; Contrasting action of flavonoids on phototoxic effects induced in human skin fibroblasts by UVA alone or UVA plus cyamemazine, a phototoxic neuroleptic. *Photochemical & Photobiological Sciences* **2005**, 4, 420-428, [10.1039/b416811a](#).
88. Sewon Kang; J.H. Chung; Joo Heung Lee; Gary J. Fisher; Yian Sheng Wan; Elizabeth A. Duell; John J. Voorhees; Topical N-Acetyl Cysteine and Genistein Prevent Ultraviolet-Light-Induced Signaling That Leads to Photoaging in Human Skin in vivo. *Journal of Investigative Dermatology* **2003**, 120, 835-841, [10.1046/j.1523-1747.2003.12122.x](#).
89. K.Indira Priyadarsini; Sujata M. Khopde; S. Santosh Kumar; Hari Mohan; Free Radical Studies of Ellagic Acid, a Natural Phenolic Antioxidant. *Journal of Agricultural and Food Chemistry* **2002**, 50, 2200-2206, [10.1021/jf011275g](#).
90. Begoña De Ancos; Esther M. Gonzalez; M. Pilar Cano; Ellagic acid, vitamin C, and total phenolic contents and radical scavenging capacity affected by freezing and frozen storage in raspberry fruit.. *Journal of Agricultural and Food Chemistry* **2000**, 48, 4565-4570, [10.1021/jf0001684](#).
91. You-Cheng Hseu; Chih-Wei Chou; K.J. Senthil Kumar; Ke-Ting Fu; Hui-Min Wang; Li-Sung Hsu; Yueh-Hsiung Kuo; Chi-Rei Wu; Ssu-Ching Chen; Hsin-Ling Yang; et al. Ellagic acid protects human keratinocyte (HaCaT) cells against UVA-induced oxidative stress and apoptosis through the upregulation of the HO-1 and Nrf-2 antioxidant genes. *Food and Chemical Toxicology* **2012**, 50, 1245-1255, [10.1016/j.fct.2012.02.020](#).
92. Ji-Young Bae; Jung-Suk Choi; Sang-Wook Kang; Yong-Jin Lee; Jinseu Park; Young-Hee Kang; Dietary compound ellagic acid alleviates skin wrinkle and inflammation induced by UV-B irradiation. *Experimental Dermatology* **2010**, 19, e182-e190, [10.1111/j.1600-0625.2009.01044.x](#).
93. Jack N. Losso; Rishipal R Bansode; Alfred Trappey; Hiba A Bawadi; Robert Truax; In vitro anti-proliferative activities of ellagic acid. *The Journal of Nutritional Biochemistry* **2004**, 15, 672-678, [10.1016/j.jnutbio.2004.06.004](#).