

Your AntiOxiDense™ Product Science – Antioxidant Abstracts

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[Curr Med Chem.](#) 2008;15(4):404-14.

Antioxidants and free radical scavengers for the treatment of stroke, traumatic brain injury and aging.

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The overproduction of reactive oxygen species (ROS) and reactive nitrogen species (RNS) is a common underlying mechanism of many neuropathologies, as they have been shown to damage various cellular components, including proteins, lipids and DNA. Free radicals, especially superoxide ($O(2)^{\bullet-}$), and non-radicals, such as hydrogen peroxide ($H(2)O(2)$), can be generated in quantities large enough to overwhelm endogenous protective enzyme systems, such as superoxide dismutase (SOD) and reduced glutathione (GSH). Here we review the mechanisms of ROS and RNS production, and their roles in ischemia, traumatic brain injury and aging. In particular, we discuss several acute and chronic pharmacological therapies that have been extensively studied in order to reduce ROS/RNS loads in cells and the subsequent oxidative stress, so-called "free-radical scavengers." Although the overall aim has been to counteract the detrimental effects of ROS/RNS in these pathologies, success has been limited, especially in human clinical studies. This review highlights some of the recent successes and failures in animal and human studies by attempting to link a compound's chemical structure with its efficacy as a free radical scavenger. In particular, we demonstrate how antioxidants derived from natural products, as well as long-term dietary alterations, may prove to be effective scavengers of ROS and RNS.

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[Int J Cancer.](#) 2008 Sep 15;123(6):1227-39.

Impact of antioxidant supplementation on chemotherapeutic

toxicity: a systematic review of the evidence from randomized controlled trials.

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Much debate has focused on whether antioxidants interfere with the efficacy of cancer chemotherapy. The objective of this study is to systematically review the randomized, controlled clinical trial evidence evaluating the effects of concurrent use of antioxidants with chemotherapy on toxic side effects. We performed a search of literature from 1966-October 2007 using MEDLINE, Cochrane, CinAhl, AMED, AltHealthWatch and EMBASE databases. Randomized, controlled clinical trials reporting antioxidant-based mitigation of chemotherapy toxicity were included in the final tally. Searches were performed following a standardized protocol for systematic reviews. Only 33 of 965 articles considered, including 2,446 subjects, met the inclusion criteria. Antioxidants evaluated were: glutathione (11), melatonin (7), vitamin A (1), an antioxidant mixture (2), N-acetylcysteine (2), vitamin E (5), selenium (2), L-carnitine (1), Co-Q10 (1) and ellagic acid (1). The majority (24) of the 33 studies included reported evidence of decreased toxicities from the concurrent use of antioxidants with chemotherapy. Nine studies reported no difference in toxicities between the 2 groups. Only 1 study (vitamin A) reported a significant increase in toxicity in the antioxidant group. Five studies reported the antioxidant group completed more full doses of chemotherapy or had less-dose reduction than control groups. Statistical power and poor study quality were concerns with some studies. This review provides the first systematically reviewed evidence that antioxidant supplementation during chemotherapy holds potential for reducing dose-limiting toxicities. However, well-designed studies evaluating larger populations of patients given specific antioxidants defined by dose and schedule relative to chemotherapy are warranted.

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[Antioxid Redox Signal.](#) 2008 Mar;10(3):475-510.

Cancer chemoprevention through dietary antioxidants: progress and promise.

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It is estimated that nearly one-third of all cancer deaths in the United States could be prevented through appropriate dietary modification. Various dietary antioxidants have shown considerable promise as effective agents for cancer prevention by reducing oxidative stress which has been implicated in the development of many diseases, including cancer. Therefore, for reducing the incidence of cancer, modifications in dietary habits, especially by increasing consumption of fruits and vegetables rich in antioxidants, are increasingly advocated. Accumulating research evidence suggests that many dietary factors may be used alone or in combination with traditional chemotherapeutic agents to prevent the occurrence of cancer, their metastatic spread, or even to treat cancer. The reduced cancer risk and lack of toxicity associated with high intake of fruits and vegetables suggest that specific concentrations of antioxidant agents from these dietary sources may produce cancer chemopreventive effects without causing significant levels of toxicity. This review presents an extensive analysis of the key findings from studies on the effects of dietary antioxidants such as tea polyphenols, curcumin, genistein, resveratrol, lycopene, pomegranate, and lupeol against cancers of the skin, prostate, breast, lung, and liver. This research is also leading to the identification of novel cancer drug targets.

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[Brain Nerve.](#) 2008 Feb;60(2):157-70.

[The role for oxidative stress in neurodegenerative diseases]

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A growing body of evidence suggests oxidative stress involvement in neurodegenerative diseases; however, it remains to be determined whether oxidative stress is a cause, result, or epiphenomenon of the pathological processes. This review concerns the current issue, focusing on Alzheimer disease (AD), Parkinson disease (PD), and amyotrophic lateral sclerosis (ALS). Several studies have indicated that oxidative stress initially occurs in the disease-specific, site-restricted sources such as amyloid-beta in the cerebral cortex of AD brain, alpha-

synuclein in the brain stem of PD brain, and glutamate receptor-coupled Ca²⁺ channel in the motor system of ALS spinal cord. Subsequent events in the neurons common to these diseases are glutamate-induced neurotoxicity and increased cytosolic Ca²⁺ levels, resulting in activation of Ca²⁺-dependent enzymes including NADPH oxidase, cytosolic phospholipase A₂, xanthine oxidase, and neuronal nitric oxide synthase (NOS). These enzymes produce reactive oxygen and nitrogen species (ROS/RNS), which oxidatively modify nucleic acid, lipid, sugar, and protein, leading to nuclear damage, mitochondrial damage, proteasome inhibition, and endoplasmic reticulum (ER) stress. Mitochondrial damage results in both ROS leakage from the electron transport system and Ca²⁺ release. Nuclear damage induces p53 activation, and proteasome inhibition reduces p53 degradation. The resultant increased p53 levels in the nucleus induce Bax activation and Bcl-2 inhibition, followed by a release of cytochrome c into the cytosol that truncates procaspase-9. ER stress triggers activation of caspase-12 as well as caspase-9 via the tumor necrosis factor (TNF) receptor-associated factor-2 / apoptosis-signaling kinase-1 / c-Jun N-terminal kinase pathway. Oxidative stress also stimulates astrocytes and microglia to yield and secrete cytokines such as TNF α and FasL that cause not only neuronal caspase-8 activation but also glial inflammatory response through induction of nuclear factor-kappaB-mediated, proinflammatory gene products including cytokines, chemokines, growth factors, cell adhesion molecules, and ROS/RNS-producing enzymes. The activated caspases truncate procaspase-3 to exert classical apoptosis. Moreover, oxidative DNA damage leads to the release and nuclear truncation of mitochondrial apoptosis-inducing kinase, which triggers apoptosis-like programmed cell death via cyclophilin A. These observations could indicate crucial implications for oxidative stress in several steps of the pathomechanisms of neurodegenerative diseases.

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Air pollution, oxidative stress and dietary supplementation: a review.

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The aim of the present review was to provide an up-to-date overview of the biological and epidemiological evidence of the role of oxidative stress as a major underlying feature of the toxic effect of air pollutants, and the potential role of dietary supplementation in enhancing antioxidant defences. A bibliographic search was conducted through PubMed. The keywords used in the search were "air pollutant", "oxidative stress", "inflammation", "antioxidant polyunsaturated fatty acids" and "genetics". In addition, the authors also searched for biomarkers of oxidative stress and nutrients. The review presents the most recent data on: the biological and epidemiological evidence of the oxidative stress response to air pollutants; the role of dietary supplementation as a modulator of these effects; and factors of inter-individual variation in human response. The methodology for further epidemiological studies will be discussed in order to improve the current understanding on how nutritional factors may act. There is substantial evidence that air pollution exposure results in increased oxidative stress and that dietary supplementation may play a modulating role on the acute effect of air pollutants. Further epidemiological studies should address the impact of supplementation strategies in the prevention of air-pollution-related long-term effects in areas where people are destined to be exposed for the distant future.

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[Int J Biochem Cell Biol.](#) 2007;39(1):44-84.

Free radicals and antioxidants in normal physiological functions and human disease.

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Reactive oxygen species (ROS) and reactive nitrogen species (RNS, e.g. nitric oxide, NO(*)) are well recognised for playing a dual role as both deleterious and beneficial species. ROS and RNS are normally generated by tightly regulated enzymes, such as NO synthase (NOS) and NAD(P)H oxidase isoforms, respectively. Overproduction of ROS (arising either from mitochondrial electron-transport chain or excessive stimulation of NAD(P)H) results in oxidative stress, a deleterious process that can be an important mediator of damage to cell structures, including lipids and membranes, proteins, and DNA. In contrast, beneficial effects of ROS/RNS (e.g. superoxide radical and

nitric oxide) occur at low/moderate concentrations and involve physiological roles in cellular responses to noxia, as for example in defence against infectious agents, in the function of a number of cellular signalling pathways, and the induction of a mitogenic response. Ironically, various ROS-mediated actions in fact protect cells against ROS-induced oxidative stress and re-establish or maintain "redox balance" termed also "redox homeostasis". The "two-faced" character of ROS is clearly substantiated. For example, a growing body of evidence shows that ROS within cells act as secondary messengers in intracellular signalling cascades which induce and maintain the oncogenic phenotype of cancer cells, however, ROS can also induce cellular senescence and apoptosis and can therefore function as anti-tumourigenic species. This review will describe the: (i) chemistry and biochemistry of ROS/RNS and sources of free radical generation; (ii) damage to DNA, to proteins, and to lipids by free radicals; (iii) role of antioxidants (e.g. glutathione) in the maintenance of cellular "redox homeostasis"; (iv) overview of ROS-induced signaling pathways; (v) role of ROS in redox regulation of normal physiological functions, as well as (vi) role of ROS in pathophysiological implications of altered redox regulation (human diseases and ageing). Attention is focussed on the ROS/RNS-linked pathogenesis of cancer, cardiovascular disease, atherosclerosis, hypertension, ischemia/reperfusion injury, diabetes mellitus, neurodegenerative diseases (Alzheimer's disease and Parkinson's disease), rheumatoid arthritis, and ageing. Topics of current debate are also reviewed such as the question whether excessive formation of free radicals is a primary cause or a downstream consequence of tissue injury.

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A review of the interaction among dietary antioxidants and reactive oxygen species.

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During normal cellular activities, various processes inside of cells produce reactive oxygen species (ROS). Some of the most common ROS are hydrogen peroxide (H₂O₂), superoxide ion (O₂⁻), and hydroxide radical (OH⁻). These compounds, when present in a high

enough concentration, can damage cellular proteins and lipids or form DNA adducts that may promote carcinogenic activity. The purpose of antioxidants in a physiological setting is to prevent ROS concentrations from reaching a high-enough level within a cell that damage may occur. Cellular antioxidants may be enzymatic (catalase, glutathione peroxidase, superoxide dismutase) or nonenzymatic (glutathione, thiols, some vitamins and metals, or phytochemicals such as isoflavones, polyphenols, and flavonoids). Reactive oxygen species are a potential double-edged sword in disease prevention and promotion. Whereas generation of ROS once was viewed as detrimental to the overall health of the organism, advances in research have shown that ROS play crucial roles in normal physiological processes including response to growth factors, the immune response, and apoptotic elimination of damaged cells. Notwithstanding these beneficial functions, aberrant production or regulation of ROS activity has been demonstrated to contribute to the development of some prevalent diseases and conditions, including cancer and cardiovascular disease (CVD). The topic of antioxidant usage and ROS is currently receiving much attention because of studies linking the use of some antioxidants with increased mortality in primarily higher-risk populations and the lack of strong efficacy data for protection against cancer and heart disease, at least in populations with adequate baseline dietary consumption. In normal physiological processes, antioxidants effect signal transduction and regulation of proliferation and the immune response. Reactive oxygen species have been linked to cancer and CVD, and antioxidants have been considered promising therapy for prevention and treatment of these diseases, especially given the tantalizing links observed between diets high in fruits and vegetables (and presumably antioxidants) and decreased risks for cancer.

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[Curr Pharm Des.](#) 2006;12(27):3521-33.

Dual effects of antioxidants in neurodegeneration: direct neuroprotection against oxidative stress and indirect protection via suppression of glia-mediated inflammation.

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Oxidative stress, in which production of highly reactive oxygen species (ROS) and reactive nitrogen species (RNS) overwhelms antioxidant defenses, is a feature of many neurological diseases and neurodegeneration. ROS and RNS generated extracellularly and intracellularly by various processes initiate and promote neurodegeneration in CNS. ROS and RNS can directly oxidize and damage macromolecules such as DNA, proteins, and lipids, culminating in neurodegeneration in the CNS. Neurons are most susceptible to direct oxidative injury by ROS and RNS. ROS and RNS can also indirectly contribute to tissue damage by activating a number of cellular pathways resulting in the expression of stress-sensitive genes and proteins to cause oxidative injury. Moreover, oxidative stress also activates mechanisms that result in a glia-mediated inflammation that also causes secondary neuronal damage. Associated with neuronal injuries caused by many CNS insults is an activation of glial cells (particularly astrocytes and microglia) at the sites of injury. Activated glial cells are thus histopathological hallmarks of neurodegenerative diseases. Even though direct contact of activated glia with neurons per se may not necessarily be toxic, the immune mediators (e.g. nitric oxide and reactive oxygen species, pro-inflammatory cytokines and chemokines) released by activated glial cells are currently considered to be candidate neurotoxins. Therefore, study of the protective role of antioxidant compounds on inhibition of the inflammatory response and correcting the fundamental oxidant/antioxidant imbalance in patients suffering from neurodegenerative diseases are important vistas for further research. The purpose of this review is to summarize the current evidence in support of this critical role played by oxidative stress of neuronal and glial origin in neurodegenerative diseases. The mechanistic basis of the neuroprotective activity of antioxidants does not only rely on the general free radical trapping or antioxidant activity per se in neurons, but also the suppression of genes induced by pro-inflammatory cytokines and other mediators released by glial cells. We propose that combinations of agents which act at sequential steps in the neurodegenerative process can produce additive neuroprotective effects. A cocktail of multiple antioxidants with anti-inflammatory agents may be more beneficial in the prevention of neurodegenerative disease. A clearer appreciation of the potential therapeutic utility of antioxidants would emerge only when the complexity of their effects on mechanisms that interact to determine the extent of oxidative damage in vivo are more fully defined and understood.

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Chronic fatigue syndrome: oxidative stress and dietary modifications.

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Chronic fatigue syndrome (CFS) is an illness characterized by persistent and relapsing fatigue, often accompanied by numerous symptoms involving various body systems. The etiology of CFS remains unclear; however, a number of recent studies have shown oxidative stress may be involved in its pathogenesis. The role of oxidative stress in CFS is an important area for current and future research as it suggests the use of antioxidants in the management of CFS. Specifically, the dietary supplements glutathione, N-acetylcysteine, alpha-lipoic acid, oligomeric proanthocyanidins, Ginkgo biloba, and Vaccinium myrtillus (bilberry) may be beneficial. In addition, research on food intolerance is discussed, since food intolerance may be involved in CFS symptom presentation and in oxidation via cytokine induction. Finally, recent evidence suggests celiac disease can present with neurological symptoms in the absence of gastrointestinal symptoms; therefore, celiac disease should be included in the differential diagnosis of CFS.

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