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Viewpoint

Oxidized forms of dietary antioxidants: Friends or foes?

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Many clinical trials in which individuals received one or more dietary antioxidants failed to demonstrate conclusive effects of antioxidant supplementation. Antioxidant supplements do not seem to protect sufficiently against oxidative stress, oxidative damage or to increase lifespan. Some recent studies implied that antioxidant therapy can even increase mortality. In this paper, the idea is presented that antioxidants in their oxidative forms may have more health-beneficial effects than their reduced forms. It seems that it is not the anti-oxidative potential of the antioxidants that has the major role in health-improvement, but rather their involvement in cell signaling processes, regulation of transcription factor activities and other determinants of gene expression. Although oxidized forms of dietary antioxidants may be toxic, their low concentrations might trigger an adaptive stress response (hormesis) and provoke an increased endogenous antioxidant protection and an activation of damage repair processes. Thus, if proved beneficial, the food supplements should contain also low to moderate concentration of specific antioxidants in their oxidized forms.

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Introduction

Natural antioxidants like vitamin C, E, carotenoids, and polyphenols, seem to be beneficial components of fruit and vegetables (Rietjens *et al.* 2002). Consumption of fresh fruit and vegetables is associated with improved cardiovascular and neurological health, reduced cancer incidence, and increased longevity in humans (Boeing *et al.*, 2012; Traka & Mithen, 2011). A statistically significant protective effect of fruit and vegetable consumption regarding the cancer incidence was found in 128 of 156 dietary studies in which the results were expressed in terms of relative risks (Block, Patterson, & Subar, 1992). The intake of foods, naturally rich in antioxidants, has been recommended to the general public as the way to protect against cancer (Gorrini, Harris, & Mak, 2013). However, many of the reported health claims of synthetic antioxidants have been derived from *in vitro* studies, studies using animal models or observational epidemiological studies in which specific diets were associated with a reduced risk of specific diseases. In contrast, many clinical trials where individuals received one or more synthetic antioxidants, did not significantly demonstrate their benefits. The requirement of ROS for cell signaling may explain why many antioxidant-based trials have failed. While antioxidants protect healthy cells and tumor-free people from developing cancer, they can accelerate the growth of an existing precancerous lesion or undiagnosed tumor by reducing ROS (Sayin *et al.*, 2014). Virtually no report of the major clinical trials using mortality or morbidity as the end point described positive effects of supplementation with antioxidants like vitamin C, vitamin E or β-carotene. Identification of specific ingredient of diet that could improve health and contribute to prevention of age-related diseases is an important bottleneck for translating the observational epidemiology to development of functional food ingredients (Rietjens *et al.*, 2002). The issue is complex as addition of antioxidants during food preservation may contribute to food safety and bioavailability of some antioxidants. Another factor is the oxidation of antioxidants during food processing and storage. For example, bioavailability of lycopene can increase because of food processing (Shi and Le Maguer, 2000). The fully oxidized form of vitamin C

(ascorbic acid, AA), dehydroascorbic acid/dehydroascorbate (DHA) is transported more efficiently into cells than its reduced form (Bánhegyi *et al*., 2014, see below). We shall provide an overview of the oxidized forms of antioxidants to stimulate a discussion whether there are positive effects of oxidized forms of dietary antioxidants on health.

Reduced forms of natural antioxidants

Antioxidants and human trials

Dietary antioxidants are molecules that are ingested and theoretically react with free radicals in human cells and thus protect vital biomolecules (DNA, lipids, proteins) against function-altering damage. Numerous studies using various model organisms were unable to prove that lowering reactive oxygen species (ROS) delays the onset of age-related disease nor that increasing antioxidant capacity extends the life span (Ristow and Schmeisser, 2011 and references therein). Additionally, the results of many clinical trials in which individuals received one or more synthetic antioxidants failed to obtain beneficial results. The antioxidant therapy may even increase the mortality (Age-Related Eye Disease Study Research Group, 2001; Bardia *et al*., 2008; Bjelakovic, Nikolova, Gluud, Simonetti, & Gluud, 2008; Bjelakovic, Nikolova, Simonetti, & Gluud, 2004; Heart Protection Study Collaborative Group, 2002; Hercberg *et al*., 2007; Klein *et al*., 2011; Lawenda *et al*., 2008; Miller *et al*., 2005; Mursu, Robien, Harnack, Park, & Jacobs, 2011; Myung, Kim, Ju, Choi, & Bae, 2010; Omenn *et al*., 1996).

Trials of antioxidant supplements in large numbers of people have failed to demonstrate that high doses of antioxidant supplements prevented diseases. In contrast, consuming greater amounts of antioxidant-rich foods may delay diseases. Could this discrepancy between the benefits of consumption of antioxidant-rich food and synthetic supplements be also due to the positive role of oxidative forms of natural antioxidants obtained from fruits, vegetables and beverages?

Autoxidation of natural antioxidants and generation of H_2O_2

It is well known that antioxidants in food can easily autoxidize (Fig. 1). For example, Akagawa, Shigemitsu, and Suyama (2003) reported that pyrocatechol, hydroquinone, pyrogallol, 1,2,4-benzenetriol, and polyphenols such as catechins and polyphenol-rich beverages (green tea, black tea, and coffee) under semi-physiological conditions yield significant amounts of H_2O_2. Also coffee ingestion is associated with significant amounts of H_2O_2; drinking coffee increases urinary hydrogen peroxide levels (Hiramoto, Kida, & Kikugawa, 2002; Long & Halliwell, 2000). A cup of brewed or canned coffee generates 120–420 μmol of hydrogen peroxide when incubated in a neutral medium at 37 °C for 6 h. Soon after preparation at 37 °C and 80 °C, a cup of instant coffee (150 ml) of normal strength (15 mg/ml) contains about 500 and 750 μg of hydrogen peroxide, respectively, but the concentration of hydrogen peroxide in the coffee increases up to 24 h after preparation (Fujita, Wakabayashi, Nagao, & Sugimura, 1985). Autoxidation and loss of total antioxidant activity during storage was observed in different fruits and vegetables (Szeto, Tomlinson, & Benzie, 2002); antioxidants are readily degraded by light, heat, and oxygen. Paradoxically, storage or processing can sometimes improve the antioxidant activity of naturally occurring antioxidants (e.g. polyphenols at an intermediate oxidation state can exhibit higher radical scavenging activity than the completely non-oxidized ones (Nicoli, Anese, & Parpinel, 1999).

Redox homeostasis

Low levels of ROS may act as signaling molecules and activators of stress response survival pathways. Dosing cells with exogenous antioxidants might interfere with signaling pathways important for cell proliferation, differentiation and apoptosis (Janssen-Heininger *et al*., 2008) as well as decrease the rate of synthesis of endogenous antioxidants, so that the total "cell antioxidant potential" remains unaltered (Poljsak, Šuput, & Milisav, 2013 and references therein). For example, adding caffeine, taurine, and guarana in concentrations found in energy drinks to SH-SY5Y cells resulted in excessive removal of intracellular ROS to non-physiological levels (or "antioxidative stress"), reduced activities of superoxide dismutase (SOD) and catalase (CAT) and triggered apoptosis (Zeidán-Chuliá *et al*., 2013). Cutler introduced – The oxidative stress compensation model to explain why dietary supplements of antioxidants have minimum effect on longevity (Cutler, 2003; Cutler & Mattson, 2003). It seems that most humans are able to maintain their set point of oxidative stress and no matter how much additional antioxidant supplements they consume through diet this does not result in further decrease of oxidative stress.

Limited ability of antioxidants for quenching free radicals *in vivo*

Some ROS are extremely reactive, e.g. the estimated half-life of the HO• is 10^{-9} s. Within this time HO• can diffuse the distance between 3 and 10 nm (Halliwell & Gutteridge, 1984) and reacts with any cellular component. The reactivity of HO• is so great that it does not diffuse more than two or three molecular diameters before reacting with a cellular component (Pryor, 1994). HO• thus cannot be efficiently scavenged by synthetic antioxidants (e.g. vitamin C, E, polyphenols), unless the antioxidants are present in concentrations/amounts, much higher than the nearby biomolecules (Cheeseman & Slater, 1993). As this is not feasible, even the intake of additional synthetic antioxidants cannot scavenge efficiently all of the ROS formed within the cells.

Oxidative reactions of antioxidants

Antioxidants, which are reducing agents, can also act as pro-oxidants, since they react with molecular oxygen, and