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Editorial

Mechanisms involved in oxidative stress regulation

Reactive oxygen species (ROS) are produced constantly in living organisms as a result of aerobic processes. Under physiological conditions, the production of ROS is low and is related to physiological cell procedures as, for example, ROS can act like signaling molecules. However, under pathological situations, ROS production is significantly increased, and as a result, adverse impact and toxic effects can result. Thus, each organism has a defense system against ROS production. This system includes antioxidant molecules and antioxidant enzymes. The antioxidant molecules can be either produced endogenously or received through the diet. When, however, ROS production is increased and the organism's antioxidative defense is impaired, then oxidative stress appears. Oxidative stress is the result of the redox deficiency in the organism and can cause damage to biomolecules, such as DNA, lipids and/or proteins.

The current issue includes topics that cover diseases related to toxic effects caused by oxidative stress and studies investigating the confrontation of the oxidative stress-induced toxic effects either through antioxidant supplementation and/or exercise. Increased oxidative stress is observed in a number of diseases, such as those related to immune system disorders. For example, allergic contact dermatitis is an important occupational and environmental disease caused by topical exposure to chemical allergens (Corsini et al.). It has been suggested that oxidative stress may cause allergic contact dermatitis, as it leads to the activation of transcription factors and signalling pathways, including NF-kB and p38 MAPK, which, in turn, lead to the release of cytokines and chemokines. ROS also are involved in the activation of the NLRP3/NALP3 inflammasome, which is required to direct the proteolytic maturation of inflammatory cytokines such as IL-1β and IL-18, which are all integral to the process of dendritic cells mobilization, migration and functional maturation. Some other diseases that correlate oxidative stress with immune system disturbances are sarcoidosis and idiopathic pulmonary fibrosis (IPF) (Malli et al.). Sarcoidosis and IPF both are associated with deregulated inflammatory mechanisms partially triggered by aggravated oxidative stress. Serum 8-isoprostane levels, a marker of oxidative stress-induced pulmonary diseases, increased in patient groups of both sarcoidosis and IPF diseases compared to controls. Therefore, one could hypothesize that regulating oxidative stress levels may have protective effects in the clinical course of these diseases. Oxidative stress also has an active role during sepsis evolution (Karapetsa et al.). Oxidative stress markers in plasma and erythrocyte lysate were assessed in the 1st, 3rd, 5th and 8th day after sepsis appearance and at sepsis resolution in patients with severe septic shock. Patients were divided into two groups: survivors and non-survivors. A longstanding antioxidant deficiency in non-surviving patients was noted, while in surviving patients there was a reduction of oxidative stress over time. This phenomenon was clearly prominent in patientś erythrocytes.

Except to different diseases, oxidative stress occurs when the organism comes into contact with different xenobiotics that cause toxicity. For example, much interest has been shown in the pesticides' toxic action in relation to oxidative stress. Thus, exposure to anticholinesterase pesticides decreased the activity of the antioxidant enzyme paraoxonase and the levels of the endogenous antioxidant urate, whereas long-term pesticide exposure showed an association with increased paraoxonase activity (Hernandez et al.). Thus, it has been suggested that pesticide exposure may affect plasma antioxidant potential. Also, cypermethrin, a type II synthetic pyrethroid insecticide, produced mild signs of toxicity in buffalo calves (Kaur et al.). There was also a marked increase in various markers of oxidative stress, including the activity of certain antioxidant enzymes. These changes were higher in dermally exposed animals than oral administration. Thus, it has been suggested that oxidative stress is an important mechanism involved in cypermethrin-induced toxicity and the oxidative insult produced by dermal route is more severe as compared to oral intoxication. Atrazine is an herbicide that has toxic effects on animals. Atrazine treatment caused changes in selected oxidative stress parameters and detoxifying system in zebrafish (Blahová et al.). Subchronic exposure to atrazine showed increased production of ROS leading to oxidative damage to lipids and changes in antioxidant capacity and in detoxifying system. Moreover, administration of anabolics such as turinabol and methanabol may influence cardiac mass and oxidative stress markers in young rabbits (Germanakis et al.). In both anabolic steroids, the low dose had no significant effects on the oxidative stress markers monitored, while the high dose created a hostile oxidative environment. Another drug, hydroxylamine sulphate, has been shown to cause hepatotoxicity and hematotoxicity associated with oxidative stress (Prodanchuk et al.). Moreover, carbon tetrachloride (CCl_4), another toxic molecule, produces ROS in brain tissue of rats (Lavrentiadou et al.). Carbon tetrachloride-treated Wistar rats exhibited elevated brain tissue plasminogen activator (t-PA) activity.

However, administration of antioxidant molecules such as vitamin E, oregano and rosemary decreased CCl4-induced t-PA activity in brain. Consequently, antioxidants may protect against neuronal cell death and brain damage. Antioxidant supplementation has been proposed for protection against oxidative stress and diseases associated with oxidative stress. Plant polyphenols are largely studied for their beneficial action in various pathologies, but a correlation with their effects on cell membranes is still elusive. The polyphenols quercetin, epigallocatechin gallate and curcumin had beneficial effects on cell membranes altered in diabetic conditions, by restoring transmembrane potential and by

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membrane "stiffening" (Ionescu et al.; Margina et al.). Moreover, they limited the release of pro-inflammatory factors, like monocyte chemotactic protein-1. These effects were more obvious in cells exposed to advanced glycation end products specific at the late stages of diabetes. Apparently, the inhibitory activity of polyphenols on lipid peroxidation was associated with a decrease of membrane fluidity.

Cancer is a multifactorial disease that has also been associated with oxidative stress, since increased production of free radicals have been observed in cancer tissues and cell lines derived from cancer tissues. Antioxidants recruited from the diet can interact with free radicals to neutralize and limit ROS-induced detrimental effects. Thus, it was shown that antioxidant molecules can inhibit the growth of cancer cells through various mechanisms. Specifically, six herbal infusions rich in antioxidants, *Cretan marjoram*, pink savory, oregano, mountain tea, pennyroyal and chamomile, have been reported to have anticarcinogenic effect as a result of their ability to scavenge free radicals, inhibit proliferation, decrease IL-8 levels and regulate nuclear factor-kappa B in epithelial colon cancer (HT29) and prostate (PC3) cancer cells (Kogiannou et al.). Interestingly, grape extract known for its antioxidant activity (Apostolou et al.) has been shown to inhibit cancer cell growth by exerting pro-oxidant activity (Raina et al.). Thus, grape seed extract (GSE) caused a significant inhibitory effect on cell viability of bladder cancer cell lines T24 and HTB29, which were apoptotic in nature, suggesting its effectiveness against this deadly malignancy. Detailed *in vitro* studies established that GSE generated oxidative stress triggering an apoptotic response, as indicated by the reversal of GSE-mediated apoptosis, when the cells were pre-treated with antioxidants prior to GSE. Furthermore, administration of curcumin to rats, another polyphenol, protected from oxidative stress and cholestasis-induced injuries in the liver and kidney tissues (Tokaç et al.). Another antioxidant, pycnogenol (PYC), has been found to have antioxidant activity and protective effects against H_2O_2-induced chromosome breakage and loss and DNA damage in cultured human lymphocytes (Taner et al.). Lipoic acid, another common antioxidant, has beneficial effects on redox status of adults with G6PD deficiency (Georgakouli et al.). Interestingly, it has been shown to improve the oxidative markers not only in adults with G6PD deficiency but also in control group. Another natural polyphenolic compound, resveratrol, has been shown to exert beneficial effects against cardiovascular and cerebrovascular diseases attributed basically to its antioxidant properties (Carrizzo et al.).

Apart from receiving antioxidants, chronic aerobic exercise like nordic walking or resistance exercise training, has been shown to decrease oxidative stress and atherogenic index of plasma (AIP), prevalence of metabolic syndrome (MetS) and MetS score in middle-aged men with impaired glucose regulation (IGR) (Venojärvi et al.). Moreover, a 3-week high-intensity interval training (HIT) regimen attenuated oxidative stress and up-regulated antioxidant activity after only nine training sessions, further supporting its positive effect, not only on physical conditioning, but also on health promotion (Bogdanis et al.). However, concerning the exercise of athletes with high performance, things are different, because they maintain a heavy training program throughout the year. Thus, in elite female water polo players, blood biomarkers of redox status, oxidative stress, inflammation and angiogenesis were studied over the course of a competitive season (Varamenti et al.). The findings indicated that oxidative stress and inflammation varies over the season in elite female water polo athletes and this information might be used to apply remedies for optimizing athletic performance and accelerating training recovery. It has also been studied how the administration of antioxidants could affect the levels of oxidative stress and muscle damage induced by exercise. Anaerobically trained athletes with elevated lactate dehydrogenase (LDH) and creatinine phosphokinase (CPK) baseline levels, received tomato juice containing the antioxidant phytochemical lycopene replacing carbohydrate supplementation beverages commonly used during training for over a two-month period (Tsitsimpikou et al.). Tomato juice administration significantly reduced LDH, CPK, homocysteine and C-reactive protein levels. Moreover, the beneficial effects of resveratrol supplementation have been demonstrated in endurance running (Hart et al.). It was found that resveratrol supplementation enhances aerobic performance due to the activation of the AMPK-SIRT1-PGC-1α pathway.

This special issue of Food and Chemical Toxicology consists of 27 articles of original contribution and 3 reviews. The issue provides new findings regarding the toxic mechanisms through which oxidative stress induces certain diseases as well as the protective effects of antioxidant supplementation and exercise against oxidative stress-induced conditions.

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