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Antioxidants as Adjuvants - A Review

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Running title: Antioxidants as adjuvants

Abstract: ***Oxidative stress is a common factor in all the chronic degenerative diseases. Whereas medicines combat the disease itself, another therapeutic modality like antioxidants prevents and aims to restrict the culprit 'Oxidative stress' itself. Lately, antioxidants have been more in demand due to increased prevalence of chronic debilitating diseases like diabetes, Alzheimer's and cancer. Due to the increased awareness about antioxidants amongst the general population, these are consumed daily by some, without being aware of the indications and side effects of certain antioxidants if consumed beyond the dietary guidelines. The purpose of this review is to provide an updated information of antioxidants and their limitations as adjuvants for certain diseases like cancer.***

Keywords: Antioxidants, Selenium, Glutathione peroxidase, Cancer, Free radicals, oxidative stress

1. Introduction

There has been a shift in the paradigm of health care regarding the management of diseases, predominantly chronic diseases. Prophylactic approach and preventive therapies have been gaining a lot of momentum owing to the increased prevalence of chronic diseases and the side effects of medications. Research has provided enough evidence that chronic diseases like atherosclerosis, cancer, inflammatory joint disease, asthma, diabetes, senile dementia and degenerative eye disease have an association with free radicals and oxidative stress. Oxidative/Nitrosative stress results from disequilibrium between oxidant/antioxidant, which occurs due to continuous increase in the concentration or production of Reactive Oxygen and Reactive Nitrogen Species. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are collectively described as free radicals. A molecule with one or more unpaired electron in its outer shell is called a free radical.[1]These free radicals are formed via various reaction like the breakage of a chemical bond such that each fragment keeps one electron, by cleavage of a radical to give another radical and, also via redox reactions. Few examples of free radicals include hydroxyl ($OH^{\bullet}$), superoxide ($O_2^{\bullet-}$), nitric oxide ($NO^{\bullet}$), nitrogen dioxide ($NO_2^{\bullet}$), peroxyl ($ROO^{\bullet}$) and lipid peroxyl ($LOO^{\bullet}$).[1-3]At low concentrations, free radicals, are beneficial for the body as they play an important role in guarding the defence mechanism of the body and mediate the cellular signalling mechanism of the body.[4,5]However, at higher concentrations these molecules can reverse their roles and be deleterious to the body. When produced in excess, free radicals and oxidants generate a phenomenon called Oxidative stress, a deleterious process that can seriously alter the cell membranes and other structures such as proteins, lipids, lipoproteins, and deoxyribonucleic acid.[6,7]Antioxidants avert oxidative stress related diseases by counteracting the deteriorating effect of ROS. Antioxidants have proven their worth in the prevention and therapy of the above-mentioned chronic diseases. However, these agents are like double edged sword and their uses can only be applied for the benefit of certain pathologies. Controversial researchregarding the wide application of antioxidants as adjuvants in diseases like cancer warrants precaution. The purpose of this review is to provide an updated insight on the antioxidants, their importance as well as limitations in combating diseases like cancer.

2. Classification of Antioxidants

2.1 Based on origin

1) Natural: These are further subclassified as

Endogenous: Endogenous oxidants are of two types:

- Enzymatic oxidants: These work by breaking down and removing free radicals.[8] Examples: Glutathione peroxidase, superoxide dismutase and catalase
- Non enzymatic oxidants: These work by interrupting free radical chain reactions.[8]Examples: Uric acid, lipoic acid, bilirubin, glutathione and melatonin.

Exogenous: Carotenoids, vitamin E, A and C, natural flavonoids or different other compounds.

2) Synthetic antioxidants are petroleum centredantioxidants which comprises of butylated hydroxytoluene (BHT),octyl gallate (OG), butylated hydroxyanisole (BHA), propyl gallate(PG) and tert-butylhydroquinone (TBHQ). TBHQ (tert-Butylhydroquinone).[9]

a) Based on solubility[8]:

- Water soluble: These are present in cytosol or cytoplasmic fluids. Eg: Vitamin C

- Lipid soluble: These are found in cytoplasmic membranes. Eg: Vitamin E, Carotenoids and lipoic acid.

b) Based on size[8] :
- Small-molecule antioxidants: These neutralize the ROS in a process called radical scavenging. Eg: vitamin C, vitamin E, carotenoids, and glutathione (GSH).
- Large-molecule antioxidants: Enzymes (SOD, CAT, and GSHPx) and sacrificial proteins (albumin) that absorb ROS and prevent them from attacking other essential proteins.

c) Based on mechanism of action[9]:
- Inhibiting the creation of new radicals: Superoxide dismutase (SOD), catalase (CAT), Se, Cu, Zn),
- Catching the free radicals to evade chain reaction (vitamins E and C, carotenoids),
- Restoring the impairment affected by free radicals (lipases, proteases).

2.2 Antioxidants and their applications

1) Glutathione: Reduced form of glutathione is GSH, which is also the biologically active form. It functions as an antioxidant defence against reactive oxygen/nitrogen species (ROS/RNS). GSH is involved in mitochondrial protection via direct or indirect oxidative damage. The mechanisms include preventing the generation of oxidants, scavenging free radicals, or inhibiting oxidant reactivity.[10]
2) Coenzyme Q: It is considered as endogenous lipid soluble antioxidant and is found in all membranes. In the inner mitochondrial membrane, CoQ has multiple functions which includes being a redox carrier, antioxidant, activator of uncoupling proteins, as well as influencing the permeability transition pore (PTP).[11]
3) Glutathione peroxidase (GPx): This enzyme has two different forms: Selenium dependent and selenium independent.[12]GPx, in the presence of GSH, catalyses the reduction of H2O2 or organic peroxide (ROOH) to water or alcohol.[13]It is found in high concentrations in kidney and liver.[14] It has been proposed that under conditions of oxidative stress, it is one of the first enzymes to be activated.[15]Selenium-dependent glutathione peroxidase acts in association with tripeptide glutathione (GSH), which exists in high concentrations in cells. It catalyses the conversion of hydrogen peroxide or organic peroxide to water or alcohol while simultaneously oxidizing GSH. It competes with catalase for hydrogen peroxide as a substrate and is the major source of protection against low levels of oxidative/ nitrosative stress.[16]
4) Superoxide dismutase (SOD):These are one of the first defence enzymes which dismutate highly reactive superoxide radicals.[17]Four isoenzymes of SOD have been identified.[18-22]
   a) SOD1: It is a metalloprotein with Zn and Cu as cofactors. Localized in the cytosol of the cell. These work together withglutathione peroxidase and catalase to convert the superoxide radical into hydrogen peroxide.
   b) SOD2: Mn and Fe are the cofactors and it is localized in the mitochondria. SOD2 has been found to be associated with delaying the progression of diabetes and its complications.[23]
   c) SOD3: Cu and Zn are the cofactors and it is located extracellular. SOD3 has high affinity for heparin and heparin sulphate. Studies have suggested that recombinant administration of SOD3 can lessen the chances for cardiovascular damage.[24]
   d) Catalases, Glutathione peroxidase and superoxide dismutase show synergism in their action against scavenging of free radicals.
5) Selenium (Se): Se is a trace mineral found in soil, water, meat, yeast, vegetables like garlic, onion, grains and sea food.[25]Selenium works as an immunomodulator, anti-carcinogenic and antioxidant at low doses.[26]It has been suggested that high Se as antioxidant selenoenzymes and selenoproteins may help to reduce the production of oxidised LDL and, therefore, would reduce the incidence of heart diseases.[27]A huge amount of evidence has demonstrated inverse relationship between the amount of Se and cancer. The hallmark study of Clark and colleagues reported that people who supplemented their diet with selenized yeast, predominantly in the form of selenomethionine (200 µg/day), had a reduction of nearly 50% in overall cancer morbidity.[28]Possible anticancer mechanisms of Se include the induction of apoptosis, arresting the cell cycle and DNA-repair genes, inhibition of protein kinase C activity and cell growth and via its effect on estrogenand androgen-receptor expression.[29,30] Se has been suggested to be playing an important role in modulating immunity. A number of mechanisms have been proposed including the increased activity of natural killer (NK) cells, the proliferation of T-lymphocytes, increased production of interferon γ, increased high-affinity interleukin-2 receptors, stimulation of vaccine-induced immunity and increased antibody-producing B-cell numbers.[31,32]
6) Antioxidants like Vitamin C, Lycopene, Tocopherol are associated with resisting oxidative stress in ageing. Dietary lycopene has been suggested to reduce the levels of nitric oxide, ROS and lipid peroxyl radicals.[33]Tomatoes and tomato-based products are an important source of lycopene. Curcumin is one of the natural antioxidants that has proved its role in preventing diseases like prostate cancer and cataract.[34]Curcumin is considered one of the major antioxidants owing to its role as immune-potentiator. Its slow bioavailability due to absorption has limited its use an anti-cancer agent.[35]Vitamin C in conjunction with Vitamin E regenerates α-tocopherol from α- tocopherol radicals in membranes and lipoproteins, and raises glutathione levels in the cell, thus playing an important role in preventing oxidation of proteins. Vitamin C is a reducing agent and thereby neutralizes ROS such as hydrogen peroxide.[36]

2.3 Antioxidants supplements and their limitations as adjuvants

Antioxidants have gained major importance in the past few years owing to the advances made in research. The benefits of antioxidants as anti-ageing, anti-cancer, cardiac and

neuroprotective and more has led people consuming more fruits and vegetables, which are the natural sources of antioxidants. However, new concerns have been emerging concerning the harmful effects of excess doses of antioxidants on the human body. It has been pointed out that the removal of too many ROS/RNS and their derived products by antioxidant supplementation may upset the cell signalling pathways and increase the risk of chronic disease.[37,38] Antioxidants can also work as pro-oxidants if consumed in excess or beyond the recommended dietary guidelines. For example, it has been demonstrated in studies that tocopherol loses its antioxidant effects at low oxygen tension while carotenoids tend to show the reverse.[39] The in vivo pro-oxidant/antioxidant effects of beta-carotene and lycopene has also been found to be dependent on their interaction with various biological membranes and other co-antioxidant molecules like vitamin C or E.[40]

The role of antioxidants as adjuvants to radiotherapy and chemotherapy is also debated. Vitamin C, carotenoids, CoQ10, leucopene, carotenoids have been largely associated with chemopreventive actions and preventing organ as well as tissue damage caused by radiotherapy and chemotherapy.[41,42]In a study by Leitzmann et al. , it was observed that a high intake of zinc supplementation (>100 mg/day) would increase the risk of prostate cancer, while, according to Ho, the dietary deficiency of this mineral would increase the production of oxidative stress, and, thus, it would increase cell damage both *in vitro* and *in vivo*.[43]However certain studies have shown that antioxidants do not prevent cancer but may accelerate cancer by targeting ROS in the cells.[44,45]A systematic review conducted to determine the efficacy of antioxidants as adjuvant therapy in anticancer treatment suggested that it was unclear if the antioxidants affect treatment outcomes or whether antioxidants ameliorate adverse effects induced by chemotherapy and radiotherapy.[46]

3. Conclusion

With the increase in the prevalence and severity of various chronic and degenerative diseases, antioxidants specifically the natural antioxidants have become an attractive topic of discussion and research. These antioxidants have been proven to be of importance in delaying the onset and in combating diseases like Alzheimer's, diabetes, cardiovascular diseases. Although the antioxidants obtained from natural dietary sources have been shown tobe beneficial for boosting the metabolic system of the body, an extra care and medical advice is warranted while incorporating the antioxidant supplements as adjuvants especially in patients with cancer.

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