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Review Article

Antioxidant Supplements and their Judicious Use

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Abstract

Oxidative stress has been proven to be the under-current mechanism for most of the modern epidemics like diabetes, hypertension, cardiovascular diseases, cancer, cataract and many other chronic diseases and hence antioxidant supplements are advised to prevent or halt the progression of such diseases. However, in excess dosage and under different altered physico-chemical conditions many antioxidants can turn in to pro-oxidant and may rather lead to further damage. The communication gap between researchers and the healthcare providers pose more harm than good and is a real matter of concern. Hence a proper dosage and duration has to be delineated after longer prospective studies.

Keywords: Antioxidant Supplements; Pro-Oxidant; Modern Epidemics; Free Radical Damage

Abbreviations

DM: Diabetes Mellitus; ROS: Reactive Oxygen Species; RNS: Reactive Nitrogen Species.

Introduction

Since the end of nineteenth century when research on oxidative damage was first conceptualized, gradually oxidative stress found a common link to aetiopathogenesis of many modern epidemics like diabetes mellitus (DM), hypertension, cardiovascular disorders (CVD), cancers, degenerative diseases, skin diseases like lichen planus, vitiligo, chronic inflammatory diseases, cataract, autism, retrolental fibroplasia etc [1,2]. And it has also shown involvement in the most dreadful natural phenomenon of mankind i.e. ageing [3]. Thereafter as panacea to oxidative damage, the antioxidant supplements came into the picture. The antioxidant supplements turned into the much hyped 'wonder drugs' and the natural food products rich in antioxidants became the 'super-foods'.

What is oxidative stress?

Oxidative stress is the imbalance between antioxidants and the oxidative products generated in the body. Usually the atoms are composed of a central nucleus and paired electrons orbit around it. When the electrons are unpaired, it is known as a free radical. Such free radicals can be reactive oxygen species (ROS) and reactive nitrogen species (RNS) that include superoxide radical ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2), hydroxyl radical ($OH^{\cdot}$), singlet oxygen ($^1O_2$), hydroperoxy radical ($HOO^{\cdot}$), alkylhydroperoxide (ROOH), alkylperoxyl radical ($LOO^{\cdot}$), nitric oxide ($NO^{\cdot}$), $Fe^{4+}O$ (Ferryl ion), hypochlorite ion (ClO^-) etc [4].

These free radicals are generated by oxygen interacting with biomolecules such as lipids, proteins, carbohydrates and DNA. These can be generated during normal metabolic processes or by different environmental factors like UV rays, irradiation, toxic chemicals, tobacco smoke etc. Internally they can be generated from leakage of electrons from ETC (Electron transport chain), from xanthine oxidase and aldehyde oxidase activity, in inflammatory cells by activity of NADPH oxidase, in macrophages in the form of nitric oxide (NO), in the platelets and leucocytes due to Lipoxygenase activity, in Peroxisomes, from cytochrome P450 system during Xenobiotics metabolism [5-7]. Also they are generated during various stressful conditions, inflammation, ischemia, reperfusion and even during exercises [8].

The free radicals being highly reactive and unstable can attack other molecules to acquire electron and become stable. Thus the attacked molecule becomes a free radical and the chain reaction

cascade goes on, accumulating free radicals. These free radicals can cause lipid peroxidation, protein carbonylation or modify DNA bases and thus damage different tissues.

How does our body defend against free radicals

Our body has an innate antioxidant defense against these free radicals which can be described under two categories- i) Preventive antioxidants ii) Chain breaking antioxidants. Preventive antioxidants intercept oxidizing species before the damage can be done, whereas chain-breaking antioxidants slowdown or stop the oxidative process after it has ensued, by intercepting the chain-carrying free radicals [9].

Preventive antioxidants act by different ways- i) Deactivating metals e.g. transferrin, ferritin, desferral, EDTA, DETAPAC (Diethylenetriaminepentaacetic acid); ii) By removing hydroperoxides- e.g. catalase, glutathione peroxidase, pyruvate etc; iii) By quenching singlet oxygen e.g. beta carotene, lycopene, bilirubin etc [10-12].

In general, chain breaking antioxidants act by reacting with alkyl peroxyl radicals ($ROO^{\cdot}$). They can be i) Donor antioxidant like tocopherol, ascorbate, urate etc or ii) Sacrificial antioxidant like nitric oxide. The donor antioxidants donate an electron to the free radical and acquire a free electron themselves whereas the sacrificial antioxidant which gets used up in order to produce a new product [13].

The different antioxidants though get oxidized, cannot generate free radicals themselves. They have reduction potential that places them in the middle of pecking order. This location in the pecking order provides antioxidants with enough reducing power to react with reactive oxidizing species. At the same time they are too weak to initiate reductive reactions [14].

$LOO^{\cdot} + TOH \rightarrow LOOH + TO^{\cdot}$ (Termination)

Depending on their reduction potential, the antioxidants recycle each other. For example, ascorbate (reduction potential +282mV) can recycle tocopherol (+480 mV) and urate (+590mV). However, not all antioxidants can be recovered and hence they are to be replenished from time to time.

Replenishing antioxidants

The replenishment can be done by food rich in antioxidants or by supplements. Dietary antioxidants can be obtained from spices, herbs, essential oils, cocoa, tea, dried foods, red wine, deeply pigmented food like mango and pomegranate, fig etc. In cabbage and beetroot also antioxidants are found after they are cooked. Especially beta carotene, tocopherol and ascorbate are obtained from the dietary sources. Vitamin cofactors like Coenzyme Q10 and minerals like Manganese and iodine also show antioxidant property. Carotenoids and terpenoids form another group of natural antioxidants. Alpha carotene from carrot, tomato etc, astaxanthin from marine food, lycopene from tomato, guava, watermelons etc and Zeaxanthin from spinach, corn, broccoli etc are few to name some [15]. Polyphenols and natural phenols obtained from legumes, berries, tea, coffee and fruits constitute another group of antioxidants. They include flavonoids from berries, coffee and tea, Resveratrol in dark-coloured grapes, isoflavones etc.

However, for easier availability and commercial uses different antioxidant extracts are sold under different brands which are now amply available in the pharmacy, clinics, wellness centers, salons etc. These antioxidant supplements are being prescribed by physicians during convalescence, in metabolic disorders, cardiovascular morbidities, neurological disorders and cancer conditions. They are also considered powerful anti-ageing molecules. In most of the cases the prices of antioxidant supplements exceed the price of the primary drugs for therapy. Albeit their high prices it has been quite popular among people for being available easily as over-the-counter drug and even as online supply.

Who decides dosage and duration of antioxidant supplement intake

Antioxidants are usually combined with multi-vitamin or multi-mineral supplements in commercial preparations. Most important ones are beta carotene, tocopherol, vitamin C (ascorbate), lycopene, lutein and zeaxanthin, lycopene, quercetin, resveratrol and glutathione. However, one thing is common on the labels i.e. lack of a strict dosage or duration of intake.

Who decides the dose and duration of antioxidant administration? The common notion among the physicians is that since these are preventing oxidative damage and beneficial in many organ diseases, they can be continued as long as anyone wants. But the behaviour of antioxidants *in vivo* is not as simple as *in vitro* experiments. One antioxidant may regenerate another e.g. ascorbate recycling tocopheryl radical in the aqueous-lipid interface to regenerate tocopherol. Similarly, glutathione can regenerate ascorbate from dehydroascorbate [16]. Hence due to this complex interplay of antioxidants, no single antioxidant can be marked as most efficacious.

Antioxidants can turn into pro-oxidants

Especially the chain-breaking antioxidants turn out to be pro-oxidants in different physico-chemical conditions and in excess.

Ascorbate known to be a good antioxidant either scavenging or neutralizing an array of ROS (hydroxyl, alkoxyl, peroxyl, superoxide anions, hydroperoxyl radicals) and reactive nitrogen radicals (RNS) (nitrogen dioxide, nitroxide, peroxynitrites) can actually produce the cytotoxic hydroxyl radical when oxidized by hydrogen peroxide (H_2O_2) in presence of iron or copper [17].

$H_2O_2 + Fe^{2+} (Cu^{+}) \rightarrow Fe^{3+} (Cu^{2+}) + OH- + OH.$

Uric acid is an effective free radical scavenger of singlet oxygen and radicals. Also it reduces the oxo-heme oxidants formed by peroxide reaction with hemoglobin. This protects lipid peroxidation of erythrocyte ghosts [18]. But uric acid while scavenging peroxynitrite produces an intermediate aminocarbonyl ion which can lead to oLDL (oxidized LDL) production which may lead to atherosclerosis in the long run [19,20].

In higher oxygen tension, beta carotene produces isoprostane, which leads to lipid peroxidation. Alpha-tocopherol and ascorbate also had a similar effect and led to oxidation of protein by carbonyl formation and caused DNA damage by p53 protein accumulation apart from causing lipid peroxidation by isoprostane [21]. Individually and as a mixture however, they showed antioxidant activity in lower oxygen tension. This gives an insight to the judicious use of antioxidant supplements when a person regains back his health.

Alpha-tocopherol, most effective antioxidant for LDL-C, acts as a pro-oxidant in lipid dispersion, chain reaction initiated by $LOO^{\cdot}$ (alkyl peroxyl radical). Alpha tocopherol radical produced thus is unable to escape the LDL molecule and reacts with PUFA lipid within the molecule [22].

With the above discussion it can be understood that antioxidant supplements in excess or in unwarranted body conditions, may actually be detrimental and lead to pro-oxidant generation. This can be realized from reported prospective studies by observing long term effects of such supplements on the body.

In a 10 year trial, "Women's health study", 39,876 apparently healthy women took 600IU of natural source of vitamin E or placebo on alternate day. There was no lowering of cardiovascular morbidity in both the groups but a 24% decrease in the cardiovascular mortality in the antioxidant takers group was seen [23].

In the HOPE (Heart Outcomes Prevention Evaluation) study also there was no significant difference between the vitamin E and placebo group and participants taking Vitamin E had shown higher risk of heart failure and hospitalization rate [24]. Similarly, in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI) trial also mixed result of benefit was observed. After 3 years of use, there was no preventive effect seen [25]. In Physician's Health Study, it was seen that beta carotene had no preventive effects on cardiovascular morbidity and with a mixed antioxidant supplement of vitamin C, E and beta carotene did not show any significant effect on heart after seven and half year trial by Supplementation en Vitamines et Mineraux Antioxydants (SU.VI.MAX) study [26].

Physician's health study and HOPE trial showed no significant benefit of antioxidant supplements on cancer. SU.VI.MAX study showed a reduction of cancer risk in men but they had less beta carotene and other vitamins level than women. In another study beneficial effect of selenium on skin cancer showed significant reduction of cancer and cancer mortality at various sites including colon, lung and prostate. But here also the effects were strongest among those who had low baseline levels of antioxidants [27].

A six-year trial, the Age-Related Eye Disease Study (AREDS), found that a combination of vitamin C, vitamin E, beta-carotene, and zinc offered some protection against the development of advanced age-related macular degeneration. However, in cataract, no reduction of the disease was seen [28].

A trial with antioxidant supplements in smokers having risk for developing lung cancer had to be stopped mid-way due to increased lung cancer incidence in supplement group rather than the placebo group [29].

Conclusion

On observing the mechanism of action and different long term trials with antioxidant supplements it must be understood that there is a complex interplay between different antioxidants. The supplements may behave differently *in vivo* and *in vitro* and thence are unpredictable at times. Antioxidants taken from natural sources behave differently than extracts of isolated single component. Moreover, it is still unknown which factor interacts from natural resources and regulates the absorption and utilisation of the antioxidants from the food. To decide the dosage and ideal duration of intake of these supplements require longer clinical trials and thorough *in vitro* studies. It is only prudent on the part of physicians to prescribe antioxidant supplements judiciously and for a short time. If it is prescribed for a longer period for its preventive effect, it is wise to prescribe the natural sources through intake of fruits, vegetables, berries, grains etc for a healthier living.

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