CHAPTER 5

ANTIOXIDANTS IN DERMATOLOGY

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OXIDANTS AND ANTIOXIDANTS

Reactive oxygen species: Oxygen free radicals or, more generally, reactive oxygen species (ROS), as well as reactive nitrogen species (RNS), are products of normal cellular metabolism continuously produced in all aerobic organisms, mostly as a consequence of aerobic respiration.[1] Reactive oxygen species belong to the class of free radicals derived from oxygen and are highly reactive oxidizing agents such as superoxide (O_2) anion, hydrogen peroxide (H_2O_2), the very reactive hydroxyl (OH), peroxyl (ROO) radicals and can also be taken to cover nitric oxide-derived reactive molecules such as nitric oxide (NO) and peroxynitrite anion (ONOO). A free radical contains one or more unpaired electrons ready to be shared by other molecules, and this makes them very reactive. These different metabolites called ROS are either free radicals (with an unpaired electron in their outer orbital sphere) (O_2, OH) or nonradical [H_2O_2, singlet oxygen ($^1O_2$)].[2] Free radicals and other ROS are derived either from normal essential metabolic processes in the human body or from external sources such as exposure to ionizing radiation, ozone, cigarette smoking, air pollutants, herbicides, pesticides, fried foods, and other industrial chemicals.[3] Free radical formation occurs continuously in the cells as a consequence of both enzymatic and non enzymatic reactions. Enzymatic reactions, which serve as source of free radicals, include those involved in cellular respiration chain, in phagocytosis (NADPH oxidase, myeloperoxidases), in prostaglandin synthesis, and in the cytochrome P-450 system.[4] Electron transport chain is the major site of oxidative stress cause of premature electron leakage to oxygen generating superoxide. Superoxide released by oxidative phosphorylation is first converted to hydrogen peroxide and then further reduced to give water. This detoxification pathway is the result of multiple enzymes, with superoxide dismutases catalyzing the first step and then catalases and various peroxidases removing hydrogen peroxide.[5]

ROS and RNS are well recognised for playing a dual role as both deleterious and beneficial species, since they can be either harmful or beneficial to living systems.[1] Beneficial effects of ROS occur at low/moderate concentrations and exert essential intracellular functions, as second messengers, gene regulators, and mediators for cell activation (kinases and transcription factors). They also play a key role in our body's defense against infectious organisms. Besides, ROS are modulators of cell death, whether apoptosis or necrosis.[6] The harmful effect of free radicals causing potential biological damage is termed oxidative stress and nitrosative stress.[7,8] Oxidative stress occurs in biological systems when there is an overproduction of ROS/RNS on one side and a deficiency of enzymatic and non-enzymatic antioxidants on the other. In other words, it is defined by an imbalance between ROS and antioxidants, ROS being in excess.[9]

Antioxidants: Living organisms have a control mechanism to keep ROS in balance. Antioxidants, in general, are compounds and reactions that scavenge and/or suppress the formation of ROS, or oppose their actions.[2] Antioxidant and other cell redox state modulating enzyme systems act as the first-line defense against ROS in all cellular compartments and also extracellularly. Their relative importance depends upon which ROS are generated, how and where they are generated, and which target of damage is considered. Our body defends itself from these phenomena via endogenous antioxidants. Defense mechanisms against free radical-induced oxidative stress involve: (i) preventative mechanisms, (ii) repair mechanisms, (iii) physical defences, and (iv) antioxidant defences. Antioxidants act as radical scavenger, hydrogen donor, electron donor, peroxide decomposer, singlet oxygen quencher, enzyme inhibitor, synergist, and metal-chelating agents. Both enzymatic and nonenzymatic antioxidants exist in the intracellular and extracellular environment to detoxify ROS.[10] Enzymatic antioxidant defenses include superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT). Non-enzymatic antioxidants are represented by ascorbic acid (Vitamin C), tocopherol (Vitamin E), glutathione (GSH), carotenoids, flavonoids, and other antioxidants. Under normal conditions, there is a balance between both the activities and the intracellular levels of these antioxidants.[11-13]

Polyphenols such as green tea possess antioxidant, antiinflammatory, immunomodulatory, anticarcinogenic, proapoptotic, and photoprotective properties. Naturally occurring polyphenols, such as green tea polyphenols (GTPs), silymarin from milk thistle and proanthocyanidins from grape seeds (GSPs), against UV radiation-induced inflammation, oxidative stress, DNA damage and suppression of immune responses.[69] Various polyphenols have been reported to be photoprotectors. Oral as well as topical application of green tea polyphenols to mice protected in a time-dependent manner against UV-induced cutaneous edema, depletion of the epidermal antioxidant defense, and cyclooxygenase induction.[70]

Resveratrol: Resveratrol (RES), a trihydroxy derivative of stilbene (3,5,4'-trihydroxystilbene), is a naturally occurring polyphenolic phytoalexin antioxidant present in grapes, berries, peanuts and red wine. Resveratrol and its chemical analogues have photoprotective, antioxidant, antiinflammatory, and anticarcinogenic capabilities. The introduction of resveratrol in cell cultures and topical application in human skin resulted in increased cell survival, decreased production of reactive oxygen species, and diminished clinical erythema after UV irradiation.[71,72] Because resveratrol has strong antioxidant properties, and oxidative stress is believed to be a critical factor in a variety of cutaneous conditions including skin cancers, a number of in vitro and in vivo studies have been done to determine the anti-proliferative effects as well as photo-protective effects of resveratrol. Ndiaye et al demonstrated that the topical application of skin with resveratrol (both pre- and post- treatment) resulted in a highly significant inhibition in tumor incidence, and delay in the onset of tumorigenesis in their recent study that they evaluated the skin cancer chemopreventive effects of resveratrol in a photocarcinogenesis model of skin cancer.[73]

Conclusions

As it is known, skin is the major target of oxidative stress mostly due to ROS originating from both normal and abnormal epidermal physiology as well as the environment. Endogenous and exogenous antioxidants such as vitamin C and E, ubiquinone, superoxide dismutase, glutathione, catalase, selenium, polyphenols and resveratrol reduce the harmful effects of ROS and mediate molecular mechanism and the identification of distinct ROS involved in a variety of dermatologic disorders. Although it is still unknown the molecular mechanism of the regulation of ROS-mediated signaling pathways, antioxidant strategies have proven to be beneficial therapeutics in dermatology. Finally, targeting oxidative stress by using antioxidants may play a role in reduction of dermatologic disorders.

REFERENCES

1. Valko M, Rhodes CJ, Moncol J, Izakovic M, Mazur M. Free radicals, metals and antioxidants in oxidative stress-induced cancer. Chem Biol Interact 2006; 160: 1–40.
2. Halliwell B, Gutteridge JMC.Free Radicals in Biology and Medicine. 4th ed. New York: Oxford University Press, 2007.
3. Bagchi K, Puri S. Free radicals and antioxidants in health and disease. East Mediterranean Health Jr. 1998; 4:350–60.
4. Ebadi M. Antioxidants and free radicals in health and disease: An introduction to reactive oxygen species, oxidative injury, neuronal cell death and therapy in neurodegenerative diseases. Arizona: Prominent Press 2001.
5. Magnenat JL, Garganoam M, Cao J. The nature of antioxidant defense mechanisms: A lesson from transgenic studies. Environ Health Perspect. 1998; 106: 1219–28.
6. Brown JR, Goldblatt D, Buddle J, Morton L, Thrasher AJ. Diminished production of anti-inflammatory mediators during neutrophil apoptosis and macrophage phagocytosis in chronic granulomatous disease (CGD). J Leukoc Biol.2003;73(5):591–599.
7. Kovacic P, Jacintho JD. Mechanisms of carcinogenesis: Focus on oxidative stress and electron transfer. Curr. Med. Chem 2001; 8: 773–796.
8. Ridnour LA., Isenberg JS, Espey MG. Thomas DD, Roberts DD, Wink DA. Nitric oxide regulates angiogenesis through a functional switch involving thrombospondin-1. Proc.Natl. Acad. Sci. USA, 2005; 102: 13147–13152.
9. Droge, W. (2002). Free radicals in the physiological control of cell function. Physiol. Rev., 82, 47–95.
10. Frie B, Stocker R, Ames BN. Antioxidant defences and lipid peroxidation in human blood plasma. Proc Natl Acad Sci. 1988;37: 569–71.
11. Cadenas E. (Basic mechanisms of antioxidant activity. Biofactors, 1997; 6, 391–397.
12. Sies H. Oxidative stress: introduction. In Oxidative Stress: Oxidants and Antioxidants. ed. Sies H. Academic Press, London. 1991, pp. xv-xxii.
13. Stanner SA, Hughes J, Kelly CN, Buttriss J. A review of the epidemiological evidence for the 'antioxidant hypothesis'. Public Health Nutr. 2004; 7(3):407–22
14. Black HS. ROS: a step closer to elucidating their role in the etiology of light-induced skin disorders. J Invest Dermatol 2004; 122:xiii–v
15. Mailloux, R.J.; Harper, M.E. Mitochondrial proticity and ROS signaling: Lessons from the uncoupling proteins. Trends Endocrinol. Metab. 2012, 23, 451–458. 90.
16. Lenaz, G. Mitochondria and reactive oxygen species. Which role in physiology and pathology? Adv Exp Med Biol 2012; 942: 93–136.
17. Gomes EC, Silva AN, de Oliveira MR. Oxidants, antioxidants, and the beneficial roles of exercise-induced production of reactive species. Oxid Med Cell Longev. 2012:756132.
18. Pastore S, Korkina L Redox imbalance in T cell-mediated skin diseases. Mediators Inflamm. 2010;:861949.
19. Chen L, Hu JY, Wang SQ. The role of antioxidants in photoprotection: a critical review. J Am Acad Dermatol. 2012; 67(5):1013-24.

20. Shindo Y, Witt E, Han D, Epstein W, Packer L.Enzymic and non-enzymic antioxidants in epidermis and dermis of human skin. J Invest Dermatol. 1994; 102(1):122-4.
21. J. Thiele, C. O. Barland, R. Ghadially, and P. Elias, Permeability and antioxidant barriers in aged skin, in Skin Aging, B. Gilchrest and J. Krutmann, Eds., Springer, Berlin, Germany, 2006.
22. Padayatty SJ1, Katz A, Wang Y, Eck P, Kwon O, Lee JH, Chen S, Corpe C, Dutta A, Dutta SK, Levine MJ. Vitamin C as an antioxidant: evaluation of its role in disease prevention. Am Coll Nutr. 2003; 22(1):18-35.
23. Telang PS. Vitamin C in dermatology. Indian Dermatol Online J 2013; 4:143-6.
24. Burke KE. Interaction of Vit C and E as better Cosmeseuticals. Dermatol Ther. 2007; 20:314–9.
25. R. Pandel, B. Poljsak, A. Godic, and R. Dahmane, "Skin photoaging and the role of antioxidants in its prevention," ISRN Dermatology, vol. 2013;930164; 11.
26. Morganti, P.; Bruno, C.; Guarneri, F.; Cardillo, A.; Del Ciotto, P.; Valenzano, F. Role of topical and nutritional supplement to modify the oxidative stress. Int. J. Cosmet. Sci. 2002; 24: 331–339.
27. Eberlein-Konig, B.; Ring, J. Relevance of vitamins C and E in cutaneous photoprotection. J. Cosmet. Dermatol. 2005; 4: 4–9.
28. Chow CK. Vitamin E and oxidative stress. Free Radic Biol Med 1991; 11: 215-232.
29. Sorg O, Tran C, Saurat JH. Cutaneous vitamins A and E in the context of ultraviolet or chemically-induced oxidative stress. Skin Pharmacol Appl Skin Physiol 2001; 14: 363-72.
30. Vuleta G, Savić S. The rationale for use of vitamins and minerals in cosmetic products. Arh pharm 2009; 59: 212-225.
31. Stojiljković D, Pavlović D, Arsić I. Oxidative Stress, Skin Aging and Antioxidant Therapy. Scientific Journal of the Faculty of Medicine 2014;31(4):207-217.
32. Pehr K, Roy Forsey. Why don't we use vitamin E in dermatology? Can Med Assoc J 1993; 149: 9.
33. Maia Campos PM, Gianeti MD, Kanashiro A, et al. In vitro antioxidant and in vivo photoprotective effects of an association of bioflavonoids with liposoluble vitamins. Photochem Photobiol 2006;82: 683-8.
34. Lenaz G, Faro R, DeBernardo S, Jarreta D, Costa, A, Genova ML, Parenti Castelii G: Location and mobility of coenzyme Q in lipid bilayers and membranes. Biofactors 1999; 9: 87–94.
35. Lopez-Lluch G, Barroso MP, Martin SF, Fernandze-Ayala DJM, Viallaba JM, Navas P: Role of plasma membrane coenzyme Q on the regulation of apoptosis. Biofactors 1999; 9: 171–177.
36. Burke K: Cosmeceuticals, Nutritional antioxidants, Edited by Zoe Diana Draclos 2005; 18: 125-131.
37. Yue Y, Zhou H, Liu G et al. The advantages of a novel CoQ10 delivery system in skin photo-protection. Int J Pharm 2010; 392:57-63.
38. Zelko I, Mariani T, Folz R. Superoxide dismutase multigene family: A comparison of the CuZn-SOD (SOD1), Mn-SOD (SOD2), and EC-SOD (SOD3) gene structures, evolution, and expression. Free Radic Biol Med. 2002; 33:337–49.
39. Banniste J, Bannister W, Rotilio G. Aspects of the structure, function, and applications of superoxide dismutase. CRC Crit Rev Biochem. 1987; 22:111–80.
40. Bafana A, Dutt S, Kumar A, Kumar S, Ahuja P. The basic and applied aspects of superoxide dismutase. J Molec Catal B 2011; 68(2):129–138
41. Kwon MJ, Kim B, Lee YS, Kim TY. Role of superoxide dismutase 3 in skin inflammation. J Dermatol Sci 2012; 67(2):81–87.
42. Kim Y, Kim BH, Lee H et al Regulation of skin inflammation and angiogenesis by EC-SOD via HIF-1α and NF-κB pathways. Free Radic Biol Med 2011; 51(11):1985–1995
43. Delanian, S.; Baillet, F.; Huart, J.; Lefaix, J.L.; Maulard, C.; Housset, M. Successful treatment of radiation-induced fibrosis using liposomal Cu/Zn superoxide dismutase: Clinical trial. Radiother. Oncol. 1994; 32: 12–20.
44. Lefaix, J.L.; Delanian, S.; Leplat, J.J.; Tricaud, Y.; Martin, M.; Nimrod, A.; Baillet, F.; Daburon, F. Successful treatment of radiation-induced fibrosis using Cu/Zn-SOD and Mn-SOD: An experimental study. Int. J. Radiat. Oncol. Biol. Phys. 1996; 35: 305–312.
45. Goldman MP, Hexsel D. Cellulite: pathophysiology and treatment (2nd ed.). Informa Healthcare. 2009
46. Basak P, Gultekin F, Kilinc I The role of the antioxidative defense system in papulopustular acne. J Dermatol 2001; 28(3):123–127.
47. Chelikani P, Fita I, Loewen PC. Diversity of structures and properties among catalases. Cell Mol Life Sci. 2004;61:192–208
48. K.U. Schallreuter, J.M. Wood, J. Berger, Low catalase levels in theepidermis of patients with vitiligo, J. Invest. Dermatol. 1991; 97: 1081–1085.
49. Sravani PV1, Babu NK, Gopal KV, Rao GR, Rao AR, Moorthy B, Rao TR. Determination of oxidative stress in vitiligo by measuring superoxide dismutase and catalase levels in vitiliginous and non-vitiliginous skin. Indian J Dermatol Venereol Leprol. 2009; 75(3): 268-71
50. Hazneci E, Karabulut AB, Oztürk C, Batçioğlu K, Doğan G, Karaca S, Eşrefoğlu M. A comparative study of superoxide dismutase, catalase, and glutathione peroxidase activities and nitrate levels in vitiligo patients. Int J Dermatol. 2005;44(8):636-40.
51. Rhie, G, Shin, MH, Seo, JY, et al: Aging- and photoaging-dependent changes of enzymic and nonenzymic antioxidants in the epidermis and dermis of human skin in vivo. J Invest Dermatol 2001; 117:1212–1217.
52. Shin MH, Rhie GE, Kim YK, Park CH, Cho KH, Kim KH, Eun HC, Chung JH. H2O2 accumulation by catalase reduction changes MAP kinase signaling in aged human skin in vivo. J Invest Dermatol. 2005; 125(2):221-9.
53. Meister A, Anderson M. Glutathione. Annu Rev Biochem. 1983; 52:711–60.
54. Hayes J, Flanagan J, Jowsey I. Glutathione transferases. Annu Rev Pharmacol Toxicol. 2005; 45:51–88.
55. Pastore S, Mariani V, Gubineli E, et al. Glutathione peroxidase activity in the blood cells of psoriatic patients correlates with their responsiveness to efalizumab. Free Radic Res. 2011; 45(5):585–599.
56. Maresca V, Roccella M, Roccella F, Camera E, Del Porto G, Passi S. Increased sensitivity to peroxidative agents as a possibile pathogenic factor of melanocyte damage in vitiligo. J Invest Dermatol. 1997; 109:1081–5.

57. Ikeno H, Tochio T, Tanaka H, Nakata S. Decrease in glutathione may be involved in pathogenesis of acne vulgaris. J Cosmet Dermatol. 2011; 10(3):240-4.
58. Watanabe F, Hashizume E, Chan GP, Kamimura A. Skin-whitening and skin-condition-improving effects of topical oxidized glutathione: a double-blind and placebo-controlled clinical trial in healthy women. Clin Cosmet Investig Dermatol. 2014;7:267-74
59. Schrauzer, G.N.; Surai, P.F. Selenium in human and animal nutrition: Resolved and unresolved issues. Crit. Rev. Biotechnol. 2009; 29: 2–9.
60. Zhang, Y.; Zhou, Y.; Schweizer, U.; Savaskan, N.E.; Hua, D.; Kipnis, J.; Hatfield, D.L.; Gladyshev, V.N. Comparative analysis of selenocysteine machinery and selenoproteome gene expression in mouse brain identifies neurons as key functional sites of selenium in mammals. J Biol Chem 2008; 283: 2427–2438.
61. Foster LH, Sumar S. Selenium in health and disease: a review. Crit Rev Food Sci Nutr 1997; 37: 211-28.
62. Allan CB, Lacourciere GM, Stadtman TC. Responsiveness of selenoproteins to dietary selenium. Annu Rev Nutr 1999;19: 1-16
63. Harvima RJ, Jagerroos H, Kajander EO et al. Screening of effects of selenomethionine-enriched yeast supplementation on various immunological and chemical parameters of skin and blood in psoriatic patients. Acta Derm Venereol (Stockh) 1993; 73: 88–91.
64. Fairris GM, Lloyd B, Hinks L et al. The effect of supplementation with selenium and vitamin E in psoriasis. Ann Clin Biochem 1989; 26: 83–8.
65. Clark LC, Graham GF, Crounse R, Hulka BS, and Shy CM: Plasma selenium and skin cancer: a case control study. Nutr Cancer 1984;6: 13-21,
66. Manach C, Scalbert A, Morand C et al Polyphenols: food sources and bioavailability. Am J Clin Nutr 2004:79:727–747.
67. Harborne JB. Nature, distribution, and function of plant flavonoids. In Plant Flavonoids in Biology andMedicine, Cody V, Middleton E, Harborne JB (eds). Alan R. Liss: New York, 1986: 15–24.
68. Quideau S, Deffieux D, Douat-Casassus C, Pouységu, L. Plant polyphenols: chemical properties, biological activities, and synthesis. Angew Chem Int Ed 2011; 50: 586–621.
69. Katiyar SK. Skin photoprotection by green tea: antioxidant and immunomodulatory effects. Curr Drug Targets Immune Endocr Metabol Disord 2003; 3: 234-42.
70. Agarwal, R.; Katiyar, S.K.; Khan, S.G.; Mukhtar, H. Protection against ultraviolet B radiation-induced effects in the skin of SKH-1 hairless mice by a polyphenolic fraction isolated from green tea. Photochem. Photobiol. 1993; 58: 695–700.
71. Aggarwal BB, Bhardwaj A, Aggarwal RS, Seeram NP, Shishodia S, Takada Y. Role of resveratrol in prevention and therapy of cancer: preclinical and clinical studies. Anticancer Res 2004; 24: 2783-840.
72. Wu Y, Jia LL, Zheng YN, Xu XG, Luo YJ, Wang B, et al. Resveratrate protects human skin from damage due to repetitive ultraviolet irradiation. J Eur Acad Dermatol Venereol 2013;27: 345-50.
73. Ndiaye M, Philippe C, Mukhtar H, Ahmad N. The grape antioxidant resveratrol for skin disorders: promise, prospects, and challenges. Arch Biochem Biophys. 2011: 15; 508(2):164-70.