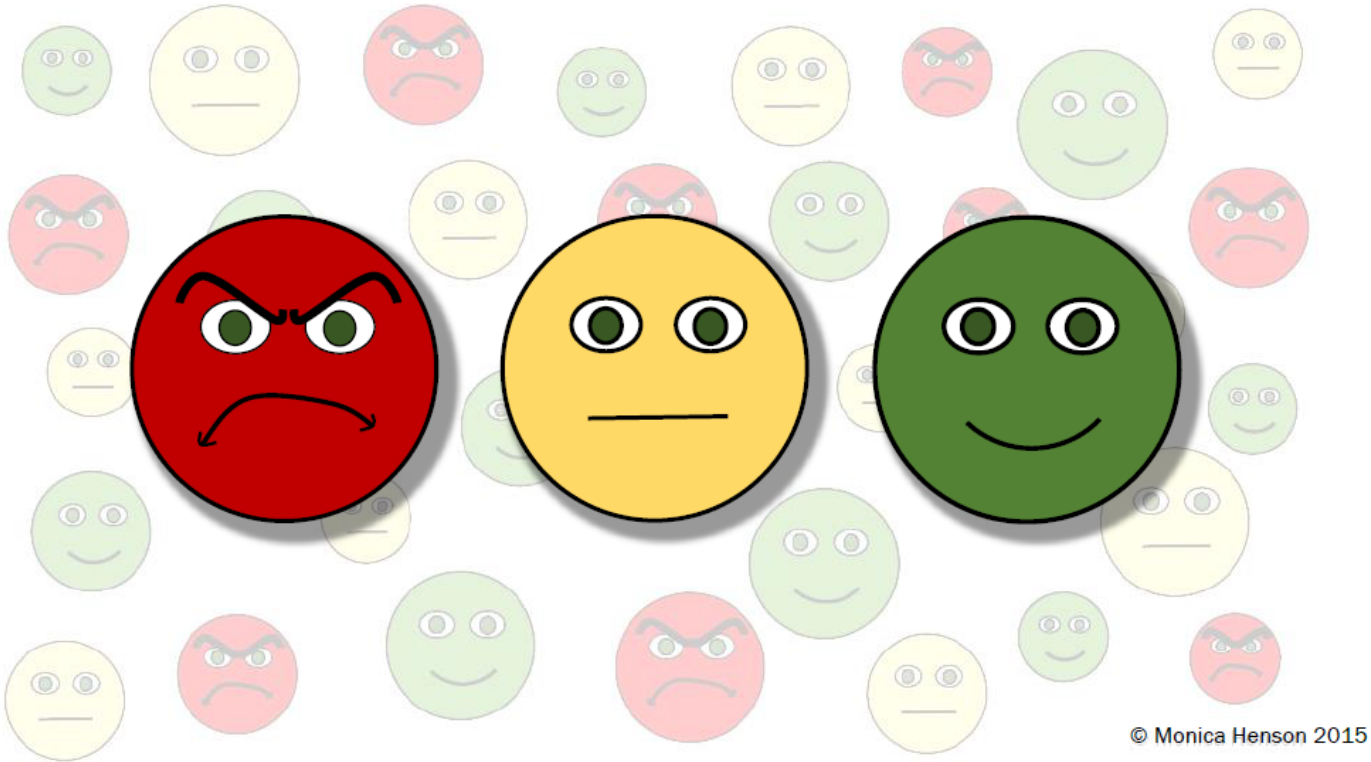
Nanocarrier-based antioxidant therapy: promise or delusion?

It has been well established that the damage produced by Reactive Oxygen Species (ROS), which are highly reactive molecules with an unpaired electron, plays an important role in a large number of human diseases. Because of this association, the common belief is that certain compounds, i.e. antioxidants, which are able to neutralize such reactive molecules, can be used to cure or prevent these human diseases. On this premise, even a billion-industry has emerged to sell a huge variety of antioxidant supplements. In our article, we have reviewed the outcome of numerous large-scale clinical trials, which evaluated the effect of the administration of antioxidants in a variety of human diseases.



This cartoon illustrates the existence of three concentration levels of reactive oxygen species (ROS). At a low level (in green) ROS are essential for the proper function of human cells, tissues and organs. At an elevated level (in yellow) ROS help the cell to adapt to stressful situations in order to survive. ROS present in excess (in red) cause damage and cell death. Any antioxidant therapy should aim at only neutralizing or removing the excess of ROS, i.e. ROS depicted in red.

We found that hardly any clinical trial has proven the benefit of taking antioxidants. In some cases, clinical trials even had to be stopped due to the fact that the administration of large doses of

antioxidants further deteriorated the patient's condition or favored the development of the disease. Low-water solubility, rapid elimination from the body, and instability in the blood stream were some of the suggested reasons for the failure of these clinical trials. To overcome these obstacles and make antioxidants better available to the body, scientists have developed tiny little containers (nanocontainers / nanocarriers) made of different materials to encapsulate antioxidants and other drugs (nanodrugs or nanomedicines). Because the size of such nanocontainers is extremely small (between 1 and 100 nm, a single sheet of paper is 100,000 nm thick!), they are invisible to the naked eye and can only be visualized by very powerful microscopes. During the last 20 years, it has indeed been shown that the encapsulation of drugs into these nanocontainers can improve their therapeutic effect. The major focus of our article lies on addressing whether the general promise of Nanomedicines will also hold true for "Nanoantioxidants". Based on astonishing findings published over the last 15 in the field of redox biology, a discipline dedicated to investigating the role of ROS in biological pathways, we became aware that these ROS, which can be harmful to the cells actually play an extremely essential role for the normal function of healthy human cells, but only when present at low concentrations. The general concept of ROS, still existent in current College Textbooks, about ROS being merely toxic byproducts of the energy production within a human cell is no longer correct and, therefore, needs to be revised. Using traffic light colors, we have described in our article the existence of three possible concentration levels of ROS inside human cells. The "green level" describes the amount of ROS needed/required for the correct functioning and survival of any human cell. The "yellow level", which indicates a slight increase in ROS has been found to help the cell to adapt to stressful situations in order to survive. Finally, the "red level" indicates an excess of ROS, which is indeed harmful to any cells, tissues and organs. In our view, the currently tested antioxidant therapies overload the body with antioxidants to kill ROS; however, in their attempt to eliminate the bad ones i.e. "red ones", they also eliminate the beneficial ROS, i.e. "green ones". In conclusion, we propose the design and development of nanocarriers able to distinguish between "bad, i.e. red ROS" and "good, i.e. green ROS" in order to make antioxidant therapy truly beneficial for all patients.

Publication

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Weissig V, Guzman-Villanueva D
Expert Opin Drug Deliv. 2015 Nov