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Review Article

Time to Take a Closer Look at the Controversial Effects of Antioxidants: Important Points to Be Remembered

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Abstract
The beneficial effects of antioxidants have been investigated and reported for decades. These include (but are not limited to) the positive effects on the endocrine, reproductive, and central nervous systems. Free radicals, which have been known to be formed during many processes, including drug metabolism, and introduced as the main player in oxidative stress conditions, would be scavenged and neutralized by antioxidant agents. Whether endogenous or exogenous, they have been known to stand against many pathologies such as neurodegeneration, nephrotoxicity, inflammation, cancer, and aging, as well as pain and related challenges, namely, tolerance and dependence on analgesics. Despite the numerous reports of the benefits, the volume of studies focusing on the potential harms seems to be insufficient. It is important to note that some of the negative effects can be serious and challenging. In fact, the words "negative" or "positive" would be defined under a particular condition. Most likely, the most well-known example would be the challenges of antioxidant consumption in carcinogenesis, although many other conditions would be the focus. In this regard, the overuse of many antioxidant nutraceuticals, such as vitamin E, β-carotene, and lipoic acid, has been reported to be associated with serious complications. In this review, in addition to the bright side, we are going to scrutinize the controversies surrounding antioxidant administration.
Keywords: Oxidative stress, Antioxidant, Free radical, Scavenger, Controversies

Introduction

Oxidative stress (OS) has become an important concept in recent decades, which would be defined as an imbalance between pro-oxidant and antioxidant protective mechanisms throughout the body where reactive oxygen species (ROS) are overproduced or the antioxidant capacity is dropped below normal. In fact, natural antioxidant defenses can be considered an important buffering system that maintains the oxidative status of the body within an acceptable range on a limited scale.[1-4]

From the point of view of chemistry, hydrogen peroxide, superoxide anion, nitric oxide, singlet oxygen, and hydroxyl radicals have been categorized as important ROS. The mentioned structures can cause serious damage to biological structures, including deoxyribonucleic acid, the initiator of important physiological procedures in cells, as well as proteins and lipids, so that they would be cytotoxic or cytostatic depending on the exposed concentration.[5-7]

The close relationship between ROS overproduction and many medical conditions has been found and reported in relevant studies. Particularly, complications of obesity, diabetes mellitus, chronic kidney diseases, Parkinson's disease, Alzheimer's disease, cardiac hypertrophy, and age-related disorders can be mentioned in this regard.[8]

On the other hand, the administration of antioxidants seems to be an approach to better treating ROS-mediated disorders. As examples, many pathologies such as neurodegeneration, nephrotoxicity, inflammation, cancer, aging,[5] and pain,[9] as well as related challenges, namely, tolerance[10] and dependence[11] to analgesics, seem to be alleviated by antioxidants.

Furthermore, numerous studies support the neuroprotective ability of antioxidants.[12-16] As an example, we can point to our previous reports, which were related to stress-related disorders[17] and sleep disturbances.[18]

Antioxidants are compounds able to stand against OS and related disorders by scavenging free radicals. In fact, the activity of the radicals seems to be antagonized by antioxidants.[5,19] Therefore, many believe that providing antioxidants for the body would be an efficient way to alleviate the medical conditions resulting from OS.[20,21]

By reviewing the literature, it was found that the number of articles concerning the controversies of antioxidant therapy is much less than the ones focusing on the benefits. In other words, the toxicology of these compounds is not as developed as their pharmacology. Therefore, as a basis for future research projects, we decided to gather important and informative documents focusing on the controversies surrounding antioxidant therapy (Figure 1).

Antioxidants and Cancer

Cancer has been known as one of the most life-threatening pathologies.[22] One important and controversial issue about antioxidants would be raised in cancer chemotherapy.[23] While some studies claimed the ability of antioxidants to alleviate chemotherapy side effects, others indicated antagonizing effects, resulting in a reduction in the efficacy of the treatment.[24] Since many chemotherapy agents act as oxidants,[25] interference with the effect of antioxidants would be justifiable.[26]

Antioxidants and Diabetes

Today, it is clear that OS is a key factor in the pathogenesis of diabetes and its complications.[27,28] The involvement of advanced glycation end-products, namely, protein kinase C and hexosamine, as well as glycolytic pathways has been demonstrated in this regard.[29] While previous research has demonstrated that controlling ROS overproduction is an important concern in diabetic and pre-diabetic patients,[30] the exact role of antioxidants in this regard has been reported to be controversial.[31]

Antioxidants and Male Infertility

Reviewing the literature shows that many endogenous and exogenous factors can cause infertility in men.[32-35] The other controversial issue regarding antioxidant therapy would be the outcomes in the treatment of male infertility. Although some supplements, including folic acid,[36] vitamin E,[37] vitamin C,[37], L-carnitine,[38] and *N*-acetyl cysteine,[39] are well-known for their improving effects on male fertility, some studies have claimed that their overuse may lead to infertility.[40]

Conclusions and Future Perspectives

In this study, it was aimed to focusing on the controversial effects of antioxidant therapy (Figure 2), which have been discussed less when compared to the benefits. The delegated and gathered documents revealed that, despite the popular belief of today's society, important contraindications and negative consequences have been introduced for antioxidant therapy. In this regard, many studies have discussed the harms; nonetheless, reviewing the literature clearly indicates a lack of sufficient clinical and preclinical studies evaluating the negative aspects of the compounds. Therefore, designing relevant toxicological studies would strongly be recommended. Some important points can be mentioned by scrutinizing the studies (Figure 3):

- Similar to any other drug category, the benefits and risks of antioxidants would be dose-dependent, and the amount of consumption must be considered and adjusted accordingly.
- The toxicology varies from one particular antioxidant to another.
- Antioxidants would be beneficial where a lack of the required amounts is detected throughout the body.
- Preclinical and clinical studies are strongly needed to better clarify the toxicology of the antioxidants.

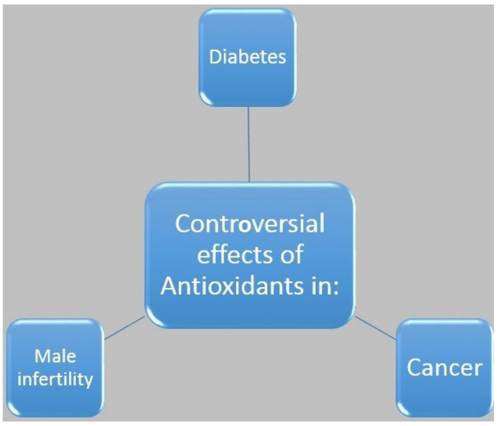

Figure 2. Some Complications Where Antioxidant Therapy May be Controversial

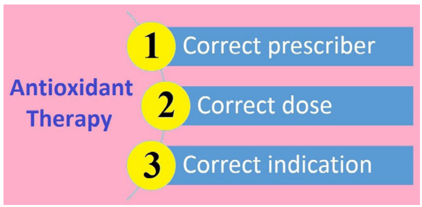

Figure 3. Considerations for Antioxidant Therapy

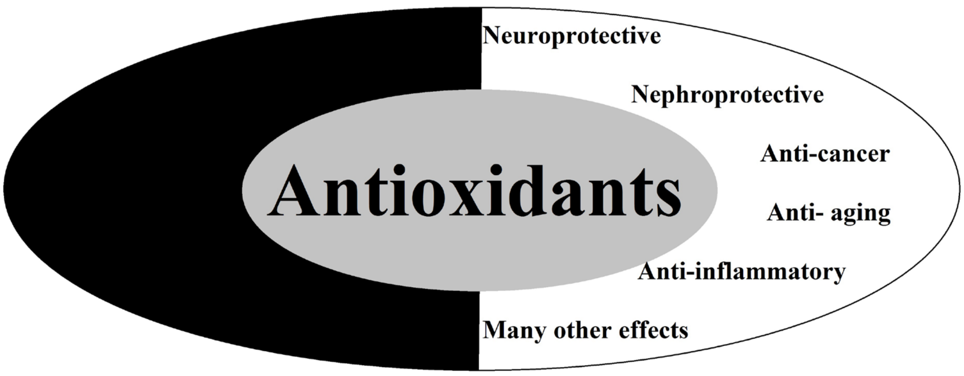

Figure 1. Dark Side of Antioxidant Therapy Versus the Bright Side

- A healthcare provider must always be consulted before using antioxidants.

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Authors' Contribution

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Competing Interests

None to declare.

Ethical Approval

Not applicable.

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