

Review

Open Access

The role of antioxidant supplement in immune system, neoplastic, and neurodegenerative disorders: a point of view for an assessment of the risk/benefit profile

Daria Brambilla¹, Cesare Mancuso², Mariagrazia Rita Scuderi¹, Paolo Bosco³, Giuseppina Cantarella¹, Laurence Lempereur¹, Giulia Di Benedetto¹, Salvatore Pezzino¹ and Renato Bernardini*¹

Address: ¹Department of Experimental and Clinical Pharmacology, University of Catania, Catania, Italy, ²Institute of Pharmacology, Università Cattolica del Sacro Cuore, Roma, Italy and ³IRCSS OASI Maria SS, Troina, Italy

Email: Daria Brambilla - bramzilla@unict.it; Cesare Mancuso - cmancuso@rm.unicatt.it; Mariagrazia Rita Scuderi - m.scuderi@inwind.it; Paolo Bosco - pbosco@oasi.en.it; Giuseppina Cantarella - gcantare@unict.it; Laurence Lempereur - lempereu@unict.it; Giulia Di Benedetto - giuliadibenedetto@libero.it; Salvatore Pezzino - salvatore.pezzino12@virgilio.it; Renato Bernardini* - bernardi@unict.it

* Corresponding author

Published: 30 September 2008

Received: 15 April 2008

Nutrition Journal 2008, **7**:29 doi:10.1186/1475-2891-7-29

Accepted: 30 September 2008

This article is available from: <http://www.nutritionj.com/content/7/1/29>

© 2008 Brambilla et al; licensee BioMed Central Ltd.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/2.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract

This review will discuss some issues related to the risk/benefit profile of the use of dietary antioxidants. Thus, recent progress regarding the potential benefit of dietary antioxidants in the treatment of chronic diseases with a special focus on immune system and neurodegenerative disorders will be discussed here. It is well established that reactive oxygen species (ROS) play an important role in the etiology of numerous diseases, such as atherosclerosis, diabetes and cancer. Among the physiological defense system of the cell, the relevance of antioxidant molecules, such as glutathione and vitamins is quite well established. Recently, the interest of researchers has, for example, been conveyed on antioxidant enzyme systems, such as the heme oxygenase/biliverdin reductase system, which appears modulated by dietary antioxidant molecules, including polyphenols and beta-carotene. These systems possibly counteract oxidative damage very efficiently and finally modulate the activity of oxidative phenomena occurring, for instance, during pathophysiological processes. Although evidence shows that antioxidant treatment results in cytoprotection, the potential clinical benefit deriving from both nutritional and supplemental antioxidants is still under wide debate. In this line, the inappropriate assumption of some lipophilic vitamins has been associated with increased incidence of cancer rather than with beneficial effects.

Introduction

The term "free radicals" designates a family of compounds characterized by great reactivity due to the impaired electron in the outer orbital. To this group belong reactive oxygen species (ROS), such as superoxide anion, hydroxyl radical and hydrogen peroxide, as well as reactive nitrogen

species (RNS) which include nitric oxide and peroxynitrite. Although structurally different, free radicals share similar mechanisms to harm body's cells and tissues through damage on proteins, DNA and lipids [1]. The alterations of membrane functions occurring as a consequence of phospholipid modifications represent a rele-

vant, radical species-dependent injury, either when considering the organism as a whole, or a specific integrated function, such as the immune response [2]. The potential therapeutic applications of antioxidants in free radical-related diseases led to the hypothesis of their use to slow down or reverse, for example, symptoms associated with neurodegenerative disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD), or spongiform encephalopathies. Such effect could occur through a block of proinflammatory cytokines action and the resulting oxidative damage [3-7]. However, several clinical studies demonstrated that not only malnutrition, but also the excess of certain nutrients (e.g. iron, alpha-tocopherol, beta-carotene, ascorbic acid) may set into motion oxidation phenomena and, therefore, cell injury [8,9]. Thus, it is of relevance that prior to considering introducing antioxidant therapy into mainstream medicine, significant advances in basic cell biology, pharmacology and clinical bioanalysis will be required.

Oxidative Stress

The body is normally under a dynamic equilibrium between free radical generation and quenching. The physiological defense systems to counteract free radicals encompass endogenous enzyme systems, such as catalase, glutathione reductase and superoxide dismutase, as well as glutathione, urate and coenzyme Q, or exogenous factors (β -carotene, vitamin C, vitamin E and selenium) [10]. All these molecules have an antioxidant effect due to their ability to transform ROS into stable and harmless compounds or by scavenging both ROS and RNS with a redox-based mechanism [10]. Very recently, a main role in the fight against oxidative stress has been assumed by enzymes such as heme oxygenase (HO) and biliverdin reductase (BVR). Heme oxygenase is a microsomal enzyme which metabolizes heme into ferrous iron, carbon monoxide and biliverdin (BV); the latter is then reduced by BVR into bilirubin (BR), a molecule endowed with strong antioxidant and antinitrosative activities [11-14]. Interestingly, all these protective factors act in a concerted way, enhancing the antioxidant defense system of the cell. When the balance between ROS/RNS and antioxidants turns in favor of the former, oxidative/nitrosative stress occurs. Although oxidative stress is associated with most diseases, routine assay methods are not nowadays available in the clinical practice. A strategy widely used to determine oxidative stress is measurement of malonyldialdehyde, F2-isoprostanes, or 8-hydroxydesoxyguanosine. Actually, these molecules are regarded as the most reliable markers available [15]. A classic example of an oxidation product apparently leading to disease, is oxidized cholesterol in low-density lipoprotein (LDL), which displays a higher atherogenic potential than native LDL, and mainly involved in the pathogenesis of atherosclerosis and coronary heart disease (CHD) [16].

At the cellular level, a large body of data clearly demonstrated that ROS, when produced in low amounts and in a controlled manner, are physiological components of the signalling generated by cytokines, growth factors and neurotrophic peptides [17-22], although they may also activate apoptotic cell death [23]. Extracellularly generated ROS can diffuse through anion channels into the cytoplasm; the resulting variation in the cell redox state leads to modulation of an array of transcription factors (eg. NF- κ B, AP-1), protein kinases (e.g. AKT, JNK, p38), and receptor activated MAP kinases involved in apoptosis [17,24-26]. Moreover, the proapoptotic molecules Fas and Fas ligand (FasL) undergo positive transcriptional regulation after exposure to oxidants [27]. Interestingly, Krammer and Colleagues demonstrated that in vitro administration of vitamin E suppresses FasL mRNA expression and protects T cells of HIV-1 infected individuals from Fas mediated apoptosis [28]. Moreover, it was demonstrated that administration of combinations of vitamin E and C to cultures of human umbilical vein endothelial cells (HUVEC) treated with lipopolysaccharide could prevent apoptosis by upregulation of *Bcl-2* [29].

Antioxidants, The Immune System And Related Disorders

The protective function against external pathogens carried out by the immune system is by itself a source of ROS, since activated neutrophils, produce free radicals to a significant extent [30]. Moreover, during the inflammatory process, activation of phagocytes through the interaction of proinflammatory mediators, or bacterial products with specific receptors results in the assembly of the multicomponent flavoprotein NADPH oxidase which catalyzes the production of large quantities of the superoxide anion radical ($O_2^{\cdot-}$) [31]. In addition to classical reactive oxygen metabolites, activated neutrophils and monocytes release the hemoprotein myeloperoxidase (MPO) into the extracellular space, where it catalyzes the oxidation of Cl^- by H_2O_2 to yield hypochlorous acid (HClO) [32]. HClO is a non-specific oxidizing and chlorinating agent that reacts rapidly with a variety of biological compounds, such as sulphhydryls, polyunsaturated fatty acids, DNA, pyridine nucleotides, aliphatic and aromatic aminoacids and nitrogen-containing compounds [33-35]. Moreover, apart from their direct toxic effects, neutrophil-derived oxidants may promote tissue injury indirectly by altering the protease/antiprotease equilibrium that normally exists within the intestinal interstitium. The oxidative inactivation of important protease inhibitors, coupled to the oxidant-mediated activation of latent proteases, creates a favorable environment for neutrophils that allows degradation of the interstitial matrix through elastases, collagenases and gelatinases, as well as injury to epithelial cells [36,37]. However, not only immune cell produce ROS necessary for the microbicidal activity, but they are also sensitive to external ROS, due to their high polyunsaturated fatty

acids (PUFA) content. Immune cells are atypical, as compared with other somatic cells, in that they contain high levels of antioxidant vitamins, presumably providing protection against lipid peroxidation and immunosuppression, both of which are well known risks posed by high PUFA content [38]. The reactivity of immune cells to exogenous ROS has been shown to be age-dependent. In fact, lymphocytes from elderly individuals appear to be more sensitive to exposure to hydrogen peroxide than those from young adults [39]. Moreover, it has been demonstrated that a micronutrient deficiency can be the cause of suppression of immune function affecting both innate T-cell-mediated immune response and adaptive antibody response, thus altering the balanced host response. Therefore, an adequate intake of vitamins and antioxidant elements seems to be essential for an efficient function of the immune system. Micronutrient deficiency occurs in various conditions, such as eating disorders, tobacco smokers, chronic diseases, aging. During aging, changes in the immune system are frequent and associated with increased susceptibility to infections. Antioxidant vitamins and trace elements contribute to maintain an effective immune response [40]. For example, administration of vitamin E supplement to healthy elderly patients produced an increased antibody titer to both hepatitis B and tetanus vaccine [41], thus enhancing T-cell mediated functions. In conclusion, maintaining adequate antioxidant status may provide a useful approach in attenuating cell injury and dysfunction observed in some inflammatory/autoimmune disorders [42,43].

Autoimmunity has been for decades considered the result of a breakdown in self-tolerance. At the present, it is known that autoimmunity is a physiological process [44]. This phenomenon becomes pathological when the number of autoreactive cells, and particularly the avidity of their receptors for autoantigens, increases [44]. Triggering of the disease usually depends both on the increase in immunogenicity of the target cell, which may be secondary to a viral infection (Chediak-Higashi syndrome and Griscelli syndrome by EBV), and on the individual's own capacity to recognize the autoantigens (HLA, or T cell repertoire in Familial hemophagocytic lymphohistiocytosis [FHL]) [45]. Moreover, apart from the genetic defects that may predispose to autoimmune diseases, one must take into account the environmental factors that are implicated in the development of such pathologies. Among them, an important role is played by xenobiotics such as chemicals, drugs and metals [46]. Iron, aluminum, and manganese readily cross the blood brain barrier via specific or non-specific carriers, and contribute to the nervous tissue damage [47,48]. The toxic effects of metals are mediated through free radical formation, or enzyme inhibition [49-53]. In addition, metals may act as immunosuppressants (cytostatically), or as immunoadjuvants (through non-

specific activation of the immune response) [54,55]. Several mechanisms are proposed on how metals may act within the immune system to induce autoimmunity. Patients suffering from scleroderma develop autoantigens with metal-binding sites. After metal binding, free radical species are generated which fragment auto-antigens thereby exposing cryptic epitopes, which may then trigger autoimmunity [56,57]. Taken together, these findings underlie the importance of exogenous factors in the pathogenesis of autoimmunity. Nevertheless, all these elements do not appear sufficient to provoke *chronic* autoimmune diseases such as Multiple Sclerosis (MS), myasthenia gravis, Insulin Dependent Diabetes Mellitus (IDDM) or Hashimoto's thyroiditis, and the passage to chronic disease is usually secondary to a defect in immunoregulation.

Several classes of regulatory T cells, such as Th2, CD25+ and natural killer (NK) T cells, are implied in autoimmune pathologies. In an animal model of a Th2-dominated autoimmune syndrome, the administration of the antioxidant N-acetyl-cysteine (NAC) induced a decrease in mast-cell expression of both IgE and IL-4 [58]. Of major interest is the discovery of the therapeutic potential of a new benzoquinone-containing product derived from wheat germ fermentation. This latter has been shown to have immune restorative properties because it affects the Th1/Th2 network by inhibiting the Th2 response [59]. Another beneficial effect of this molecule is its anti-metastatic activity, shown in various human malignancies and Jurkat leukemia cell line [60]. Intriguingly, the combined treatment with wheat germ and vitamin C profoundly inhibited metastasis formation in various tumor models of different origin (Lewis lung carcinoma, B16 melanoma and human colon carcinoma xenografts [HCR25]) [61]. On the contrary, wheat germ had no toxicity on peripheral blood leukocytes (PBLs) at doses that affected tumor cells. The crude powder extract of fermented wheat germ inhibits nucleic acid ribose synthesis primarily through the non-oxidative steps of the pentose cycle [60]. Curiously, another quinone compound, carnosic acid quinone, like wheat germ, recovers potent antioxidant activity upon standing [62].

Keeping in mind the importance of oxidative stress in the regulation/dysregulation of immune system, the use of antioxidants in such diseases has been reasonably proposed. Rheumatoid arthritis (RA) is a classic example of autoimmune disease. Joint inflammation in rheumatoid arthritis (RA) is characterized by invasion of T cells in the synovial space and proliferation of activated macrophages and fibroblasts in the synovial intima [63]. Therefore, in the rheumatic joint there is an increased activity of fibroblasts and leucocytes which produce ROS [64,65]. Very recently, antioxidants have been successfully used as adju-

vant therapy in RA [66,67]. Although the results obtained with RA seemed to be very promising, the indiscriminate use of antioxidants in autoimmune disorders is not recommended. In fact, autoimmune lymphoproliferative syndrome (ALPS), MS, type 1 diabetes and multiple autoimmune syndrome, have been linked to decreased Fas functionality [68] and, as discussed previously, antioxidants may up-regulate Fas and FasL *in vitro*. Increasing evidence provides support that oxidative stress and apoptosis are closely related physiological phenomena and are implicated in diseases including autoimmune diseases. Therefore molecules that target both apoptosis-related signal transduction and oxidative stress, like antioxidants, are likely to result in the improvement of these pathologies.

A novel possible approach to modulate immune system thus preventing autoimmunity or transplant rejection is the activation of cytoprotective and antioxidant enzymes such as HO-1. Heme oxygenase-1, the inducible isoform of HO, is a key protein in the cell stress response and its up-regulation is a common event during pro-inflammatory conditions [11,69-72]. Recent work clearly demonstrated that regulatory T cells overexpress HO-1 and release CO under pro-oxidant conditions. Carbon monoxide may inhibit the proliferation of effector T cells, thus reducing the immune response and prevent autoimmunity and/or graft reaction [73,74]. Dietary antioxidants, in particular polyphenols, has been shown to increase HO-1 expression in different *in vitro* systems [3,75,76] and the potential use of this natural substances to regulate immune response should be carefully addressed.

Antioxidants, Cancer And Neurodegenerative Disorders

It is well known that the dietary consumption of fruits, vegetables, herbs, or their phytochemical constituents aid in cancer prevention [77-79]. It is believed that the antioxidant properties of such foods protect cells from ROS-mediated DNA damage that can result in mutation and subsequent carcinogenesis. ROS-induced DNA damage can take many forms, ranging from specifically oxidized purine and pyrimidine bases, to DNA lesions such as strand breaks, sister chromatid exchanges (SCEs), and the formation of micronuclei [80]. However, the equation "antioxidant = benefit" is not always true. *In vivo* experiments demonstrated that retinol increases both the humoral and the cell-mediated immune response and could enhance immune surveillance against tumorigenesis [81-83]. Retinol may influence the immune response by quenching free radicals, which could lower the level of immunosuppressing lipid peroxides, alter arachidonic acid metabolism, etc. [82,84]. In the last few years many studies have been conducted to investigate the effects of vitamins on disease prevention. The first results have been encouraging and a wide number of people are taking anti-

oxidant supplements with the aim to improve their health. These studies, initially, have shown that a high consumption of fruit and vegetables decreases risks of lung cancer in healthy individuals and a combination of β -carotene, vitamin E and selenium reduced stomach cancer mortality in China [85,86]. Conversely, supplemental β -carotene alone or in combination with retinol or vitamin E did not have any effect on cancer risk, or increased the development of lung cancer in smokers [87,88]. In the light of these first contrasting result, and also as a consequence of the wide antioxidant consumption in the general population, various systematic reviews to estimate the association between antioxidant use and disease prevention, in particular for primary cancer incidence and mortality, have been issued. These reviews share the opinion that antioxidant supplementation *per se* does not prevent cancer. On the contrary, some antioxidant elements seem to be harmful for health. Recent studies have confirmed the relationship between beta-carotene and an increased incidence of cancer among smokers, but not among non-smokers. Moreover, beta carotene supplementation is associated with increased cancer-related mortality [89]. Vitamin E treatment also appears to be associated with a slightly increased incidence of lung cancer [90]. Other studies report that combination of vitamin A and other antioxidants, significantly increases mortality related to neoplastic diseases [91]. According to these studies, selenium would be the only element displaying beneficial effects, as it has been shown that it reduces total cancer incidence, an apparently sex-related effect, as it is predominant among males, rather than in females [89].

The reason why β -carotene may exert dual activity, namely antioxidant or pro-carcinogenic has been debated for quite a long time. The first hypothesis is that at high concentrations, β -carotene stimulates free radical production, whereas at lower concentrations β -carotene exerts antioxidant activity [90,91]. Furthermore, in the presence of cigarette smoke-derived free radicals β -carotene is cleaved into many derivatives which are very unstable and may trigger further oxidation [92-95]. A recent corollary to this theory is the evidence that β -carotene, either alone or in combination with cigarette smoke condensate, repressed HO-1 expression both in rat fibroblasts and human lung cancer cells [96]. The reduced expression of HO-1 accounted for a reduced production of CO and BR both of which have a marked antiproliferative effects [96-100]. Vitamin E has also been shown to act at the immune system level; in fact, supplementation with this vitamin can increase production of antibodies and enhance cell-mediated immunity in both experimental animals and in humans [101].

Neurodegenerative diseases, such as Parkinson's disease (PD), Alzheimer's disease (AD), and amyotrophic lateral

sclerosis (ALS), as well as multiple sclerosis (MS), are triggered, at least in part, by oxidative and nitrosative stress and also sustained by inflammatory cytokine production [11,70,102-104]. Similarly, autoimmunity mainly contributes to the pathogenesis of MS, characterized by central and peripheral loss of nerve myelin [105,106]. Although the specific sources of the damaging ROS and the affected target structures differ between the neuronal pathologies, the following general features can be defined. Increased levels of oxidation-altered metabolites are found in post-mortem tissues in many of the neurodegenerative diseases listed above [107-113]. An oxidative stress response and compensatory defense reactions can be seen in the affected neural cells; further, disturbances of the mitochondrial metabolism are observed, which may account for an increased leakage of ROS originating from the respiratory chain [11,70,104,114]. However, in addition to the direct induction of oxidative stress, metabolic disorders underlying every single disease can also indirectly generate an oxidative microenvironment, for example via the induction of a local immune response [115,116]. On this basis, antioxidant and anti-inflammatory drugs, such as polyphenols and non-steroidal anti-inflammatory drugs (NSAIDs), have been proposed in the treatment of different neurodegenerative diseases [117-119]. However, both polyphenols and NSAIDs gave rise to some problems when used in clinical setting. Due to their scarce bioavailability, only a negligible amount of polyphenols reaches brain tissue and the concentrations achieved are much lower than those efficacious in vitro [3]. As far as NSAIDs, *ad hoc* designed clinical trials with a large number of patients, clearly demonstrated that these drugs do not have any significant effect in slowing cognitive decline in patients suffering from mild-to-moderate AD [120,121]. Similar disappointing results have been obtained in the treatment of ALS, a systemic motor neuron disease that affects corticospinal and corticobulbar tracts, ventral horn motor neurons and motor cranial nerve nuclei [122,123]. Approximately 10% of cases are familial and have been linked to point mutation in the gene encoding for Cu/Zn superoxide dismutase (SOD) [124]. Mice transgenic for mutated SOD1 develop symptoms and pathologies similar to those in human ALS. Mutant SOD1 toxicity is mediated by damage to mitochondria in motor neurons, and this may trigger the functional decline of motor neurons and the onset of ALS in mice [125]. Unfortunately, although the role played by free radical to the pathogenesis of ALS has been demonstrated, antioxidants did not have any effect to prevent or slow down its progression. Desnuelle et al., clearly demonstrated that alpha-tocopherol, given together with riluzole, did not affect the survival and motor functions in ALS patients respect to the group treated with riluzole alone [126]. Novel compound, such as AEOL-10150 (Aeolus), structurally related to the SOD catalytic site, is

under phase I clinical investigation, but further clinical trials will be necessary to evaluate the real efficacy of this compound for the therapy of ALS [127,128].

Conclusion

The field of antioxidants is moving rapidly. About 20 years ago the hypothesis that diet might have a substantial influence on the development of some pathologies, such as cancer, has been raised by many scientists. In this light, during the last decade, efforts have been made to analyze the effects of plant food and synthetic antioxidants on the development and prevention of chronic diseases. Nowadays, antioxidants are used on a large scale to try to obtain and preserve optimal health. While there is no doubt that the correct balance between endogenous and exogenous antioxidant capacity is essential to life, the curative power of antioxidants has often been overestimated. In fact, according to the popular idea "if one is good two is better", antioxidants are taken in excess too often and the risk to originate diseases instead of preventing them is quite high. It is noteworthy to underline that as for all drugs, antioxidants may give important side effects if not correctly used or in combination with other drugs. Vitamin A, E and β -carotene for instance, have been shown to have pro-oxidant effects at higher doses or under certain conditions [39].

Another point of criticism is the possibility to take experimental results "from the bench to the bedside". In fact, although the promising results obtained by in vitro experiments, the use of antioxidants in the treatment of human disease states has not been as successful as might have been envisaged due to intrinsic pharmacokinetic or pharmacodynamic limitations.

In addition, conclusions on beneficial effect of antioxidant are often drawn from studies conducted with synthetic antioxidant supplement, whereas fruits and vegetable are a complex mixture of antioxidant, as well as other potentially beneficial micronutrients and macronutrients, which may, thus, work with different kinetics and dynamics [89].

In conclusion, the correct use of antioxidants may be useful to prevent free radical-related disorders. However, the repair of existing critical structural damage may be beyond the possibilities of antioxidants and therefore they may not be considered to be useful in therapeutic clinical applications, where their limits and eventual side effects must be better understood.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

DB & GC wrote the manuscript. MRS & GDB edited the manuscript and did the work on references. CM contributed to the work with update of data on effects of antioxidants. PB, SP & LL contributed to the literature as recipients of a grant for the study of the effects of antioxidants in cancer cells and in neurodegeneration models. RB conceived of the study, and participated in its design and coordination. All authors read and approved the final manuscript.

Acknowledgements

The Authors acknowledge the Ph.D. School in Preclinical and Clinical Pharmacology, University of Catania, Catania; the Co.Ri.Bi.A. Consortium, Palermo; Regione Siciliana, Assessorato per l'Agricoltura for their generous support.

References

- Pauwels EK, Erba PA, Kostkiewicz M: **Antioxidants: A tale of two stories.** *Drug News Perspect* 2007, **20(9)**:579-585.
- Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J: **Free radicals and antioxidants in normal physiological functions and human disease.** *Int J Biochem Cell Biol* 2007, **39(1)**:44-84.
- Mancuso C, Bates TE, Butterfield DA, Calafato S, Cornelius C, De Lorenzo A, Dinkova Kostova AT, Calabrese V: **Natural antioxidants in Alzheimer's disease.** *Expert Opin Investig Drugs* 2007, **16(12)**:1921-1931.
- Whitton PS: **Inflammation as a causative factor in the aetiology of Parkinson's disease.** *Br J Pharmacol* 2007, **150(8)**:963-976.
- Ramassamy C: **Emerging role of polyphenolic compounds in the treatment of neurodegenerative diseases: a review of their intracellular targets.** *Eur J Pharmacol* 2006, **545(1)**:51-64.
- Pham DQ, Plakogiannis R: **Vitamin E supplementation in Alzheimer's disease, Parkinson's disease, tardive dyskinesia, and cataract: Part 2.** *Ann Pharmacother* 2005, **39(12)**:2065-2072.
- Drisko JA: **The use of antioxidants in transmissible spongiform encephalopathies: a case report.** *J Am Coll Nutr* 2002, **21(1)**:22-25.
- Fang Y, Yang S, Wu G: **Free radicals, antioxidants and nutrition.** *Nutrition* 2002, **18(10)**:872.
- The Alpha-Tocopherol Beta Carotene Cancer Prevention Study Group: **The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers.** *N Engl J Med* 1994, **330**:1029-1035.
- Valko M, Rhodes CJ, Moncol J, Izakovic M, Mazur M: **Free radicals, metals and antioxidants in oxidative stress-induced cancer.** *Chem Biol Interact* 2006, **160(1)**:1-40.
- Mancuso C, Scapagnini G, Curro D, Giuffrida Stella AM, De Marco C, Butterfield DA, Calabrese V: **Mitochondrial dysfunction, free radical generation and cellular stress response in neurodegenerative disorders.** *Front Biosci* 2007, **12**:1107-1123.
- Mancuso C, Pani G, Calabrese V: **Bilirubin: an endogenous scavenger of nitric oxide and reactive nitrogen species.** *Redox Rep* 2006, **11(5)**:207-213.
- Mancuso C, Bonsignore A, Capone C, Di Stasio E, Pani G: **Albumin-bound bilirubin interacts with nitric oxide by a redox mechanism.** *Antioxid Redox Signal* 2006, **8(3-4)**:487-494.
- Mancuso C, Bonsignore A, Di Stasio E, Mordente A, Motterlini R: **Bilirubin and S-nitrosothiols interaction: evidence for a possible role of bilirubin as a scavenger of nitric oxide.** *Biochem Pharmacol* 2003, **66(12)**:2355-2363.
- Grune T, Berger MM: **Markers of oxidative stress in ICU clinical settings: present and future.** *Curr Opin Clin Nutr Metab Care* 2007.
- Gouni-Berthold I, Sachinidis A: **Possible non-classic intracellular and molecular mechanisms of LDL cholesterol action contributing to the development and progression of atherosclerosis.** *Curr Vasc Pharmacol* 2004, **2(4)**:363-370.
- Bedogni B, Pani G, Colavitti R, Riccio A, Borrello S, Murphy M, Smith R, Eboli ML, Galeotti T: **Redox regulation of cAMP-responsive element-binding protein and induction of manganese superoxide dismutase in nerve growth factor-dependent cell survival.** *J Biol Chem* 2003, **278**:16510-16519.
- Finkel T: **Oxidant signals and oxidative stress.** *Curr Opin Cell Biol* 2003, **15(2)**:247-254.
- Colavitti R, Pani G, Bedogni B, Anzevino R, Borrello S, Waltenberger J, Galeotti T: **Reactive oxygen species as downstream mediators of angiogenic signaling by vascular endothelial growth factor receptor-2/KDR.** *J Biol Chem* 2002, **277**:3101-3108.
- Pani G, Colavitti R, Bedogni B, Anzevino R, Borrello S, Galeotti T: **A redox signaling mechanism for density-dependent inhibition of cell growth.** *J Biol Chem* 2000, **275**:38891-38899.
- Pani G, Colavitti R, Borrello S, Galeotti T: **Endogenous oxygen radicals modulate protein tyrosine phosphorylation and JNK-1 activation in lectin-stimulated thymocytes.** *Biochem J* 2000, **347**:173-181.
- Schulze-Osthoff K, Beyaert R, Vandevorode V, Haegeman G, Fiers W: **Depletion of the mitochondrial electron transport abrogates the cytotoxic and gene-inductive effects of TNF.** *EMBO J* 1993, **12**:3095-3104.
- Jabs T: **Reactive oxygen intermediates as mediators of programmed cell death in plants and animals.** *Biochem Pharmacol* 1999, **57**:231-245.
- Hawkins BJ, Madesh M, Kirkpatrick CJ, Fisher AB: **Superoxide flux in endothelial cells via the chloride channel-3 mediates intracellular signaling.** *Mol Biol Cell* 2007, **18(6)**:2002-2012.
- Bubici C, Papa S, Dean K, Franzoso G: **Mutual cross-talk between reactive oxygen species and nuclear factor-kappa B: molecular basis and biological significance.** *Oncogene* 2006, **25(51)**:6731-6748.
- Cakir Y, Ballinger SW: **Reactive species-mediated regulation of cell signaling and the cell cycle: the role of MAPK.** *Antioxid Redox Signal* 2005, **7(5-6)**:726-740.
- Suhara T, Fukuo K, Sugimoto T, Morimoto S, Nakahashi T, Hata S, Shimizu M, Ogihara T: **Hydrogen peroxide induces up-regulation of Fas in human endothelial cells.** *J Immunol* 1998, **160**:4042-4047.
- Weber ML, Weigand MA, Giaisi M, Suss D, Treiber MK, Baumann S, Ritsou E, Breitkreutz R, Krammer PH: **Vitamin E inhibits CD95 ligand expression and protects T cell from activation-induced cell death.** *J Clin Invest* 2002, **110**:681-690.
- Haendeler JH, Zeiher AM, Dimmeler S: **Vitamin C and E prevent lipopolysaccharide-induced apoptosis in human endothelial cells by modulation of Bcl-2 and Bax.** *Eur J Pharmacol* 1996, **317**:407-411.
- Fialkow L, Wang Y, Downey GP: **Reactive oxygen and nitrogen species as signaling molecules regulating neutrophil function.** *Free Radic Biol Med* 2007, **42(2)**:153-164.
- Behe P, Segal AV: **The function of the NADPH oxidase of phagocytes, and its relationship to other NOXs.** *Biochem Soc Trans* 2007, **35(Pt 5)**:1100-1103.
- Malle E, Furtmüller PG, Sattler W, Obinger C: **Myeloperoxidase: a target for new drug development?** *Br J Pharmacol* 2007, **152(6)**:838-854.
- Messner MC, Albert CJ, Hsu FF, Ford DA: **Selective plasmenylcholine oxidation by hypochlorous acid: formation of lysophosphatidylcholine chlorohydrins.** *Chem Phys Lipids* 2006, **144(1)**:34-44.
- Shen Z, Wu W, Hazen SL: **Activated leukocytes oxidatively damage DNA, RNA, and the nucleotide pool through halide-dependent formation of hydroxyl radical.** *Biochemistry* 2000, **39(18)**:5474-5482.
- Winterbourn CC, Berg JJ van den, Roitman E, Kuypers FA: **Chlorohydrin formation from unsaturated fatty acids reacted with hypochlorous acid.** *Arch Biochem Biophys* 1992, **296(2)**:547-555.
- Rice WG, Weiss SJ: **Regulation of proteolysis at the neutrophil-substrate interface by secretory leukoprotease inhibitor.** *Science* 1990, **249(4965)**:178-181.
- Weiss SJ: **Tissue destruction by neutrophils.** *N Engl J Med* 1989, **320**:365.
- Bendich A: **Vitamin E and immune functions.** *Basic Life Sci* 1988, **49**:615-620.
- Lopez-Hellin J, Garcia-Arumi E, Schwartz S: **Oxidative stress induces age-dependent changes in lymphocyte protein synthesis and second messenger levels.** *Life Sci* 1998, **63(1)**:13-21.

40. Wintergerst ES, Maggini S, Hornig DH: **Contribution of selected vitamins and trace elements to immune function.** *Ann Nutr Metab* 2007, **51(4)**:301-23.
41. Meydani SN, Meydani M, Blumberg JB, Leka LS, Siber G, Loszewski R, Thompson C, Pedrosa MC, Diamond RD, Stollar BD: **Vitamin E supplementation and in vivo immune response in healthy elderly subjects. A randomised controlled trial.** *JAMA* 1997, **277(17)**:1380-1386.
42. De la Fuente M, Hernanz A, Vallejo MC: **The immune system in the oxidative stress conditions of aging and hypertension: favorable effects of antioxidants and physical exercise.** *Antioxid Redox Signal* 2005, **7(9-10)**:1356-1366.
43. De la Fuente M: **Effects of antioxidants on immune system ageing.** *Eur J Clin Nutr* 2002, **56(Suppl 3)**:5-8.
44. Zelenay S, Moraes Fontes MF, Fesel C, Demengeot J, Coutinho A: **Physiopathology of natural auto-antibodies: the case for regulation.** *J Autoimmun* 2007, **29(4)**:229-235.
45. Pasic S, Micic D, Kuzmanovic M: **Epstein-Barr virus-associated haemophagocytic lymphohistiocytosis in Wiskott-Aldrich syndrome.** *Acta Paediatr* 2003, **92(7)**:859-861.
46. Stejskal J, Stejskal VD: **The role of metals in autoimmunity and the link to neuroendocrinology.** *Neuro Endocrinol Lett* 1999, **20(6)**:351-364.
47. Bressler JP, Olivi L, Cheong JH, Kim Y, Maerten A, Bannon D: **Metal transporters in intestine and brain: their involvement in metal-associated neurotoxicities.** *Hum Exp Toxicol* 2007, **26(3)**:221-229.
48. Yokel RA: **Blood-brain barrier flux of aluminum, manganese, iron and other metals suspected to contribute to metal-induced neurodegeneration.** *J Alzheimers Dis* 2006, **10(2-3)**:223-253.
49. Galaris D, Pantopoulos K: **Oxidative stress and iron homeostasis: mechanistic and health aspects.** *Crit Rev Clin Lab Sci* 2008, **45(1)**:1-23.
50. Wright RO, Baccarelli A: **Metals and neurotoxicology.** *J Nutr* 2007, **137(12)**:2809-2813.
51. Donnelly PS, Xiao Z, Wedd AG: **Copper and Alzheimer's disease.** *Curr Opin Chem Biol* 2007, **11(2)**:128-133.
52. Finkelstein Y, Milatovic D, Aschner M: **Modulation of cholinergic systems by manganese.** *Neurotoxicology* 2007, **28(5)**:1003-1014.
53. Valko M, Morris H, Cronin MB: **Metals, toxicity and oxidative stress.** *Curr Med Chem* 2005, **12(10)**:1161-1208.
54. Havarinasab S, Hultman P: **Organic mercury compounds and autoimmunity.** *Autoimmun Rev* 2005, **4(5)**:270-275.
55. HogenEsch H: **Mechanisms of stimulation of the immune response by aluminum adjuvants.** *Vaccine* 2002, **20(Suppl 3)**:34-39.
56. Casciola-Rosen L, Wigley F, Rosen A: **Scleroderma autoantigens are uniquely fragmented by metal-catalyzed oxidation reactions: implications for pathogenesis.** *J Exp Med* 1997, **185(1)**:71-79.
57. Rosen A, Casciola-Rosen L, Wigley F: **Role of metal-catalyzed oxidation reactions in the early pathogenesis of scleroderma.** *Curr Opin Rheumatol* 1997, **9(6)**:538-543.
58. Wu Z, Turner DR, Oliveira DB: **Antioxidants inhibit mercuric chloride-induced early vasculitis.** *Int Immunol* 2002, **14(3)**:267-273.
59. Ehrenfeld M, Blank M, Shoenfeld Y, Hidvegi M: **AVEMAR (a new benzoquinone-containing natural product) administration interferes with the Th2 response in experimental SLE and promotes amelioration of the disease.** *Lupus* 2001, **10(9)**:622-627.
60. Comin-Anduix B, Boros LG, Marin S, Boren J, Callol-Massot C, Centelles JJ, Torres JL, Agell N, Bassilian S, Cascante M: **Fermented wheat germ extract inhibits glycolysis/pentose cycle enzymes and induces apoptosis through poly(ADP-ribose) polymerase activation in Jurkat T-cell leukemia tumor cells.** *J Biol Chem* 2002, **277(48)**:46408-46414.
61. Hidvégi M, Ráso E, Tömösközi-Farkas R, Paku S, Lapis K, Szende B: **Effect of Avemar and Avemar + vitamin C on tumor growth and metastasis in experimental animals.** *Anticancer Res* 1998, **18(4A)**:2353-2358.
62. Masuda T, Inaba Y, Maekawa T, Takeda Y, Tamura H, Yamaguchi H: **Recovery mechanism of the antioxidant activity from carnosic acid quinone, an oxidized sage and rosemary antioxidant.** *J Agric Food Chem* 2002, **50(21)**:5863-5869.
63. Knedla A, Neumann E, Müller-Ladner U: **Developments in the synovial biology field 2006.** *Arthritis Res Ther* 2007, **9(2)**:209.
64. Hu F, Sun WW, Zhao XT, Cui ZJ, Yang WX: **TRPV1 mediates cell death in rat synovial fibroblasts through calcium entry-dependent ROS production and mitochondrial depolarization.** *Biochem Biophys Res Commun* 2008, **16;369(4)**:989-93.
65. Cedergren J, Forslund T, Sundqvist T, Skogh T: **Intracellular oxidative activation in synovial fluid neutrophils from patients with rheumatoid arthritis but not from other arthritis patients.** *J Rheumatol* 2007, **34(11)**:2162-2170.
66. van Vugt RM, Rijken PJ, Rietveld AG, van Vugt AC, Dijkmans BA: **Antioxidant intervention in rheumatoid arthritis: results of an open pilot study.** *Clin Rheumatol* 2008, **27(6)**:771-775.
67. Helmy M, Shohayeb M, Helmy MH, el-Bassiouni EA: **Antioxidants as adjuvant therapy in rheumatoid disease. A preliminary study.** *Arzneimittelforschung* 2001, **51(4)**:293-298.
68. Dianzani U, Chiochetti A, Ramenghi U: **Role of inherited defects decreasing Fas function in autoimmunity.** *Life Sci* 2003, **72(25)**:2803-2824.
69. Calabrese V, Mancuso C, Sapienza M, Puleo E, Calafato S, Cornelius C, Finocchiaro M, Mangiameli A, Di Mauro M, Stella AM, Castellino P: **Oxidative stress and cellular stress response in diabetic nephropathy.** *Cell Stress Chaperones* 2007, **12(4)**:299-306.
70. Calabrese V, Sultana R, Scapagnini G, Guagliano E, Sapienza M, Bella R, Kanski J, Pennisi G, Mancuso C, Stella AM, Butterfield DA: **Nitrosative stress, cellular stress response, and thiol homeostasis in patients with Alzheimer's disease.** *Antioxid Redox Signal* 2006, **8(11-12)**:1975-1986.
71. Mancuso C, Perluigi M, Cini C, De Marco C, Giuffrida Stella AM, Calabrese V: **Heme oxygenase and cyclooxygenase in the central nervous system: a functional interplay.** *J Neurosci Res* 2006, **84(7)**:1385-1391.
72. Mancuso C: **Heme oxygenase and its products in the nervous system.** *Antioxid Redox Signal* **6(5)**:878-887.
73. Oliveira V, Agua-Doce A, Duarte J, Soares MP, Graca L: **Regulatory T cell maintenance of dominant tolerance: induction of tissue self-defense?** *Transpl Immunol* 2006, **17(1)**:7-10.
74. Brusko TM, Wasserfall CH, Agarwal A, Kapturczak MH, Atkinson MA: **An integral role for heme oxygenase-1 and carbon monoxide in maintaining peripheral tolerance by CD4+CD25+ regulatory T cells.** *J Immunol* 2005, **174(9)**:5181-5186.
75. Scapagnini G, Colombrita C, Amadio M, D'Agata V, Arcelli E, Sapienza M, Quattrone A, Calabrese V: **Curcumin activates defensive genes and protects neurons against oxidative stress.** *Antioxid Redox Signal* 2006, **8(3-4)**:395-403.
76. Scapagnini G, Foresti R, Calabrese V, Giuffrida Stella AM, Green CJ, Motterlini R: **Caffeic acid phenethyl ester and curcumin: a novel class of heme oxygenase-1 inducers.** *Mol Pharmacol* 2002, **61(3)**:554-561.
77. Ames BN: **Micronutrients prevent cancer and delay aging.** *Toxicol Letters* 1998, **102**:103-105.
78. Liu RH: **Potential synergy of phytochemicals in cancer prevention: mechanism of action.** *J Nutr* 2004, **134(Suppl 12)**:3479S-3485S.
79. Owen RV, Haubner R, Wurtele G, Hull E, Spiegelhalter B, Bartsch H: **Olives and olive oil in cancer prevention.** *Eur J Cancer Prev* 2004, **13(4)**:319-326.
80. McCall MR, Frei B: **Can antioxidant vitamins materially reduce oxidative damage in humans?** *Free Rad Biol Med* 1999, **26**:1034-1053.
81. Villamor E, Fawzi WW: **Effects of vitamin A supplementation on immune responses and correlation with clinical outcomes.** *Clin Microbiol Rev* 2005, **18(3)**:446-464.
82. Chew BP, Park JS: **Carotenoid action on the immune response.** *J Nutr* 2004, **134(1)**:257S-261S.
83. Stephensen CB: **Vitamin A, infection, and immune function.** *Annu Rev Nutr* 2001, **21**:167-192.
84. Giray B, Kan E, Bali M, Hincal F, Basaran N: **The effect of vitamin E supplementation on antioxidant enzyme activities and lipid peroxidation levels in hemodialysis patients.** *Clin Chim Acta* 2003, **338(1-2)**:91-98.
85. Neuhouser ML, Patterson RE, Thornquist MD, Omenn GS, King IB, Goodman GE: **Fruits and vegetables are associated with lower lung cancer risk only in the placebo arm of the beta-carotene and retinol efficacy trial (CARET).** *Cancer Epidemiol Biomarkers Prev* 2003, **12(4)**:350-358.

86. Blot WJ, Li JY, Taylor PR, Guo W, Dawsey S, Wang GQ, Yang CS, Zheng SF, Gail M, Li GY: **Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population.** *J Natl Cancer Inst* 1993, **85(18)**:1483-1492.
87. Omenn GS: **Chemoprevention of lung cancers: lessons from CARET, the beta-carotene and retinol efficacy trial, and prospects for the future.** *Eur J Cancer Prev* 2007, **16(3)**:184-191.
88. Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, Glass A, Keogh JP, Meyskens FL Jr, Valanis B, Williams JH Jr, Barnhart S, Cherniack MG, Brodtkin CA, Hammar S: **Risk factors for lung cancer and for intervention effects in CARET, the Beta-Carotene and Retinol Efficacy Trial.** *J Natl Cancer Inst* 1996, **88(21)**:1550-1559.
89. Bardia A, Tleyjeh IM, Cerhan JR, Sood AK, Limburg PJ, Erwin PJ, Montori VM: **Efficacy of antioxidant supplementation in reducing primary cancer incidence and mortality: systematic review and meta-analysis.** *Mayo Clin Proc* 2008, **83(1)**:23-34.
90. Slatore CG, Littman AJ, Au DH, Satia JA, White E: **Long-term use of supplemental multivitamins, vitamin C, vitamin E, and folate does not reduce the risk of lung cancer.** *Am J Respir Crit Care Med* **177(5)**:524-30. 2008 Mar 1
91. Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C: **Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis.** *JAMA* **297(8)**:842-57. 2007 Feb 28
92. Anonymous: **The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group.** *N Engl J Med* 1994, **330(15)**:1029-1035.
93. Palozza P, Serini S, Di Nicuolo F, Calviello G: **Mitogenic and apoptotic signaling by carotenoids: involvement of a redox mechanism.** *IUBMB Life* 2001, **52(1-2)**:77-81.
94. Palozza P, Serini S, Di Nicuolo F, Boninsegna A, Torsello A, Maggiano N, Ranalletti FO, Wolf FI, Calviello G, Cittadini A: **beta-Carotene exacerbates DNA oxidative damage and modifies p53-related pathways of cell proliferation and apoptosis in cultured cells exposed to tobacco smoke condensate.** *Carcinogenesis* 2004, **25(8)**:1315-1325.
95. Baker DL, Krol ES, Jacobsen N, Liebler DC: **Reactions of beta-carotene with cigarette smoke oxidants. Identification of carotenoid oxidation products and evaluation of the prooxidant/antioxidant effect.** *Chem Res Toxicol* 1999, **12(6)**:535-543.
96. Palozza P, Serini S, Currò D, Calviello G, Igarashi K, Mancuso C: **beta-Carotene and cigarette smoke condensate regulate heme oxygenase-1 and its repressor factor Bach1: relationship with cell growth.** *Antioxid Redox Signal* 2006, **8(5-6)**:1069-1080.
97. Li L, Grenard P, Nhieu JT, Julien B, Mallat A, Habib A, Lotersztajn S: **Heme oxygenase-1 is an antifibrogenic protein in human hepatic myofibroblasts.** *Gastroenterology* 2003, **125(2)**:460-469.
98. Peyton KJ, Reyna SV, Chapman GB, Ensenat D, Liu XM, Wang H, Schafer AJ, Durante WV: **Heme oxygenase-1-derived carbon monoxide is an autocrine inhibitor of vascular smooth muscle cell growth.** *Blood* 2002, **99(12)**:4443-4448.
99. Song R, Mahidhara RS, Liu F, Ning W, Otterbein LE, Choi AM: **Carbon monoxide inhibits human airway smooth muscle cell proliferation via mitogen-activated protein kinase pathway.** *Am J Respir Cell Mol Biol* 2002, **27(5)**:603-610.
100. Ollinger R, Bilban M, Erat A, Froio A, McDaid J, Tyagi S, Csizmadia E, Graça-Souza AV, Liloia A, Soares MP, Otterbein LE, Ushveva A, Yamashita K, Bach FH: **Bilirubin: a natural inhibitor of vascular smooth muscle cell proliferation.** *Circulation* 2005, **112(7)**:1030-1039.
101. Anonymous: **Vitamin E supplementation enhances immune response in the elderly.** *Nutr Rev* 1992, **50(3)**:85-87.
102. Sayre LM, Perry G, Smith MA: **Oxidative stress and neurotoxicity.** *Chem Res Toxicol* 2008, **21(1)**:172-188.
103. Calabrese V, Mancuso C, Calvani M, Rizzarelli E, Butterfield DA, Stella AM: **Nitric oxide in the central nervous system: neuroprotection versus neurotoxicity.** *Nat Rev Neurosci* 2007, **8(10)**:766-775.
104. Calabrese V, Mancuso C, Ravagna A, Perluigi M, Cini C, De Marco C, Butterfield DA, Stella AM: **In vivo induction of heat shock proteins in the substantia nigra following L-DOPA administration is associated with increased activity of mitochondrial complex I and nitrosative stress in rats: regulation by glutathione redox state.** *J Neurochem* 2007, **101(3)**:709-717.
105. Cassan C, Liblau RS: **Immune tolerance and control of CNS autoimmunity: from animal models to MS patients.** *J Neurochem* 2007, **100(4)**:883-892.
106. McFarland HF, Martin R: **Multiple sclerosis: a complicated picture of autoimmunity.** *Nat Immunol* 2007, **8(9)**:913-919.
107. Castegna A, Aksenov M, Aksenova M, Thongboonkerd V, Klein JB, Pierce WM, Booze R, Markesbery WR, Butterfield DA: **Proteomic identification of oxidatively modified proteins in Alzheimer's disease brain. Part I: creatine kinase BB, glutamine synthase, and ubiquitin carboxy-terminal hydrolase L-1.** *Free Radic Biol Med* 2002, **33(4)**:562-571.
108. Castegna A, Thongboonkerd V, Klein JB, Lynn B, Markesbery WR, Butterfield DA: **Proteomic identification of nitrated proteins in Alzheimer's disease brain.** *J Neurochem* 2003, **85(6)**:1394-1401.
109. Butterfield DA, Reed T, Perluigi M, De Marco C, Coccia R, Cini C, Sultana R: **Elevated protein-bound levels of the lipid peroxidation product, 4-hydroxy-2-nonenal, in brain from persons with mild cognitive impairment.** *Neurosci Lett* 2006, **397(3)**:170-173.
110. Bizzozero OA, DeJesus G, Callahan K, Pastuszyn A: **Elevated protein carbonylation in the brain white matter and gray matter of patients with multiple sclerosis.** *J Neurosci Res* 2005, **81(5)**:687-695.
111. Floor E, Wetzel MG: **Increased protein oxidation in human substantia nigra pars compacta in comparison with basal ganglia and prefrontal cortex measured with an improved dinitrophenylhydrazine assay.** *J Neurochem* 1998, **70(1)**:268-275.
112. Yoritaka A, Hattori N, Uchida K, Tanaka M, Stadtman ER, Mizuno Y: **Immunohistochemical detection of 4-hydroxynonenal protein adducts in Parkinson disease.** *Proc Natl Acad Sci USA* 1996, **93(7)**:2696-2701.
113. Zhang J, Perry G, Smith MA, Robertson D, Olson SJ, Graham DG, Montine TJ: **Parkinson's disease is associated with oxidative damage to cytoplasmic DNA and RNA in substantia nigra neurons.** *Am J Pathol* 1999, **154(5)**:1423-1429.
114. Calabrese V, Guagliano E, Sapienza M, Panebianco M, Calafato S, Puleo E, Pennisi G, Mancuso C, Butterfield DA, Stella AG: **Redox regulation of cellular stress response in aging and neurodegenerative disorders: role of vitagenes.** *Neurochem Res* 2007, **32(4-5)**:757-773.
115. Araujo DM, Lapchak PA: **Induction of immune system mediators in the hippocampal formation in Alzheimer's and Parkinson's diseases: selective effects on specific interleukins and interleukin receptors.** *Neuroscience* 1994, **61(4)**:745-754.
116. Ringheim GE, Conant K: **Neurodegenerative disease and the neuroimmune axis (Alzheimer's and Parkinson's disease, and viral infections).** *J Neuroimmunol* 2004, **147(1-2)**:43-49.
117. McGeer PL, Schulzer M, McGeer EG: **Arthritis and anti-inflammatory agents as possible protective factors for Alzheimer's disease: a review of 17 epidemiologic studies.** *Neurology* 1996, **47(2)**:425-432.
118. Calabrese V, Butterfield DA, Stella AM: **Nutritional antioxidants and the heme oxygenase pathway of stress tolerance: novel targets for neuroprotection in Alzheimer's disease.** *Ital J Biochem* 2003, **52(4)**:177-181.
119. Butterfield D, Castegna A, Pocernich C, Drake J, Scapagnini G, Calabrese V: **Nutritional approaches to combat oxidative stress in Alzheimer's disease.** *J Nutr Biochem* 2002, **13(8)**:444.
120. Reines SA, Block GA, Morris JC, Liu G, Nessly ML, Lines CR, Norman BA, Baranak CC, Rofecoxib Protocol 091 Study Group: **Rofecoxib: no effect on Alzheimer's disease in a 1-year, randomized, blinded, controlled study.** *Neurology* 2004, **62(1)**:66-71.
121. Aisen PS, Schafer KA, Grundman M, Pfeiffer E, Sano M, Davis KL, Farlow MR, Jin S, Thomas RG, Thal LJ: **Alzheimer's Disease Cooperative Study. Effects of rofecoxib or naproxen vs placebo on Alzheimer disease progression: a randomized controlled trial.** *JAMA* 2003, **289(21)**:2819-2826.
122. Neary D, Snowden JS, Mann DM: **Cognitive change in motor neuron disease/amyotrophic lateral sclerosis (MND/ALS).** *J Neurol Sci* 2000, **180(1-2)**:15-20.
123. Kiernan JA, Hudson AJ: **Changes in sizes of cortical and lower motor neurons in amyotrophic lateral sclerosis.** *Brain* 1991, **114(Pt 2)**:843-853.

124. Roberts BR, Tainer JA, Getzoff ED, Malencik DA, Anderson SR, Bomben VC, Meyers KR, Karplus PA, Beckman JS: **Structural characterization of zinc-deficient human superoxide dismutase and implications for ALS.** *J Mol Biol* 2007, **373(4)**:877-890.
125. Kong J, Xu Z: **Massive mitochondrial degeneration in motor neurons triggers the onset of amyotrophic lateral sclerosis in mice expressing a mutant SOD1.** *J Neurosci* 1998, **18(9)**:3241-3250.
126. Desnuelle C, Dib M, Garrel C, Favier A: **A double-blind, placebo-controlled randomized clinical trial of alpha-tocopherol (vitamin E) in the treatment of amyotrophic lateral sclerosis. ALS riluzole-tocopherol Study Group.** *Amyotroph Lateral Scler Other Motor Neuron Disord* 2001, **2(1)**:9-18.
127. Benatar M: **Lost in translation: treatment trials in the SOD1 mouse and in human ALS.** *Neurobiol Dis* 2007, **26(1)**:1-13.
128. Orrell RW: **AEOL-10150 (Aeolus).** *Curr Opin Investig Drugs* 2006, **7(1)**:70-80.

Publish with **BioMed Central** and every scientist can read your work free of charge

"BioMed Central will be the most significant development for disseminating the results of biomedical research in our lifetime."

Sir Paul Nurse, Cancer Research UK

Your research papers will be:

- available free of charge to the entire biomedical community
- peer reviewed and published immediately upon acceptance
- cited in PubMed and archived on PubMed Central
- yours — you keep the copyright

Submit your manuscript here:
http://www.biomedcentral.com/info/publishing_adv.asp

