Opinion

Ten misconceptions about antioxidants

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Oxidative damage is a common cellular event involved in numerous diseases and drug toxicities. Antioxidants prevent or delay oxidative damage, and therefore there has been extensive research into the discovery of natural and newly designed antioxidants. Initial excitement regarding the potential health benefits of antioxidants has diminished. Currently, it is even claimed that antioxidants increase mortality. The antioxidant pendulum appears to swing from healthy to toxic and from general panacea to insignificant ingredient. Owing to the polarity of views towards antioxidants, nutritional recommendation ranges from advice to increase antioxidant status in plasma to the notion that it is a useless measurement. Such views, lacking sufficient scientific support, lead to misconceptions, which in our opinion hinder the rational use of food supplements and impedes the design and development of new antioxidant drugs. As a result, good opportunities might easily be missed.

The antioxidant controversy

Few scientific subjects have generated as many controversial opinions as antioxidants have. The topic is discussed not only in the scientific literature but also in the lay press. A Google search combining the words 'antioxidant' and 'health' gives over 82 million hits, exemplifying the popularity of the subject. Amid the debate, claims about antioxidants can be strongly exaggerated and irrelevant and flawed arguments are even advanced to substantiate such claims. For example, a mixture of compounds is marketed as a 'life extension formula' because the compounds are antioxidants and it is claimed that long-term use of a soap that contains the antioxidant vitamin E is 'excellent for stretch marks, wrinkles, and blemishes. The soap is also suitable for people with a sensitive skin, and beneficial for eczema or psoriasis'. An accurate risk–benefit analysis of antioxidants cannot be achieved in this way.

A basic fact is that antioxidants are part of our daily diet in fruits, vegetables, beverages, spices, and herbs (Box 1), and antioxidant intake is the focus of increasing attention. More recently, designer foods have been enriched with antioxidants. Antioxidants are commonly taken as supplements, and there are also drugs with a clear antioxidant profile on the market [1]. For several decades, we have noticed that the antioxidant pendulum appears to swing vigorously from 'only healthy' to 'extremely toxic', and from 'natural antioxidants are best' to 'antioxidants cannot act'. The squabbling parties do not seem to listen to counterarguments. Erroneous statements are not corrected, and thus the pendulum oscillates to the extremes. This inevitably hampers research in the field and confuses both scientists and consumers. As a consequence, we might fail to spot opportunities for which antioxidants may aid in optimizing health.

Here we discuss ten misconceptions and try to restore the balance.

Misconception 1: antioxidants cure any disease

Antioxidants react with reactive oxygen species (ROS) and thus neutralize their chemical reactivity. It was suggested that this mechanism prevents the (cellular) damage induced by ROS. This led to the claim that ROS-mediated diseases could be treated. ROS are involved in numerous diseases [2]. Subsequently, it was suggested that antioxidants could prevent and treat many diseases [3], which boosted antioxidant research. ROS play a role in chronic obstructive pulmonary disease (COPD), for example. Patients with COPD even exhale the oxidant (ROS) hydrogen peroxide. Another example is the suggested causative role of ROS in ischemia–reperfusion damage in brain, heart, and kidney. In atherosclerosis, low-density lipoprotein (LDL) is oxidized and is subsequently taken up by macrophages, leading to foam cell formation and eventually cardiovascular complications. Compounds that can give rise to oxygen radicals (nitrofurantoin, doxorubicin) can also induce tissue damage in lung and heart, respectively.

Many studies on protection by antioxidants have been conducted. The expectations for antioxidants were set too high and it was apparent that these compounds cannot remedy everything. Moreover, unrealistic health claims disappointed consumers and scientists. Initial enthusiasm turned into disbelief, and some antioxidants, such as vitamin C, were even considered to be toxic [4,5].

Regarding healthful effects, the positive attitude towards antioxidants was primarily based on *in vitro* experiments. Effective chemical scavenging activity of antioxidants *in vitro* led to extrapolation to a protective potential *in vivo*. Identifying the bioavailability of antioxidants has been largely neglected, although polyphenolic antioxidants appeared to have low bioavailability. In addition, bioaccessibility, corresponding to the fraction that becomes available for absorption, must be considered; in other words, the antioxidant has to be liberated from the

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Keywords: oxidants; vitamin E; flavonoids; health; nutrition; redox; oxygen radicals.

0165-6147/$ – see front matter
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Box 1. Redox balance between oxidants and antioxidants

What is an oxidant?

From a chemical point of view, an oxidant takes up electrons. Biologically, oxidants damage biomolecules. They are reactive species that originate from various biological processes. Examples of oxidizing reactive species are the superoxide anion radical ($O_2^{\bullet-}$), the hydroxyl radical ($^{\bullet}OH$), hydrogen peroxide (H_2O_2), and hypochlorous acid (HOCl). Reactive oxygen species are formed as by-products of mitochondrial respiration and are also generated during inflammation from NADPH oxidase on phagocytes. Xanthine oxidase, the metabolism of arachidonic acid, cytochrome P450, nitric oxide synthase, and myeloperoxidase are also possible sources of reactive species. The biotransformation of drugs, such as the redox cycling drugs doxorubicin and nitrofurantoin, leads to the formation of reactive species.

What is an antioxidant?

From a chemical point of view, an antioxidant is a compound that prevents or delays the oxidation of another compound.

Of two compounds, the one that becomes oxidized functions as an antioxidant for the other. In this sense, antioxidants are not very special. Biologically, however, the definition of an antioxidant requires that it should be active in protecting physiological targets (e.g., fatty acids, proteins, and DNA) at relatively low concentrations. Dietary antioxidants include vitamins E and C. Drugs such as the anesthetic propofol and the recently developed antifibrotic agent pirfenidone act as antioxidants. The mucolytic agent *N*-acetylcysteine acts as a precursor for the endogenous antioxidant glutathione.

food matrix [6]. After absorption, first-pass metabolism can be very extensive, and currently there is more emphasis on the biological relevance of antioxidant metabolites [7]. We now realize that high chemical reactivity of the parent compound *in vitro* is not conclusive evidence that the compound can cure any disease associated with ROS.

We are again observing overenthusiasm towards antioxidants with the discovery of their effects on gene expression by mechanisms other via an influence on the DNA sequence (i.e., epigenetics). Presented as a new unifying mechanism to putatively explain all the activities of antioxidants [8], it seems that history repeats itself.

Misconception 2: antioxidants increase mortality

A recent meta-analysis of selected randomized clinical trials concluded that antioxidant supplementation increased all-cause mortality [9]. However, this conclusion was refuted after re-examination showed that none of the studies had mortality as a primary outcome [10]. Despite the obvious criticism, the general unjustified and unbalanced notion that antioxidants could be highly unsafe remains. Instead of the polarized view whereby antioxidants are either good or bad, a high benefit–risk ratio would be a more appropriate approach to evaluate antioxidants. Such a ratio weighs both the pros and cons, and thus provides a more realistic and balanced view.

Observational studies have suggested a protective effect of vitamin E intake on coronary heart disease [11]. However, many large, randomized, placebo-controlled trials reported disappointing results for the effect of vitamin E on risk of cardiovascular disease [12,13]. A critical evaluation of these studies suggested that a detailed analysis of the participants' diets might lead to a different conclusion. It was suggested that some apparently healthy participants have higher rates of lipid peroxidation than others. These 'rancids' might show a higher risk of cardiovascular disease and would be the individuals who might benefit from additional antioxidants [14].

Similarly, the overall null effect of vitamin E on total stroke occurrence might simply be due to a broad definition of stroke and this it might not be possible to capture the differences in pathophysiology underlying various ischemic and hemorrhagic events. A meta-analysis of studies that investigated the effect of vitamin E on stroke indeed showed that it increased the risk of hemorrhagic stroke by 22% and reduced the risk of ischemic stroke by 10% [15]. Because of the unfavorable risk–benefit ratio, that is, a relatively small risk reduction for ischemic stroke and the generally more severe outcome for hemorrhagic stroke, the authors cautioned against indiscriminate widespread use of vitamin E [15].

Articles on antioxidants and mortality [9,16] have received much attention. For example, it has recently been argued that antioxidant use is more likely to cause than to prevent cancer [16]. Blockage of oxidant-driven apoptosis in cancer cells by antioxidants was presented as a potentially hazardous phenomenon.

Because antioxidants do not have to have a beneficial effect *per se*, it is important to identify groups such as 'rancids' who might benefit from antioxidants. We should not place too much credence in unbalanced alarming news.

Misconception 3: the more the better

As the founding father of orthomolecular medicine, Linus Pauling advocated the use of the antioxidant vitamin C in doses of 1000 mg [17] to optimize health, which vastly exceeds the recommended dietary allowance of 75–90 mg/day [18]. A solid scientific justification with clinical studies supporting the assumed health benefit of mega doses of vitamin C is, however, lacking. Moreover, the Renaissance physician Paracelsus noted more than 500 years ago that every compound has negative effects at a high dose. This also holds for antioxidants. Administration of high doses of antioxidants might explain the increased toxicity that is sometimes reported. For example, supplementation with 20 mg of β-carotene in male smokers increased the incidence of lung cancer by 18% [19]. Note that the estimated average daily intake of β-carotene is only 2–7 mg [20,21]. In hindsight it is astonishing that at the time of supplementation studies, essential information on the biotransformation of β-carotene was lacking [22]. Clearly, 'the more the better' is not the case. Identification of an optimal dose with a high benefit–risk ratio is required, along with adequate knowledge of the biotransformation of antioxidants.

Misconception 4: at high doses, antioxidants become pro-oxidant

Antioxidants have the ability to donate electrons. This reducing power is essential in neutralizing radicals and other reactive species. In the presence of transition metal ions, electron donation may lead to a pro-oxidant effect. The effect of ascorbic acid on iron-induced lipid peroxidation *in vitro* is a very illustrative example of this effect [23]. Iron itself induces mild lipid peroxidation and in combination,

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