Radical scavengers as active agents:
facts, new aspects and future perspectives

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In cosmetics as well as in medicine active agents against free radicals have ranked among the top-rated substances for quite some years. Every now and then there are new substances on the market which are even more effective in scavenging free radicals. How do radicals come into being, what are their effects and how dangerous are they actually? What is the difference between radicals and free radicals? Quite a few intricate questions which are not too easy to answer!

To give a detailed answer it is necessary to make a short excursion into the love life within the field of chemistry. According to the chemical definition, a radical is a molecule which contains a so-called unpaired electron. It is important to mention here that electrons are responsible for the bonds between the atoms of a molecule and that they are generally arranged in pairs. Similar to human beings, also in this area "singles" keep actively looking for a partner to act off their surplus energy. Now, as far as "single" and "single" team up, there are few problems. Some "singles" however try to join forces with matched pairs of other molecules and thus cause a lot of troubles within the peaceful family life. This may even lead to "chain reactions" with the result that time and again new "singles" will emerge. Existing molecules are destroyed and, to explain it physiologically, this may lead to damages of the skin or other parts of the human body.

Oxygen & Co

Atmospheric oxygen is one of the main causes for the development of radicals. Whenever there is also high-energy radiation like e.g. UV-radiation or sometimes even visible light, oxygen may eventually attack organic compounds to generate radicals. In chain reaction with additional oxygen they form highly reactive peroxides. This reaction also is called auto oxidation. As far as peroxides are concerned they tend to break down to radicals which may also attack organic substances. Traces of transition metals which are almost omnipresent like e.g. iron will act as catalysts in this process. With iron ions (Fe^{2+}) around the hydrogen peroxide (H_2O_2) which is found in natural environment and in the human body may form highly reactive short-lived hydroxyl radicals (OH).

From primordial soup to modern times

In the course of evolution i.e. beginning from an oxygen free primordial atmosphere to the oxygen-containing environment of today, the organisms have acquired effective mechanisms against the negative influence of oxygen and the (free) radicals it generates in order to protect their own natural organic bonds. On the other hand, most of the organisms gain their energy by means of controlled combustion of organic material with the help of oxygen. This means, that within our cellular power plants which are called mitochondria the body selectively uses radicals to gain energy. Also for other physiological processes the human body uses radicals, and their preliminary stages or derivatives, nitrogen monoxide (NO), superoxide anion (O_2^-), and ROS (Reactive Oxygen Species) in general e.g. play a significant role as mediators for the signal transfer within the human body. Among other applications they are also involved in triggering the apoptosis of epidermal cells. A series of enzymes produces moderate amounts of defined radicals whereas others see to their destruction. This points to the fact that specific steady-state levels of radicals are not only locally existing in the human body but that they are even vital components. Persisting upward deviations of the steady-state level are called "chronic oxidative stress" and downward deviations "reductive stress"; they can be observed in pathological processes.

Scavenging and being scavenged...

This leads to the conclusion that radical scavengers which are able to inactivate or destroy free radicals should be handled carefully in order to avoid any excess reaction. The widespread and very uncritical use of radical scavenging substances seems just like applying hypotensive medication without mea-

suring the blood pressure as an expert recently has formulated in his paper. The well-known radical scavenging substances as e.g. the vitamins C and E simultaneously provide a whole series of additional features which make good medical sense in skin care products. Hence it is all the more important to encapsulate low concentrations in transport vehicles like liposomes or nanoparticles in order to apply them selectively in the areas where they are needed following a previously taken comprehensive skin diagnostic.
A product containing an effective radical scavenging substance however cannot necessarily also be seen as an effective product against skin aging.

Radical scavenging mechanisms

The mechanisms of the radical scavenging substances are very different from each other:

After reacting with a radical, **vitamin E** transforms itself into a radical, although it will remain quite inert and slow-reacting. Yet, this applies for low concentrations only. In higher concentrations Vitamin E just works the opposite way, or in other words, pro-oxidative which means that in cooperation with oxygen it can trigger a chain-reaction. This is the reason why cosmetic products should only contain a moderate dosage. In chemical respect vitamin E is a phenol compound. Hence similar properties can be found in structurally comparable polyphenols like e.g. isoflavones (phyto hormones contained in soybeans, red clover, see KOSMETISCHE PRAXIS 1/2006, page 13 ff) and flavones (green tea).

After reacting with a radical, **vitamin C** is oxidized and broken down. Vitamin C is also able to regain vitamin E out of formed vitamin E radicals (see above). It is therefore recommended to use both the substances in combination.

Typical radical scavengers also are the reduced forms (hydrochinone) of **vitamin K** and **coenzyme Q10**. While reacting with radicals they form the so-called semichinones and chinones which may be reduced to their original form by natural reduction processes of the human body.

Enzymatic radical scavengers (see below) react very selectively with superoxide & co.

The formation of free radicals can also be prevented by means of inactivating the above mentioned catalytic metal traces with the formation of chemical complexes. As an example here the formation of iron-citrate complex through reaction of **iron ions** with citric acid may be mentioned. **Saccharides** and a lot of **polyphenols** (see above) also form non-active compounds with heavy metals.

Antioxidants

Radical scavengers (antioxidants) are valued priceless for the shelf life of skin care products. They primarily protect sensitive components like vitamins and essential fatty acids against oxidation. Ethoxilated alcohols, the widespread emulsifiers of today's cosmetic products also are sensitive to oxygen. In case that they are not protected by antioxidants they will form peroxides which may cause skin irritations like Majorca acne.

New findings

There are only few data available regarding the concentration of free radicals in the stratum corneum and the deeper skin layers. The data, if available, frequently are in-vitro results which should only be applied with due care to the conditions on live skin.
In this connection it is interesting to consider the apoptosis process of the skin cells which is also called programmed cell death. On their way from the reducing milieu of the basal layer to the oxidizing atmosphere in the upper layer of the stratum corneum they cross a transitional area where the adequate redox balance is of vital importance as this is the spot where potential oxidizing attacks from outside have to be effectively inhibited. Assuming that in this transitional area the concentration of radical scavengers acting as watchdogs is specifically high seems a logical hypothesis though. As a matter of fact however, in these particular zones a multitude of different nitrogen-containing substances can be found which come from the breakdown of membrane-forming phospholipids, sphingomyelins and proteins whereas proteins, amides and amino acids like e.g. glycine and methyl glycine dominate. The highest concentrations can be found in the deepest stratum corneum layer.
Higher concentrations of the nitrogen-containing substances are very potent radical and ROS scavengers i.e. that on the one hand they are able to transform reactive radicals into inert ones (see above) and on the other hand they may directly react with peroxides and atmospheric nitrogen oxides.
Whereas the enzymatic radical scavengers in the live epidermal cells like SOD (superoxide dismutase), glutathion-peroxidase, catalase

and thioredoxin very specifically and also quite rapidly break down specific oxygen compounds into minuscule concentrations, it requires higher concentrations of nitrogen compounds due to their lower reactivity. They also react rather unspecific to externally penetrating radicals and their reaction products. They are rather doing the coarse work in cases of oxidative stress caused by external factors. As a large number of them belongs to the NMF substances which means that they also contribute to the osmotic balance of the skin, it is highly recommended to add them to the list of ingredients for skin care products. It should also be mentioned that the group of nitrogen-containing and osmotically acting substances also contains components which are effective in cases of pathologically induced reductive stress (see above).

It can be expected that the scientific data around nitrogen-containing radical scavengers will multiply. The Kligman studies on NMF substances in the field of corneotherapy point to the same direction.

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