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ACE as antioxidant: Its role in preventing diseases and promoting health

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Abstract

Reactive oxygen species are required at little or moderate concentration but at high concentrations it has harmful and deleterious effects. It is considered that sufficient level of antioxidants provided with diet can break destructive chain reaction initiated by free radicals and increases defensive abilities of cell. Vitamin A, vitamin C, and vitamin E (ACE) are known to be powerful antioxidant nutrients. This review article gives a brief view of role of ACE as an antioxidant in preventing diseases and promoting health. It has been suggested that consuming healthy food such as plant food rich in antioxidants may be considered as very effective and economical in treating and preventing many diseases.

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Introduction

Oxidation is a chemical reaction that transfers electrons or hydrogen from a substance to an oxidizing agent. A free radical is any chemical species that has one or more unpaired electron. Free radicals (FR) derivatives of oxygen as well as non-radical derivatives and singlet oxygen are collectively known as reactive oxygen species (ROS) (Tandon *et al.,* 2005). Reactive oxygen species are continuously produced in the body. Free radicals and ROS are derived from two sources. First is endogenous metabolic process in human body such as mitochondrial respiration, inflammation, peroxisomal metabolism, exercise and so on and secondly from external sources such as exposure to radiation, smoke pollutants (Langseth,1996). Free radicals can cause severe damage such as change in enzymatic activity, DNA mutation or even death. Although reactive oxygen species (ROS) at little or moderate concentrations in human tissues are required for stimulating cellular signaling, the regulation of immune responses, gene expression and fostering antioxidant defense mechanisms, but at high concentrations it has toxic and deleterious effects (Valko *et al.,* 2007; Bouayed and Bohn, 2010).

An antioxidant is a substance capable of blocking the chain propagation reaction produced by oxidants and significantly prevents or slows down the oxidation of other molecules or substrates (Rangan and Bulkley, 1993). It is believed that adequate level of antioxidants supplied with diet can break destructive chain reaction initiated by free radicals and increases defensive abilities of cell (Hercberg, 1998; Prior 2003, Grajek 2004). Endogenous defence mechanisms are insufficient for the comprehensive inhibition of the oxidative damage, and vitamin A, C, E may be very significant for their antioxidant properties (Landete, 2013). Vitamin A, vitamin C and vitamin E (ACE) are known to be powerful antioxidant nutrients. Studies suggest that some of the important micronutrients which act as antioxidants are of great interest because they play very vital role in the prevention of diseases promoted or initiated by oxygen radicals by protecting human body against damage by reactive oxygen species (ROS). In this review we will focus on the role of ACE with particular reference to the latest findings in preventing diseases which are associated with free radicals.

What is ACE?

Vitamin A, C and E are natural antioxidants that slow down the process of degradation. They play very significant role in reducing the free radicals. A brief description of ACE functions, RDAs and dietary sources are presented in table 1.

Classification of Antioxidants

Antioxidants are broadly classified into two: 1) Natural Antioxidants 2) Synthetic Antioxidants. Natural antioxidants are primarily plant phenolic (Pratt & Hudson, 1990) and they are generally found in foods consumed without much processing such as fruits and vegetables. But synthetic antioxidants are produced artificially. They function as preservatives by donating electron density to fats, and in turn prevent their breakdown but the safety of synthetic antioxidants has always been questioned. A brief classification has been presented in fig1.

Types of antioxidant defenses

Antioxidants are molecules that can safely react with free radicals and stop the chain reactions. Antioxidant systems are divided into 1) primary 2) secondary and 3) tertiary (Kumar *et al.,* 2010; Birangane *et al.,* 2011; Buitnariu and Grozea, 2012).

1) Primary antioxidants: They are also known as chain breaking antioxidants are capable of preventing the formation of new radical species by (a) preventing the formation of free radicals from other molecules (b) converting existing free radicals into harmful molecules before they are able to react. Primary antioxidant is formed of molecules of phenol, TPC, gallic acid and its derivatives, flavonoids, superoxide dismutase (SOD) convert O_2 to H_2O_2.

2) Secondary or preventive antioxidants: They act through numerous possible mechanisms like (a) Sequestration of transition metal ions which are not allowed to participate in metal catalyzed reactions

(b) Removal of peroxides by catalase and glutathione peroxidase that can react with transition metal ions to produce ROS. Examples of secondary antioxidants are vitamin E, vitamin C, Albumin.

3) Tertiary antioxidant defenses: They repair biomolecules damaged by free radicals.
Example of tertiary antioxidant is methionine sulfoxide reductase.

Role of ACE in preventing diseases and promoting health

Atherosclerosis

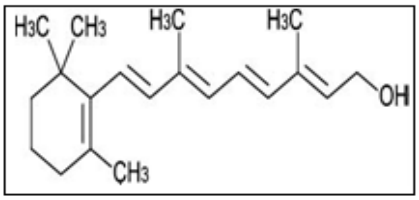
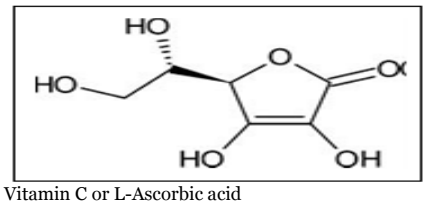
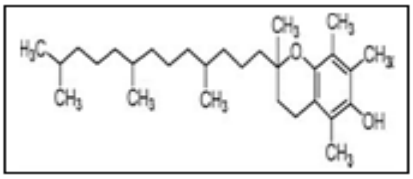
Atherosclerosis may be defined as a multifactorial, inflammatory-degenerative, progressive disease of arteries, characterized by the accumulation of lipids and fibrous elements in the large (Cherubini *et al.,* 2005). The destructive chain reaction initiated by free radicals can be broken by antioxidants, which are able to convert free radicals into harmless derivatives. Dietary antioxidants particularly vitamin E can terminate radical chain reactions by interacting with the lipid peroxylradical, preventing it from generating a new radical and perpetuating the chain reaction by oxidizing other lipids. An inverse association between per capita consumption of fruits and vegetable and the risk of atherosclerosis events were observed in previous studies (Acheson and William, 1983; Verlangieri *et al.,* 1985). High vitamin E intake can reduce the risk of coronary heart disease (CHD) by inhibition of atherogenic forms of oxidized LDL. The vitamin A and beta-carotene protect lipid peroxidation and provitamin-A activity (Zhang *et al.,* 2014). A prospective cohort (Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC)) study of 29, 092 Finnish male smokers, aged 50–69 years was followed up for 19 years. 13,380 deaths (including 4518 and 5776 due to cancer and cardiovascular disease, respectively) were identified. Men in the higher quintiles of serum α-tocopherol had significantly lower risks of mortality due to CVD than did those in the lowest quintile (Wright *et al.,* 2006). Low-grade inflammation is an independent risk factor for cardiovascular disease. Associations between baseline antioxidant circulating concentrations and elevated C-reactive protein (CRP) (>3 mg/l) were investigated in multivariate logistic regression models. Subgroup analyses were performed according to gender, supplementation group of the initial trial, smoking status, and alcohol intake. Serum α-tocopherol and vitamin C were not associated with elevated CRP concentrations (Julia *et al.,* 2014). Metabolic syndrome (MS) is a coexistence of metabolic risk factors affecting development of cardiovascular diseases. In a study on 68 patients with symptoms of MS aged 34-65, plasma vitamin A, C and E levels were estimated. The plasma vitamin A, C and E levels were significantly less ($p < 0.05$) in MS patients than in the healthy individuals without symptoms of MS. The most significant differences in the level of antioxidative vitamins in both groups were related to vitamin C and vitamin E. It has been concluded that the decreased level of vitamins A, C and E points to the weakening of antioxidative barrier in patients with MS (Godala *et al.,* 2014). Null results were also identified in many studies. A study indicated that 600 IU of natural-source vitamin E taken every other day provided no overall benefit for major cardiovascular events, did not affect total mortality, and decreased cardiovascular mortality in healthy women. These data do not support recommending vitamin E supplementation for cardiovascular disease or cancer prevention among healthy women (Lee *et al.,* 2005). In another study dietary intakes of alpha-carotene and beta-carotene are inversely associated with CVD mortality in elderly men but this study does not indicate an important role for other carotenoids, tocopherols, or vitamin C in lowering the risk of CVD death (Buijsse *et al.,* 2008). In a large, long-term trial of male physicians, neither vitamin E nor vitamin C supplementation reduced the risk of major cardiovascular events. These data provide no support for the use of these supplements for the prevention of cardiovascular disease in middle-aged and older men (Sesso *et al.,* 2008).

Cancer

Retinol inhibited all-trans-retinoic acid (ATRA)-resistant human colon cancer cell invasion via a

retinoic acid receptor-independent mechanism. Phophatidylinositol 3 kinase (PI3K) regulates cell invasion and a decrease in PI3K activity due to retinol treatment may confer the ability of retinol to inhibit ATRA–resistant colon cancer cell invasion (Park *et al.,* 2014).

Table 1. Functions, RDA and dietary sources of vitamin A, Vitamin C and vitamin E (ACE).

Vitamins	Function	RDA				Dietary Sources
		Males	Females			
			Non Pregnant	Pregnant	Lactating	
Vitamin A  The structure of retinol, the most common dietary form of vitamin A.	Vitamin A is a fat soluble vitamin that is necessary for vision, healthy bones, good and healthy skin, reproduction and for differentiation of epithelial tissue.	900	700	770	1300	Liver, mango, papaya, apricot, carrot, pumpkin, spinach, broccoli, sweet potato, butter, egg, cheddar cheese, and milk
Vitamin C  Vitamin C or L-Ascorbic acid	Vitamin C is a monosaccharide, water soluble vitamin. It is involved in the improvement of the health of cartilage, joints and skin.It is a reducing agent and can reduce, and thereby neutralize, reactive oxygen species such as hydrogen peroxide. It plays role as a cofactor for several enzymatic steps in the synthesis of monoamines, amino acids, peptide hormones, and carnitine	90	75	85	120	Broccoli, lemons, bell peppers, sprouts, zucchini, tomatoes, cauliflower, spinach, asparagus, oranges, grapefruit, raspberries, cantaloupe, pineapples, kiwifruit, papaya, kale, strawberries, watermelon
Vitamin E  Alpha tocopherol form of vitamin E	Vitamin E is a fat soluble vitamin functioning as a free radical scavenger to prevent lipid peroxidation of polyunsaturated fatty acids. Prevents the formation of blood clots. Reduces long-term risk of dementia.	15	15	15	19	Nuts, wheat germ and wholegrain foods, meat, fish, Asparagus, avocado, egg, milk, spinach, asparagus, green leafy vegetables.

The notion that vitamin C may have a preventive role in cancer was first proposed in 1949. It was demonstrated by Cameron and Campbell, 1974 that high-dose vitamin C improved the survival of patients with terminal cancer. Cancer patients commonly experience a number of symptoms of disease progression and the side-effects of radiation therapy and adjuvant chemotherapy, which adversely impact on their quality of life (QOL). Intravenous (IV) vitamin C improves a number of cancer and chemotherapy-related symptoms or toxicities associated with chemotherapy, such as insomnia, fatigue, loss of appetite, pain and nausea and improve the quality of life. Improvements in physical, role, cognitive, emotional, and social functioning, as well as an improvement in overall health, were also

observed (Carr *et al.,* 2014). It may improve time to relapse and possibly enhance reductions in tumor mass and improve survival in combination with chemotherapy. The existing evidence is preliminary and cannot be considered conclusive but is suggestive of a good safety profile and potentially important antitumor activity; however, more rigorous evidence is needed to conclusively demonstrate these effects (Fritz *et al.,* 2014). Dietary vitamin C intake was also statistically significantly associated with a reduced risk of total mortality and breast cancer-specific mortality (Harris *et al.,* 2014). Evidence supports that a high intake of vitamin C is linked with a low risk for cancer of oesophagus, oral cavity, stomach, pancreas, cervix, rectum and breast (Block, 1991). Antioxidant nutrients like vitamin E protect cell constituents from the damaging effects of free radicals that, if unchecked , might contribute to cancer development (Lee *et al.,* 2005).Vitamin E also possesses anti-cancer properties. This is possibly because of the various functions of vitamin E which include: the activation of heat shock proteins, the down regulation of mutant p53 proteins, the stimulation of the wild-type p53 tumor suppressor gene and an anti-angiogenic effect mediated by the blockage of transforming growth factor alpha (Christen *et al.,* 1997). Vitamin E (α-tocopherol) plays a key role in the regulation of cell growth and differentiation and has been studied as a potential chemopreventive agent for prostate cancer. In nested case-control study to examine whether variants in vitamin E-related genes were associated with risk of prostate cancer, 483 prostate cancer cases and 542 matched controls of European ancestry from a large U.S. multicenter trial participated that had available measurements of serum vitamin E concentrations and genotyping of 3 genome-wide association, study meta-analysis-identified single-nucleotide polymorphisms (SNPs) associated with circulating vitamin E (i.e., α-tocopherol) status. This study suggests that polymorphisms near BUD13/ZNF259/APOA5, involved in vitamin E transport and metabolism, may be associated with lower risk of prostate cancer (Major *et al.,* 2014).

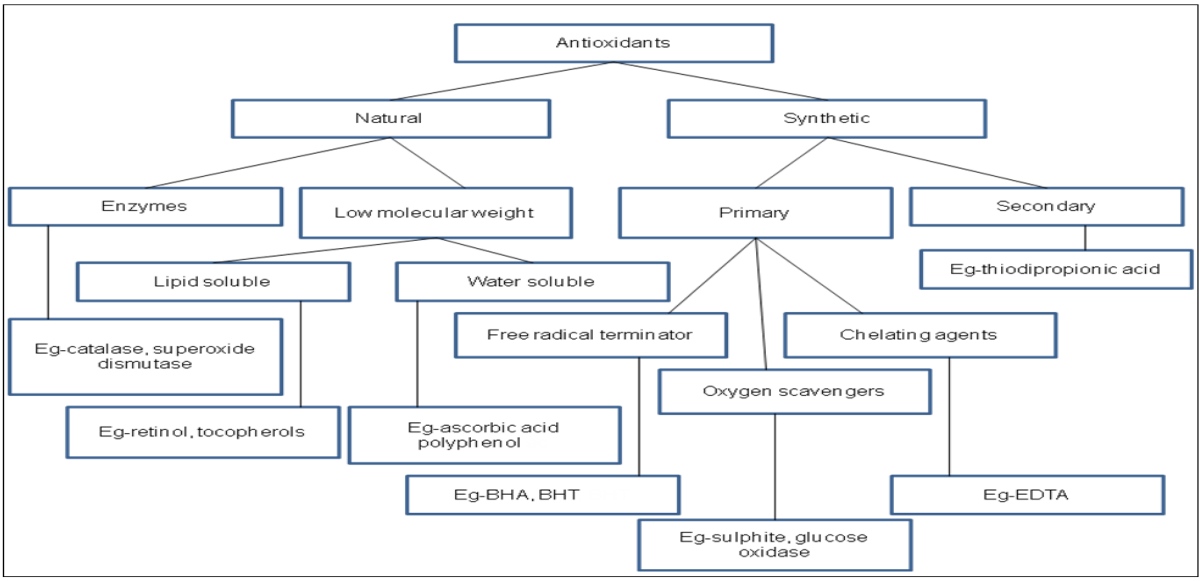


Fig. 1. Classification of Antioxidants (derived from Kumar S, 2011).

Cataracts

Cataracts are one of the most common causes of significant vision loss in older people. They basically occur due to the accumulation of proteins damaged by free radicals (Rizvi *et al.,* 2014). In a meta-analysis of 13 studies with 18,999 participants, it has been concluded that vitamin E (OR: 0.75; 95% CI: 0.58, 0.96), α-carotene (OR: 0.72; 95% CI: 0.59, 0.88), lutein (OR: 0.75; 95% CI: 0.65, 0.87), and zeaxanthin (OR: 0.70; 95% CI: 0.60, 0.82) were inversely associated with age-related cataract. Vitamins A (OR: 0.69; 95% CI: 0.58, 0.83) and C (OR: 0.67; 95% CI:

0.57, 0.78) were inversely associated with age-related cataract in Asian populations but not in Western populations (Cui *et al.,* 2013). In another study on a total of 88 patients and healthy controls who were given physical examinations that included a complete eye examination. Ascorbic acid was measured in serum with UV/Vis spectrophotometry, and fat-soluble vitamins were measured in serum. The mean serum concentration of alpha-tocopherol in patients (9.16 +/- 2.53 microg /ml) with cataract was lower than in the control group ($p < 0.001$). Patients had a moderately lower ascorbic acid concentration than the control group, which was not statistically significant. The subjects' serum retinol levels were similar to control group levels and not statistically significant. Because of the small sample size the researcher concluded that it can nonetheless be viewed as presenting support to help narrow the possibility that antioxidative agents may play a role in delaying cataract formation (Nourmohammadi *et al.,* 2008).

Conclusion

It has been suggested that consuming healthy food such as plant food rich in antioxidants can be considered as economical, easily available and safest way for treating and preventing many chronic diseases. The antioxidants in natural food have synergestic actions and plays very important role in maintain health. More studies are required to decide the doses.

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