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Antioxidant Safety and Antioxidant-induced Stress

Recep ASLAN

[1] *Department of Physiology, Faculty of Veterinary Medicine, Afyon Kocatepe University, Afyonkarahisar, TURKEY*

*Corresponding author e-mail: raslan@aku.edu.tr

ABSTRACT

The safe use of antioxidants and reliable antioxidant applications are a new and important area of debate that has been continuing for decades. Today, antioxidant plants, phytochemicals and products are the most popular supplements. Most of them are sold without a prescription, even though they are used like a medicine. We know many scientific reports on the benefits of antioxidants but there are also studies that question whether antioxidant products have harmful effects. Nowadays antioxidant safety is the one of the most important medical topics at oxidant-antioxidant balance and oxidative stress. A physiological balance exists between oxidants and antioxidants in the organism only when both of the forces are present. Studies which document that antioxidant supplementation, inhibits the reactions and effects of free radicals are common. But, it is still unclear which exogen antioxidants and doses should be used to have an efective defense and also what safe limit is for use. It is possible that many of antioxidant phytochemicals and supplements can cause harmful changes in tissues by initiating different mechanisms. The most important question related to the use of antioxidants and antioxidant safety is the names, amounts, kinds and forms of them. The term antioxidative stress is a new strategic word on oxidant-antioxidant balance as like as oxidative stress. Antioxidants may cause stress in tisssues which refers to antioxidative stress. An extraordinary attention on antioxidative stress is a necessity for today's medical disciplines. The further studies are needed to clarify the harmful effects of antioxidants and antioxidative stress for the antioxidant safety. We aimed to focuse on the antioxidant-induced stress. For this reason, some reports on the harmful effects of antioxidants have been discussed in this paper.
Keywords: antioxidative stress, harmful effects of antioxidants, antioxidant safety

Antioksidan Güvenliği ve Antioksidan Kaynaklı Stres

ÖZ

Antioksidanların güvenli kullanımı ve güvenilir antioksidan uygulamaları, on yıllar boyu devam edecek yeni ve önemli bir tartışma alanıdır. Günümüzde antioksidan bitkiler, fitokimyasallar ve antioksidan ürünler en popüler tıbbi ürünlerdir. Büyük çoğunluğu ilaç gibi kullanılmasına rağmen bu ürünler reçetesiz satılır. Antioksidanların yararları hakkında birçok bilimsel rapor biliyoruz, ancak olası zararlı etkilerini sorgulayan araştırmalar ve önemli raporlar da mevcuttur. Aslında antioksidan güvenliği, oksidan-antioksidan denge açısından çok önemlidir. Organizmadaki oksidanlar ve antioksidanlar arasındaki fizyolojik denge, bu kuvvetlerin her ikisi de geçerli olduğunda dengelenir. Antioksidan takviyesinin serbest radikal ürünleri, reaksiyonları ve etkilerini engellediğini belgeleyen çalışmalar yaygındır. Ancak, etkili bir antioksidan savunmaya sahip olmak için hangi ajanların ve hangi miktarların gerekli olduğu ve hangi dozun kullanım için güvenli limiti yansıttığı hala bilinmemektedir. Ekzojen antioksidan fitokimyasalların ve eklerin çoğu, farklı mekanizmalar başlatarak dokularda zararlı değişikliklere neden olabilir. Antioksidan kullanımı ile ilgili en önemli nokta, antioksidan güvenliği için bunların çeşitleri, formları ve dozlarıdır. Antioksidatif stres terimi oksidatif stres gibi oksidan-antioksidan dengesinde yeni bir stratejik kelimedir. Antioksidanlar, dokuları antioksidatif stres olarak adlandırılan strese yönlendirebilir. Olağanüstü bir dikkat ve antioksidan strese odaklanmak, bugünün medikal disiplinleri için bir zorunluluktur. Antioksidan güvenlik için antioksidan ve antioksidan stresin zararlı etkilerini aydınlatmak için daha ileri çalışmalara ihtiyaç olduğunu düşünüyoruz. Bu derlemenin amacı antioksidan kaynaklı strese odaklanmaktır, bu nedenle bu çalışmada antioksidanların zararlı etkileri hakkındaki mevcut kanıtlar analiz edilmiştir.
Anahtar kelimeler: Antioksidan güvenliği, antioksidatif stres, antioksidanların zararlı etkileri

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INTRODUCTION

Oxidative stress is the imbalance among the production, scavenging and removing of reactive oxygen and nitrogen metabolites (ROS/NOS) leading to potential oxidative damage. ROS and NOS are considered to be the toxic byproducts of aerobic metabolism. Despite this, they are always not harmful and they also have some benefits. Nowadays, it is clear that ROS and NOS may manage many physiological processes such as induction of stress response, systemic signaling and pathogenic defense (Aslan, 1999; Koçyiğit and Selek, 2016). Our main emphasis is not the benefical effects of reactive species. We aimed to emphasize the possible harmful effects of antioxidants.

The imbalanced antioxidant potantial and increased antioxidant activity is called antioxidative stress. It was reported that antioxidant-induced stress may be as dangerous as well as oxidative stress (Dündar and Aslan, 2000). There are various reports on harmful effects of exogenous antioxidants in case of overconsumption. Antioxidants can deactivate ROS/NOS and reduce oxidative stress. This is not always auspicious in relation to disease formation and for adjourning aging (Pechanova et al., 2009; Narwaley et al., 2011; Poljask and Milisav, 2012). There are theories that the evolution of aerobic organisms is a consequence of the gradual adaptation of oxygen. Cellular antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px) are believed to facilitate this adaptation (McCord et al., 1971).

Antioxidant enzyme activities regulate oxidant-antioxidant redox. SOD, CAT, GSH-Px, which helps the removal of over increased reactive species. However, endogenous antioxidant reactions are supported with exogenously reducing agents, such as vitamin E, vitamin C, lipoic acid, carotenoids, polyphenols and phytochemicals, which play an obligatory role in many antioxidant mechanisms in aerobic organisms. For this reason, there is a serious requisition for exogenous antioxidants to prevent the oxidative stress circule. However, this fact must also be considered. Because some studies show that many antioxidant substances such as nitric oxide and melatonin also can take an oxidative role (McCord et al., 1971; Aslan and Dündar, 1998; Munik and Ekmekcioğlu, 2015).

An antioxidant does not always exhibit the same antioxidant effect, even that it is not effective at all (Çevik and Aslan, 2015, Evcimen et al., 2018). An antioxidant has a weak antioxidant effect in some tissues, , but in the other tissues has a strong antioxidant effect (Evcimen et al., 2018). Since antioxidant safety is the target in this study, antioxidant-induced stress will be discussed. We aim to review reports and evidences on antioxidant stress-induced deleterious roles on health, disease and aging.

Antioxidant Safety

Although reactive species are always not harmful, antioxidants are not necessarily useful (Halliwell and Gutteridge, 1995). They try to give or take an electron to complete the pair. But by pairing, antioxidants cannot complete themselves and thus, act like reactive species. These reactive antioxidants are tried to recycle by other antioxidants. In aerobic metabolisms, it is all a matter of equilibrium (Villanueva and Cross, 2012). However, this balance can be broken if antioxidant levels overrun the reactive species. The term "antioxidative stress" is suggested for such unbalance (Dündar and Aslan, 2000).

Recent, extraordinary attention has been paid to effects of exogenous antioxidants and antioxidant supplements. Are exogenous antioxidants always safe? What is the safe dose of antioxidants and the safety margin? Which indicators can be antioxidative stress markers. These questions and many of others show that there must be a new approach on antioxidants and policy of antioxidant safety (Villanueva and Cross, 2012). Despite these questions, the reality does not change: Since aerobic life depends on free radicals and antioxidants, it is not possible to escape from them. For an antioxidant preparat used in medicine, ithis question should be discussed: How do these antioxidant agents fit with available physiologic free radical defense? There are to much data on reducing effects of antioxidants on oxidative stress. But, it is still unclear which antioxidants and which doses are effective (Dündar and Aslan, 2000). There are reports that physiologic amounts of beta carotene and vitamin C act as antioxidants, but at pharmacologic levels, they turn into prooxidants (Herbert, 1993). The query of whether the antioxidant-induced stress is expressed in a delicately integrated physiologic system is still unacknowledged (Gutierrez, 2006;) These are also important questions about antioxidant substances. For example, antioxidants are peroxidation inhibitors. An antioxidant as an inhibitor of lipid peroxidation, is unseemly to be benefical if the oxidative injury is mediated by an assault on DNA proteins. From this point of view, many antioxidants may be thought to have the potential to accelerate free radical damage. If the antioxidants scavenge the radicals, antioxidant-derived radicals may causetissue damage (Villanueva and Cross, 2012).

Elevated amounts of exogenous and synthetic antioxidants play prooxidant role in the entity of

iron and copper ions (Azam et al., 2004). Prooxidant activity is related to the molecular structure and concentrations of antioxidants (Yen et al., 2003). In recent cell modeling studies, some polyphenolic compounds known as antioxidants, such as quercetin, catechin, and gallic acid, also show prooxidative effects at the same time (Robaszkiewicz et al., 2007).

In environments where antioxidants are present in high concentrations, metal ions have been reported to cause undesirable effects. For example, in the presence of metal ions, some antioxidant phytocemicals like epigallocatechin has been indicated to cause damage to isolated cell DNA. Some antioxidants as natural polyphenols have prooxidant activity with iron and copper ions. The mechanism of natural antioxidants is as follows: First, it removes hydrogen atoms (-RH) or electrons (-R-) on the reactive molecules. The second mechanism acts as a single oxygen activator when the antioxidant absorbs UV radiation or enters the antioxidation reaction as a transition metal ion chelator, or converts hydroperoxides to non-radical products. However, antioxidants show the most reductive power by increasing the harmful hydroxyl radıcal formation from peroxides by the Fenton reaction in the presence of metal ions, especially Fe3+ and Cu+. When antioxidant polyphenols destroy reactive molecules, they come back into less reactive phenoxy radicals balanced by delocalization of unpaired electrons round the aromatic ring. The prooxidant activities of antioxidant phenols are thought to be related to the hydroxyl groups number in the molecule. While prooxidant activities of mono and dihydroflavonoids can not be shown, it has been shown that flavonoids with more than three hydroxyl groups in B-group, significantly increase hydroxyl radical production by Fenton reaction. The prooxidant reactions of flavonoids may also depress their beneficial effects. It has been shown that high levels of antioxidant polyphenols lead to mitochondrial impairment and apoptosis. All of these, high amounts of exogenous and synthetic antioxidants may be potent stressors for tissues by reacting with beneficial reactive species for physiological homeostazis (Koçyiğit and Selek, 2016).

Antioxidant-Induced Stress

Antioxidants can become reactive substances when they lose or receive electrons as they react with radical species and they can become harmful (Sevanian et al., 1991). This fact is often disregarded by the authors who advocate the use of exogenous antioxidants: these compounds do not only function as an antioxidant, but also have a prooxidant action. In some conditions, the well known antioxidant vitamin C, may act as a prooxidant. For example, vitamin C addition up to concentration of 0.2 mM potentiated 10 nM, increases iron induced lipid peroxidation, due to maximal increased thiobarbituric acid subtances. Reduction of Fe3+ is a common accepted explanation for the prooxidation of vitamin C. The combination of vitamin C and iron cause intense oxidation of PUFA's and the prevalence of vitamin C to act as either a threatening factor or scavenging agent (Niki, 1991). It is reported that this combination causes intestinal tissue damage via lipid peroxidation (Herbert, 1993). Similar antioxidant prooxidant transformations have been shown for vitamin E as well:

Reaction 1: Vit E + LOOH $\rightarrow$vit E• + LO• + H_2O

Reaction 2: Vit E + LOO• $\rightarrow$LOOH + vit E•

Reaction 3: LOOH + Vit E• $\rightarrow$vit E + LOO•

Reaction 4: LH + LOO• $\rightarrow$LOOH + L•

Reaction 2 is equilibrium reaction. Cell membranes contains excess fatty acid over vitamin E molecules. This suggests that vitamin E is consumed while the fatty acid concentration is stable during peroxidation. Reaction 1 declares that the vit E/ fatty acid increases. The ratio LOOH/ vit E accumulation of LOOH reverses reaction 3 and stimulates the propagation reaction 4. Optimal vitamin E should be given at such a dose that the propagation will effectively be inhibited. However, this vitamin E amount is not known exactly (Witting, 1980). Some studies demonstrate that exogenous antioxidants may also posses antioxidative stress potential under certain conditions, the interaction and cyciling of antioxidants should also be reconsidered. Common scientific approach was that any dose of antioxidants were not harmful. Nowadays, harmfu effects of antioxidants are invsetigated by different studies and furtherthe safe use of antioxidants is recommended. Taking different doses of antioxidants may cause antioxidant-induced risks in tissues. They may even cause some serious consequences such as increased risk of heart attack. (Herbert, 1993). For example, more than 600 mg/day of tocopherols can interfere with the absorption of vitamins A and K, while 200 to 600 mg/d of it appear innocuous (Clarkson, 1995). Extended doses of 1 mg/day and 5 mg/day of selenium have been reported to have antioxidant-induced stress effects (Dündar and Aslan, 2000). Not only exogenous antioxidants, but also endogenous antioxidant enzymes can some times be antioxidative risk faktors (Villanueva and Cross, 2012).

Redox potential of antioxidants could be related to the antioxidant-induced stress. The redox potential density of famous antioxidants can be listed as follows: β-carotene 0.65 V, vitamin E 0.50 V, flavonoids 0.25–0.50 V, vitamin C 0.01 V and uric acid 0.25 V (Martin et al., 1999). It is well known that the network of antioxidant called antioxidant defence is obligatory (Halliwell, 2008). α-tocopherol (α-TC) produces α-tocopheroxyl radical when it reacts with reactive moleculs such as superoxide or peroxynitrite. α tocopheroxyl radical is then recycled to α- tocopheroxyl by different antioxidants such as vitamin C and glutathione. After ascorbic acid recycles vitamin E, it is transformed to the ascorbyl radical which has a lower reactivity than vitamin E. α-TC radical is also recycled to vitamin E by β-carotene. Therefore, t application of vitamin E with other antioxidant is essential. It is also substancial to have prominent levels of antioxidants to allow recycling of antioxidants to reactive forms. Some conditions such as reduction of ascorbic acid in smokers, reduce antioxidant enzymes and endogen antioxidant subtracts, and could affect the recycling of Vitamin E or other antioxidants, and could release α-TC radical available to produce lipoperoxidation. An other major effect of ascorbic acid is to recycle oxidized glutathione to reduceglutathione, and return carotenoid radicals to carotenoids. As a reduced form, dihydro-lipoic acid returns GSSG to GSH and turn back into the ascorbic ascorbyl radical. This indicates the common prooxidant effect of lipoic acid (Villanueva and Cross, 2012). Another way for antioxidant-induced effect is that some antioxidants exhibit prooxidant activity with transition metals. This is the situation of ascorbic acid which turns into an ascorbyl radical and hydroxy cinnamic acid in which phenolic groups are transformed into phenoxy reactive groups. Beta-carotene is also a good example of converting an antioxidant to a prooxidant effective agent. The carotenoid radical is produced by oxygen and iron ions in the oxidative part of the β-carotene. (Lakshman, 2004).

The other important way of active endogenous antioxidant defense is a submaximal aerobic exercise, every day. In summary, the harmful effects of antioxidants depend on its concentration, its redox potential, availability of other antioxidants and the transition metals. Even though it was not exactly indicated, the genetic history may also help to explain the stress induced effects of antioxidants. Synthetic or organic exogenous antioxidants, supplementary antioxidants and various supplementary products to strengthen our body may be antioxidative stressors. Hence, physiological doses of antioxidants and their safety ranges must be clarified. Increased amounts of antioxidants may be risk for healthy organisms and overdoses cause damage like the one in hypervitaminosis (Poljsak and Milisav, 2012). Generally, the effects of endogenous antioxidant enzymes are not questioned because they are organismic, natural and balanced.

The other important point is the changing roles of some biomoleculs such as nitric oxide, melatonin. Therefore, melatonin acts as a strong antioxidant. Studies showing the prooxidant effects of melatonin have been published. These studies report that the oxidative effects of melatonin may be related to the involvement of an important second messenger, calmodulinin and the mitochondrial respiratory chain (Munik and Ekmekcioğlu, 2015).

Oxidants may be beneficial for many physiological reactions in cells. Recently, it has become apparent that reactive oxygen and nitrogen species might control many benefical physiological processes such as induction of stress response, pathogen defense, and systemic signaling. On the other hand, there are harmful effects of antioxidative stress that occured in the overconsumption of synthetic antioxidants (Dündar and Aslan, 2000; Koçyiğit and Selek, 2016). Since there is no evidence of adverse effects of antioxidants, they are generally accepte as safe products. This is a common scientific mistake. It was declared that antioxidant therapy does not effect the diseases, and antioxidant therapy is validated only in experimental disease and cell culture models (Halliwell, 2009). Synthetic antioxidants and the high doses of exogenous antioxidant agents are not recommended, low doses of antioxidants are suggested to be beneficial only in those with antioxidant deficiency (Koçyiğit and Selek, 2016). In this direction, lets see some of the published studies that declare the harmful effects of antioxidant supplements. In a study made in Australia, hypertensive patients received treatment with Vitamin C (500 mg/day) and grape seed polyphenols (1000 mg/day). After six weeks, systolic-diastolic pressures and endothelium dependent vasodilation increased, while oxidative stress markers did not change (Ward, 2005). In a study on HDL atherosclerosis, an antioxidant treatment was applied for male and female patients having low HDL and triglyceride in which they treated with vitamin E (800 IU / day), vitamin C (1000 mg / day), beta carotene (25 mg / day) and selenium (100 μg/day) . Other patient group had taken placebo. When the results were analyzed it is understood that antioxidant therapy did not support HDL elevation (Cheung, 2001). In another study, antioxidants vitamin C and N-acetylcysteine increased acute exercise induced oxidative stress in healthy persons. Acute exercise is already known to increase oxidative stress (Aslan et al., 1998), but

chronic or programmed exercise reduces the oxidative stress (Aslan and Dündar, 1998; Aslan et al., 1998; Ji, 2008).

It is interesting that both antioxidants can not suppress this stress, and even increase it. In this stuation, the conversion of ascorbic acid into the ascorbyl radical by reactive species generated during exercise may be major factor (Childs et al., 2001). An other important antioxidant β-carotene has also similar effects. High redox potential of β-carotene can make it an effective of oxidizing molecules. β-carotene in high concentrations may oxidize DNA (Yeum et al., 2009). Another way that the antioxidant induced stres may be the normal responses of the organism to oxidative stress (Ji, 2008; Ristow et al., 2009).

CONCLUSIONS

We have insufficient data on the long-term effects of different doses of the exogenous and synthetic antioxidant supplements. For this reason, an awareness of unsafe doses of antioxidants should be established. Use of the term "antioxidative stress" might be substantial to the formation of a scientific mind against unsafe use of antioxidants. Studies on the use of safe antioxidants in medicine are needed to determine the ways and factors causing for the antioxidant induced stress. Hopefully, this study will stimulate further research on antioxidant-induced stress in animals and human beings. It was showed that antioxidant nutrients abolish the homeostasis by inhibiting an adaptive reaction to reactive oxygen and nitrogen metabolites. There are homeostatic mechanisms in cells that govern the amount of allowable antioxidant activity. Most organisms are able to maintain their oxidant-antioxidant balance. As a result, for beneficial physiological effects, exogenous and synthetic antioxidants should be well absorbed in the body, reach the medium of reactive oxygen and nitrogen species formation in cells and should be present in appropriate amounts.

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