Antioxidants and radical scavengers – too much is too much

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Antioxidants and radical scavengers belong to the most common components of anti-aging preparations. The trend towards appropriate food supplements and cosmeceuticals still continues.

Counterproductive effects

More than twenty years ago the first studies were published on the fact that the cancer rate is not decreasing with the consumption of antioxidants but even can augment as observed in the case of beta carotene where a 28 % increase had been reported. Antioxidant vitamins such as the vitamins E and C cannot influence mortality rates in cardiovascular diseases[1] and infarcts. The provocatively entitled survey "The Free Radical Fantasy" already was published in 2006.[2] It compiles the results of the most significant studies published so far.

Antioxidants in food supplements are not beneficial unless a substantial deficiency is to be remedied. Deficiency symptoms will not appear with a well-balanced diet though. The human body usually has an equilibrated balance of antioxidants and oxidants.

Partial interventions into this control system can be counterproductive. Extreme effects are known from chemo or radiotherapies. Since the therapies are based on the oxidative effects of free radicals simultaneous administrations of antioxidants such as for instance vitamin C may interfere with the efficacy or even render it completely ineffective. [3]

Recent publications show that antioxidants such as vitamin E and N-acetyl-cysteine can stimulate the formation of metastases[4] while oxidative stress reduces the melanoma cells.[5] Tumor cells are more sensitive to oxidative stress than normal cells.[6]

Natural stress

Oxidative processes, oxidative stress and radicals are an integral part of healing processes. Also infrared rays (IR-A) which occur in the non-visible solar spectrum induce the skin to form radicals.[7] What can cause premature skin aging when exaggerated, i.e. after a sun exposure for several hours in spite of sufficient UV-A and UV-B protection, can also accelerate the skin recovery and improve the microcirculation in the case of cutaneous and sub-cutaneous inflammations when applied in the form of an appropriately dosed infrared radiotherapy. The wise saying of Paracelsus “All things are poison and nothing (is) without poison; only the dose makes that a thing is no poison” also applies to radiation and radiotherapy.

Since IR-A radiation (780 up to 1400 nm) penetrates up to 5 mm into the skin the super-

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[4] Le Gal K, Ibrahim MX, Wiel C, Sayin VI, Akula MK, Karlsson C, Dalin MG, Akyürek LM, Lindahl P, Nilsson J and Bergo MO, Antioxidants can increase melanoma metastasis in mice, Science Translational Medicine 07 Oct 2015:Vol. 7, Issue 308, pp. 308re8; DOI: 10.1126/scitranslmed.aad3740

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[6] Hohmann-Jeddi C, Antioxidantien bei Krebs – Verstärkte Metastasierung, Pharmazeutische Zeitung 2015 (43), 38

[7] Zastrow L, Groth N, Klein F, Kockott D, Lademann J, Ferrero L, UV, sichtbares Licht, Infrarot – Welche Wellenlängen produzieren oxidativen Stress in der menschlichen Haut? Der Hautarzt 60 (4), 310-317 (2009)

ficially acting cosmetic antioxidants are not very effective. The question rises though whether they are beneficial at all? If the infrared fraction of sun light is concerned, they even are counterproductive as more or less all antioxidants inhibit the tyrosinase and hence the formation of the protective melanin. As they are fast degraded in sunlight, an adequately high dosage would be necessary in sun protection preparations. In high dosage however they can form radicals themselves.

Similar to short wave IR-A light (near infrared) also the blue light of the visible sun radiation causes increased radical formation. LED blue light initiates the healing process in the case of inflammations (e.g. juvenile acne) by interacting with the metabolic products of bacteria and forming radicals. The associated phototoxic effect damages the bacteria. Similar processes can be observed with LED red light which is part of the photodynamic therapy (PDT) and destroys tumor cells. In this case the photosensitizing substance 5-amino levulinic acid is topically applied before the treatment.

The gamma radiation treatment of a tumor also involves local oxidative stress to which the tumor cells, as already mentioned above, show a more sensitive reaction than normal cells. Last but not least, also infection-related fever is associated with oxidative stress – in other words it primarily is a protective reaction of our body which often is cut short with the help of antifebrile preparations. Studies show that antifebrile drugs generally prolong the duration of diseases instead of reducing them. Fever is not the cause of the infection but the immune response of the body to it. The defense cells of the body including associated oxidative processes are at their optimal efficacy at temperatures around 38 to 41°C. There is evidence to suggest that spontaneous healing of cancer diseases may occur under the conditions of febrile infections.

The radical formation triggered by electromagnetic waves as e.g. UV-A and UV-B is harmful. By the same token, radicals are natural triggers for repair processes and protective mechanisms. This is the case with melanin formation for instance. Generally speaking, reactive oxygen compounds alias ROS (Reactive Oxygen Species) are an important part of the cellular and intracellular signal transfer. Hydrogen peroxide belongs to the ROS and also serves as a redox buffer in the body - it can have oxidizing as well as reducing effects. Exogenous antioxidants can influence these processes.

Only recently a research team has discovered that melanin can cause DNA damages when stimulated by radiation-related radicals – even after the immediate radiation effect (in the dark).[8] It should however be mentioned that exactly this mechanism then stimulates the repair process and helps destroy melanoma cells (see above). Melanin reacts with UV light - as long as it is intact and not inactivated by bond ruptures after excessive exposure to radiation – it goes into an excited state and transforms the extra energy into heat. Quantum efficiency is about 100%. Hence it corresponds to the function of an ideal UV filter in sun protection preparations. After excessive exposure to radiation and the associated bond ruptures this protective function will no longer work. Melanin then forms radicals itself in the manner of less efficient UV filters with lower quantum efficiency. The UV filter octyl methoxycinnamate for instance has a quantum efficiency of 80% which means that about 20% of the absorbed UV light is transformed into radicals.

Radical Cosmeceuticals

When it comes to blind maximization and efficacy increase of antioxidants there is strong competition among cosmeceuticals. Besides the facts that the relatively frequent overdosage of vitamin E in cosmetics will shift the antioxidative effects to prooxidative, and that supplementing alkanolamine-containing products with antioxidative vitamins results in an increased formation of carcinogenic nitrosamines, it is worthwhile to focus on the natural conditions in the skin. Exogenous radicals are scavenged there by a multitude of nitrogenous substances. Predominant are amides such as urea and amino acids as for instance glycine and methylglycine which both belong to the NMF factor and contribute to the osmolytic balance of the skin. The highest concentrations are in the lowest layer of the stratum corneum. Substances of the NMF for instance react with atmospheric nitrogen oxides into inoffensive reaction products.[9] The clinical evidence of the

[8] Premi S, Wallisch S, Mano CM, Weiner AB, Bacchiocchi A, Wakamatsu K, Bechara EJH, Halaban R, Douki T, Bras DE, Chemiexcitation of melanin derivatives induces DNA photoproducts long after UV exposure, Science 347; 6224; 842-847 (2015)

[9] Lautenschläger H, Radikalfänger – Wirkstoffe im Umbruch, Kosmetische Praxis 2006 (2), 12-14

NMF motivated A.M. Kligman to develop the corneotherapy.[10]

Therapeutic approaches

Oxidative stress can be a therapeutic approach which is not a novel finding though. Some examples are:

- Benzoyl peroxide in the acne therapy
- Ozonized olive oil as an external agent in the case of infects, of mycoses and for disinfecting purposes.[11]
- Therapeutic hyperthermia[12] [13] in analogy to fever therapies in the context of cancer treatments as for instance whole body and prostate gland hyperthermia.
- Radiations (see above).

High oxidative stress can initially involve collateral damages such as the above mentioned DNA rupture after melanin radiation. As a consequence however, the local repair process in the form of a sun burn is enhanced in analogy to the fever that follows an infection and then affects the whole organism. Hence the question arises whether antioxidants are beneficial in the treatment of sun burns. An alternative approach are active agents which will not interfere with the healing process but improve the individual impacts, as for instance moisturizers, D-panthenol and essential omega-3 and omega-6 fatty acids (linseed oil, kiwi seed oil, rose hip seed oil, evening primrose oil) in combination with native phosphatidylcholine as physiological, nanoparticular carrier substance. Antioxidants such as ascorbic acid (vitamin C) are counterproductive since they impede the melanin formation which is based on oxidative processes, and also inhibit the tyrosinase.

In analogy to the radiation based formation, melanin also develops after skin inflammations of different origin. In this case we speak of post-inflammatory hyperpigmentation (PIH).

Conclusion

It can be stated that inflammations (infection), radiation and temperature (fever) activate the immune system of the body and the skin. The initiated processes are associated with increased oxidative mechanisms. Hence most of the radicals and ROS are endogenously formed and are integral components of natural and individually different physiological immune responses. Exogenous high-energy UV and gamma radiation however cause immediate molecular damage (bond ruptures). That makes them dangerous to health and that is why they have a very high carcinogenic potential.

Nevertheless, in most cases detoxification and elimination of metabolic products, foreign substances, pharmaceutical drugs etc. are associated with oxidation processes. Glucuronidation makes these substances partly water soluble so that they can be excreted via kidney, urine or finally in the form of carbon dioxide via the lungs.

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