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# Thought-provoking Molecules for Drug Discovery: antioxidants

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## Abstract

The multifaceted aspects of antioxidants summarized in this review; their general charactarestics, properties and clinical ways are discussed. An important aspect in discovery of new antioxidants is the correlation between the structure of antioxidants and their activity. Their role in tissue injury and types of defense mechanisms gives us the opportunity to understand the role of antioxidants in disease progression and defense mechanisms. Although diseases that are been associated with oxidative stress and treatment with antioxidant supplements are present, the role of antioxidants in pathological conditions are unspesified yet.

**Keywords:** Antioxidants; Properties; Clinical aspects; Drug discovery

## Keypoints

- Affirmative influence of antioxidant vitamins may be observed in atherosclerosis and endothelial dysfunction, male infertility, Parkinson's disease (especially via lipoic acid), diabetes, brain tumors and skin maturation
- There is not yet enough data to support the use of dietary antioxidants as antiaging molecules and in the prevention of cardiovascular diseases.
- The clinical value of antioxidants for the prevention of Alzheimer's disease is ambiguous and they are not promising for cancer prevention or thearpy.

## Introduction

Once over a look to the history, extensive study was devoted to the uses of antioxidants in industrial area, such as the polymerization of fuels in the late 19th and early 20th centuries. Early research focused on their use in preventing the oxidation of unsaturated fats. The word 'antioxidant' originally was used to refer to a chemical that prevents the consumption of oxygen [1]. Halliwell and Gutteridge in 1989 defined *antioxidant* as *'any substance that, when present at low concentrations compared with that of an oxidizable substrate, significantly delays or inhibits oxidation of that substrate'*. In other words, an *'antioxidant'* is *'a molecule capable of slowing or preventing the oxidation of other molecules by being oxidized itself'*.

Human body constantly reacts with oxygen as it breathes and its cells produce energy. As a consequence of this activity, highly reactive molecules are produced known as *free radicals*. Free radicals interact with other molecules within cells. This can cause oxidative damage to proteins, membranes and genes. An imbalance between oxidants and antioxidants in favour of the oxidants, leading to damage, is termed *'oxidative stress'* [2]. Oxidative stress may be an important factor in pathological conditions. Reactive oxygen, nitrogen and chlorine species are potentially damaging species and levels of these are controlled by the 'antioxidant defense system' [3]. The production of reactive oxygen species (ROS) has been related to deleterious effects for cells. ROS are defined as oxygen-containing species that are more reactive than O(2) itself, which include hydrogen peroxide and superoxide. ROS are oxygen containing molecules including free radicals. They are capable of reacting with membrane lipids, nucleic acids, proteins and enzymes that results in cellular damage. Oxidation reactions can produce free radicals which start chain reactions that damage cells. Antioxidants neutralize free radicals by donating one of its own electrons and act as scavengers helping to prevent cell and tissue damage [2].

A new question is that whether uncontrolled formation of ROS species is a primary cause or a downstream consequence of the pathological process. While the role of free radicals causing damage to DNA in the mechanism of carcinogenesis is clear [4] the primary role of ROS in the process of post-ischemic tissue injury and some other disease states is still controversial.

The classification of antioxidants various but they can be classified basically as [5].

### Enzymatic antioxidants

Three groups of enzymes play significant roles as oxidants scavengers:

a. Superoxide dismutases are metal containing enzymes that catalyze the conversion of two superoxides into oxygen and hydrogen peroxide that is less toxic than superoxide.

b. Catalase is an enzyme found in peroxisomes degrades hydrogen peroxide to water and oxygen.

c. Glutathione peroxidase also acts to degrade hydrogen peroxide.

### Non-enzymatic antioxidants

Glutathione, vitamin E and vitamin C are non-enzymatic antioxidants.

Another comprehensive classification of antioxidants which can also be defined as the 'antioxidant hierarchy' [6].

- Enzymes (catalase, peroxidases),
- Shock absorbers (albumin, uric acid, transferrin),

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- Essential compounds (vit A, vit C, aminoacids, peptides, CQ10, lipoic acid, squalene) and *others* (caretenoids, flavonoids)

Vitamin C, vitamin E, beta carotene and polyphenols are defined as *dietary antioxidants* whereas bilirubin, glutathione, lipoic acid, N-acetylcysteine, NADPH, NADH, ubiquinone (coenzyme Q10), uric acid and enzymes like copper/zinc and manganese dependent superoxide dismutase (SOD), iron dependent catalase, selenium dependent glutathione peroxidase) can be defined as endogenous antioxidants [7].

There is a variety of substances containing antioxidants. Carotenoids, vitamins, phenols, flavonoids, dietary glutathione and endogenous metabolites are natural antioxidants occur in plants. Ascorbic acid (vitamin C), tocopherol and tocotrienol (vitamin E), carotenoids and other low moleculer weight compounds such as glutathione and lipoic acid are nutrient derived antioxidants. Ferritin, lactoferrin, albumin and ceruloplasmin are metal binding proteins that has a role in catalyzing oxidative reactions [8].

Vitamins exerts its antioxidant activity by an intrinsic free radical scavenging mechanism and by the regulation of enzymes. Retinol (vitamin A) scavenges ROS and also inhibits NO production. It is reported that retinoic acid attenuates inducible nitric oxide synthase activation in cultured rat cardia myocites and microvascular endothelial cells [9].

Vitamin E is an antioxidant that is present in lipids. The consumption of a functional drink enriched with vitamin C and vitamin E could alleviate exercise-induced oxidative damage in lymphocytes were investigated. It was found that supplementation with moderate levels of antioxidant vitamins reduces exercise-induced oxidative damage without blocking the cellular adaptation to exercise [10].

The mechanism of how vitamin C acts is still unknown although it has been attributed to an antioxidant function of the vitamin to enhance the synthesis or prevent the breakdown of NO [11].

The accumulation of knowledge regarding endothelial dysfunction and oxidative stress interrelationship led to the conduction of experimental interventions using vitamin C as an effective tool for increasing NO-bioavailability and in extrapolation for protecting the endothelium [12].

Vitamin C is a potent hydrophilic antioxidant able to scavenge free radicals and oxidative molecules such as hydroxyl radicals (.OH), superoxide anions (O2-), sulphydryl radicals, oxidized LDL. Vitamin C when acutely infused or chronically ingested, improves the defective endothelium-dependent vasodilation present in atherosclerosis, hypercholesterolemia, smoking, and hypertension. Vitamin C may act as a carrier and an antioxidant in neurodegenerative disease [13].

Riboflavin and niacin restore the reducing capabilities of antioxidant molecules [14]. Omega 3 and 6 (PUFAs) induce i NOS expression in many cell types [15]. Aminoacids like taurin has been reported to have cytoprotective actions by using different mechanisms [16].

Glutamine serves as a precursor for antioxidants [17]. L-arginine has protective effects and act as a direct antioxidant by scavenging oxygen derived free radicals [18]. Histidine prevents lipid peroxidation [19]. Glycine protects renal antioxidant enzymes, normolises nitric oxide levels [20]. N-Acetyl Cysteine was shown to inhibit TNF-alpha mediated phosphorylation of p65 in vascular cells [21]. Carnosine has a number of antioxidant properties and has been proven to scavenge ROS as well as alpha-beta unsaturated aldehydes formed from peroxidation of cell membrane fatty acids during oxidative stress. It is an antioxidant which acts as an anti-ageing molecule [22].

Albumin may function as an antioxidant. Invitro glycoxidation of human serum albumin induced a marked loss of antioxidant activity of this molecule [23]. Bilirubin has a role in cytoprotection against short and long lasting oxidant mediated cell injury [24]. Ceruloplasmin protects the CNS from iron mediated free radical injury and plays a role in maintaining iron homeostasis in the CNS [25].

## Structure-activity relationships for antioxidants

To accelerate the discovery of novel antioxidants, research has been devoted to investigate the structure-activity relationships for antioxidants. Correlation between the structure of the antioxidant and its activity has been identified for several compounds. Flavanoids are compounds that are potent antioxidants based on their phenolic hydroxyl groups. Antioxidant activity has been attributed to their electron donating ability and flavonoid B ring chemistry is the primary determinent of their antioxidant activity [26].

The secretory peptides (luteinizing hormone-releasing hormone, enkephalin, angiotensin, and oxytocin) are biochemical antioxidants in aqueous medium. These hormones scavenge free peroxyl radicals, prevent the oxidation of low density lipoprotein and lipid peroxidation in brain membranes. Secretory peptide hormones may constitute an important part of the antioxidant defense system. Their antioxidant activity is derived from the occurence of solvent exposed tyrosine tryptophan residues [27].

## Free radical induced tissue injury

Free radicals play a central role in the disease progression and aging process. Antioxidants defense our body against free radical damage and maintains our health. '*Free radicals'* are electrically charged molecules which has an unpaired electron that causes them to seek out and capture electrons from other substances inorder to neutralize themselves. Antioxidants are capable of stabilizing or deactivating free radicals [7].

## Types of antioxidant defenses

Primary or chain breaking antioxidants are called as *scavenger antioxidants*. Secondary or preventive antioxidants can act through mechanisms like sequestration of transition metal ions and removal of peroxides and tertiary antioxidant defenses are the repair processes which remove damaged biomolecules before they can accumulate and before their presence results in altered cell metabolism and viability [28].

## Clinical aspects of antioxidants

Specifically focusing on the clinical aspects of antioxidants a disparity occurs. Oxidative stress has been implicated in many pathological conditions which involves cardiovascular disease, male infertility, cystic fibrosis, liver disease, neurological disorders like Alzheimer's Diseases, Parkinson's Disease, Frederich ataxia, brain tumors, cancer and hematological disease. The use of antioxidants to prevent disease is controversial [29] (Figure 1).

Altough the use of vitamin E appears to reduce the risk of heart disease [30], no effects of ascorbic acid, vitamin E, or beta carotene was found on cardiovascular events among women at high risk for the

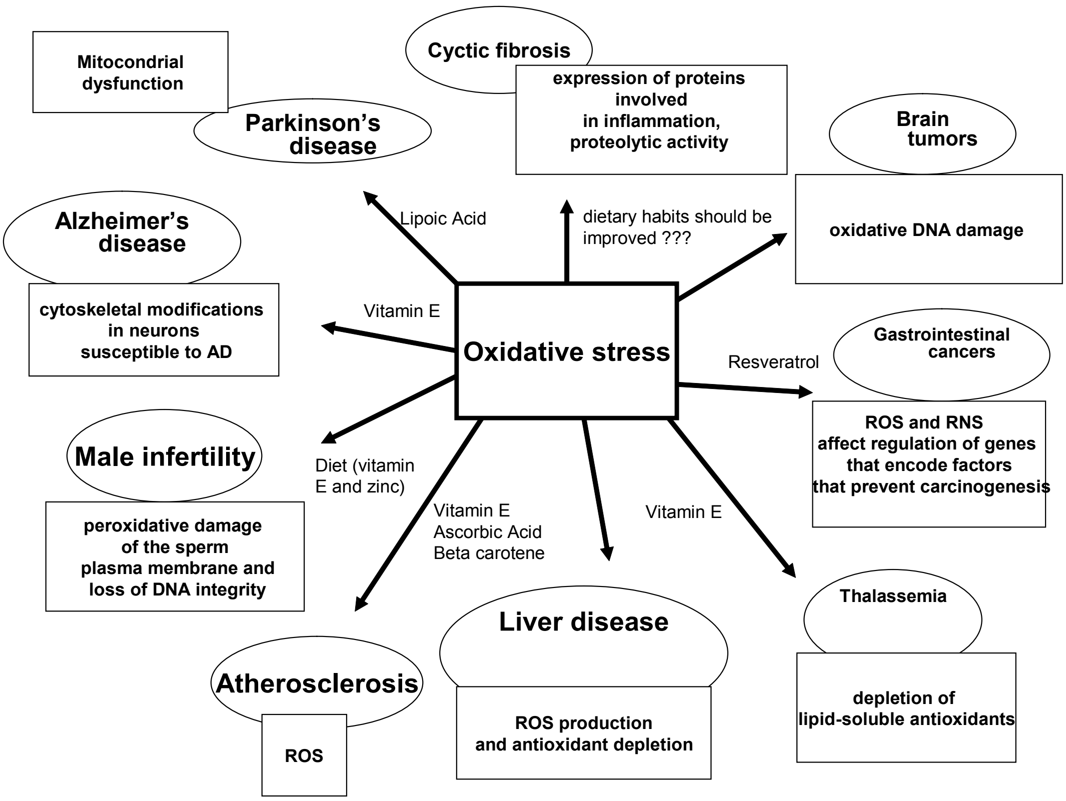


**Figure 1:** The pro-oxidant/antioxidant balance is shifted in favour of the pro-oxidants in oxidative stres. Here is a diagram showing some of the disease processes driven by oxidative stres, related mechanisms involved and the role of antioxidants discussed. ROS: Reactive oxygen species. RNS: Reactive nitrogen species. AD: Alzheimer's Disease.

secondary prevention of cardiovascular events [31]. Effect of folic acid and B vitamins on risk of cardiovascular events and total mortality among women at high risk for cardiovascular disease were investigated and it was concluded that after 7.3 years of treatment and follow-up, a combination pill of folic acid, vitamin B6 and vitamin B12 did not reduce a combined end point of total cardiovascular events among high-risk women, despite significant homocysteine lowering [32].

It is already a known fact that atherosclerosis develops from low-density lipoprotein molecules (LDL) becoming oxidized by free radicals. LDL oxidation in vitro have been shown to prevent by antioxidants and antioxidants retard the progression of atherosclerosis in animal models [33].

As a new concept, free radicals must play causal role in pathogenesis of atherosclerosis and vitamin E should be effective if given at right time to right subjects [34]. Antioxidants may influence the stability of plaques [35], antioxidant vitamins can reverse endothelial dysfunction that is induced by methionine [36], in hyperlipidemic children may restore endothelial function [37], and smokers who are young [38]. Antioxidant enzyme activities in erythrocytes of prehypertensive and hypertensive women were investigated and activities of erythrocyte antioxidant enzymes decrease in prehypertensive and hypertensive women that may lead to atherosclerosis and other high blood pressure related health problems [39].

The male factor is at least partly responsible in about 50% of infertile couples. The expanding research interest on reactive oxygen species (ROS), oxidative stress, and male infertility has led to the development of various techniques for evaluating oxidative DNA damage in human spermatozoa. Role of oxidative stress on decreased sperm function and role of antioxidants in the treatment of male infertility were investigated. Semen samples of healthy non-smoking men who took antioxidant diet were examined and it was found that those with a high daily intake of antioxidants were noted to have improved semen quality compared to men with low or moderate intake [40].

Cystic fibrosis is the most common lethal hereditary disease among Caucasians, with a prevalence of approx. 1 in 2000 [41]. The condition is characterized by chronic lung inflammation that results in life expectancy being reduced to about 45 years at best [42]. Effect of vitamin E, vitamin C, β carotene and selenium on cystic fibrotic lung disease were examined and has been found that antioxidant supplementation in cystic fibrosis is not yet recommended and antioxidants appear to decrease quality of life and oxidative stress [43]. Status of antioxidants in children with acute asthmatic attack were investigated and asthmatic patients during acute attack suffer a high degree of ROS formation causing considerable oxidative stress that is by the high levels of oxidants (MDA) and low levels of antioxidants [44].

Alcoholic liver disease is a major source of alcohol-related morbidity and mortality. The involvement of free radical mechanisms in the pathogenesis of alcoholic liver disease (ALD) is demonstrated by the detection of lipid peroxidation markers in the liver and in the serum of patients with alcoholism. Also, experiments in alcohol-feed rodents show a relationship between alcohol-induced oxidative stress and the development of liver pathology. Ethanol-induced oxidative stress is the result of the combined impairment of antioxidant defences and the production of reactive oxygen species by the mitochondrial electron transport chain [45].

It has been reported that β-carotene, vitamin C, vitamin A and vitamin E can not be recommended for the treatment of liver disease [46].

Treatment with antioxidant supplements showed an amelioration of liver enzymes aspartate aminotransferase but not of alanine aminotransferase as compared to placebo or other interventions [47].

The role of antioxidants in slowing the progression of certain neurological disorders has been suggested as oxidation may be the reason in several disorders of the nervous system. Alzheimer's disease affects over 4 million Americans and it is related to amyloid β-peptide, the principal component of senile plaques in Alzheimer's disease brain. Oxidative stress, manifested by protein oxidation and lipid peroxidation, among all other alterations is a characteristic of Alzheimer's disease brain. In Alzheimer's disease, the evidence on vitamin E supplementation is mixed [48]. The prevention of the amyloid -β-peptide -associated deleterious effects by free radical antioxidants strengthens the notion of free radical involvement in amyloid -β-peptide toxicity and suggests the potential usefulness of brain-accessible free radical antioxidants or elevating levels of endogenous antioxidants as therapeutic strategies for Alzheimer's disease [49].

Lipoic acid is an amphipathic substance and considered a universal antioxidant. Lipoic acid is found in almost all foods, but slightly more so in kidney, heart, liver, spinach, broccoli, and yeast extract [50]. Lipoic acid and its reduced form, dihidrolipoic acid, act against reactive oxygen species, reducing oxidative stress. Therefore, this antioxidant has been used in the treatment of many diseases, including a new perspective for the treatment of Parkinson's disease [51].

The efficacy of antioxidants and other pharmacological treatments for Frederich ataxia were examined. Idebenone, a synthetic antioxidant, did not help the ataxia but did have a significant effect on heart abnormality [52].

Impact of antioxidants and their role in cancer is a different window to look out. In a high-risk group like smokers, high doses of beta carotene increased the rate of lung cancer [53]. Considered closely the risk of skin cancers and antioxidants, the antioxidant supplementation especially with β carotene can increase the risk of a variety of cancers and may impair the effectiveness of cancer chemotherapy. They may facilitate the maturation of protomelanomas into melanoma by impairing anti-tumoral immunity [54]. Oxidative stress may be a factor that cause gastrointestinal cancers. It is reported that antioxidant supplements (randomised trials were identified wtih beta carotene, vitamin A, vitamin C, vitamin E and selenium) seems to increase overall mortality and can not be recommended for gastrointestinal cancer prevention [55]. Significantly lower levels of antioxidants and selenium were found in lung cancer patients compared to healy controls. Levels of retinol, α-tocopherol, β-carotene, lycopene, β-cryptoxanthin, selenium and zinc were also found low.

Vitamin E is a well known antioxidant and has natural isoforms. It has been suggested that both tocopherols and tocotrienols may have antitumor effects. It has been found that vitamin E especially tocotrienols seems to be a potent agent for cancer prevention however no large scale clinical trial on the cancer prevention effect has been conducted yet [56].

Current evidence suggests that there is a high grade oxidative stress during abdominal aortic aneurysm repair operation [57].

Red raspberries have antioxidant effects that play a minor role in the killing of stomach and colon cancer cells [58].

Resveratrol, one of the main constituents of red wine, was first isolated in 1940 as an ingredient of the roots of white hellebore and since then it has been identified in extracts in plant species. Resveratrol can be used to sensitize tumors to standart cancer chemotherapeutics [59].

The effects of tomato product supplementation containing lycopene on biomarkers of oxidative stress and carcinogenesis in human clinical trials has been investigated. It is concluded that the consumption of processed tomato products, containing lycopene, is of significant health benefit and can be attributed to a combination of naturally occurring nutrients in tomatoes [60].

It is known that oxidative stress may induce insulin resistance in peripheral tissues and impair insulin secretion from pancreatic beta cells. Antioxidants are suggested to decrease the risk of diabetes through reduction of oxidative stress. It is reported that dietary antioxidants were not associated with a decreased risk of incident diabetes in middle aged male smokers [61].

Another question is that can dietary antioxidants reduce the incidence of brain tumors and it has been found that the incidence of brain tumors could be reduced by antioxidant intake [62].

It is not known yet if the modulation of process of premature aging of the skin by dietary antioxidants can be made. Photoprotective effects of dietary antioxidants provide and improve skin structure when administred as food supplements. Carotenoids are widely used as skin protectants and supplementation with carotenoids has been shown to protect against ultraviolet induced erythema. Carotenoids, vitamin E and selenium increases skin density and thickness when ingested over a period of 12 weeks and skin surface parameters including scaling and roughness are improved upon supplementation [63].

The use of antioxidants in peripheral vascular dysfunction [64] and postnatal glucocorticoid treatment [65] has been investigated. Combined glucocorticoid and antioxidant therapy in premature infants may be safer than glucocorticoids alone in the treatment of chronic lung disease and antioxidant therapy in healty offspring is not recommended.

## Drugs with antioxidant properties

- Probucol,
- Xhantine oxidase inhibitors (allopurinol, folic acid),
- NADPH inhibitors (adenosine, calcium channel blockers),
- inhibitors of iron redox cycling (deferoxamine, apotransferin and ceruloplasmin), some non-steroidal anti-inflammatory agents,
- oral antidiabetic agents like metformin, gliclazide and troglitazone and
- statins (atorvastatin, simvastatin, pravastatin and rosuvastatin) are the drugs that have antioxidant properties [66].

### Adverse effects

Reactive oxygen species (ROS) and cellular oxidant stress have been related with cancer. ROS and oxidant stress may induce cancer. Antioxidant supplementation is widely used in attempts to prevent the development of cancer and it has been reported that antioxidants may paradoxically interfere with cancer treatments [67].

American College of Cardiology/ American Hearth Association (2002) Guideline uptake for the management of patients with chronic stable angina states that there is no basis for recommending that patients who take vitamin C or vitamin E supplements or others for the express purpose of preventing or treating coronary artery disease [68].

Evidence based guidelines for cardiovascular disease prevention in women concludes that antioxidant vitamin supplements should not be used to prevent cardiovascular diseases [69]. Antioxidant treatment alters peripheral vascular dysfunction induced by postnatal glucocorticoid therapy in rats.

### Novel antioxidant discovery

Amaranth is a valuable pseudocereal due to its nutritional quality and its nutraceutical properties. Amaranth exerts a protective effect in serum and in liver of rats intoxicated with ethanol [70].

A novel selenium containing compound selenoneine has been isolated as the major form of organic selenium in the blood and tissues of tuna [71].

Neotrophil gelatinase associated lipocalin (NGAL) is a new antioxidant that exerts its cytoprotective effect independent of heme oxygenase-1 [72]. Induction of NGAL under harmful conditions is a compensatory response to ameliorate oxidative stress mediated toxicity. Sideritis euboea is a Greek plant that is consumed as a beverage (mountain tea). Its extract has shown antioxidant and estrogenic activities [73].

Antioxidant capacity and polyphenolic components of teas has been described and tea can be an important source of what has been referred to as non-nutrient antioxidant phytochemicals [74].

Antioxidant effects of a nitrated cyclic nucleotide functioning as an endogenous electrophile has been described [75].

Compounds containing a carboline ring system belong to a large family of biological active indoles, which are very important for the function of the central nervous system. Derivatives of beta-carboline shows antioxidative activity comparable to vitamin C [76].

Effects of antioxidants on aging process and their antiaging properties are new concepts in drug discovery. There is not a specific agent that has been shown to truely reverse aging in human beings. There are not enough data to support the daily use of vitamin A, beta carotene, vitamin E or C as antiaging therapies. Vitamin E did not reduced mortality compared with control, did not significantly decrease risk of cardiovascular death, did not reduce the risk of cerebrovascular accidents according to the study that shows the effects of vitamin E on cardiovascular mortality [77,78].

Antioxidant's effects on cognitive functions also is a novel area to search for. Impact of antioxidants, zinc and copper on cognition elderly in a randomized controlled trial in 2166 elderly people non of the regimens was beneficial or harmful with respect to cognition [79].

Depleted vitamin A, vitamin C, vitamin E and carotenoid levels was found in the plasma of 25 elderly people with mild cognitive impairment and in 63 people with Alzheimer's disease compared with 53 controls [80].

## Conclusion

Especially dietary antioxidants have been considered to help against diseases that oxidative stress aggravates such as cardiovascular diseases, cancer, and disorders of neurodegenerative in origin. There is a future for antioxidants in the prevention of disease if the real mechanism of action is considered and suitable clues are found.

Current studies on the action of selected antioxidant nutraceuticals on the activity of final targets in the signal transduction cascade and gene regulation also defined as transcription factors can be a new concept for developing new treatment strategies.

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