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*Editorial*

# The Role of Natural and Synthetic Antioxidants in Modulating Oxidative Stress in Drug-Induced Injury and Metabolic Disorders 2020

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Oxidative stress is an imbalance in cellular redox reactions that plays a key role in the pathogenesis of metabolic disorders and drug-induced injury. Oxidative stress is the result of reactive oxygen species (ROS) overproduction or a decline in antioxidant defense mechanisms. Although ROS production can be beneficial in some instances as they are used by the immune system, in general, excessive generation of ROS results in deleterious effects causing damage to DNA, proteins, and lipids, ultimately leading to cell death. Several diseases, including cancer, neurodegeneration, obesity, metabolic syndrome, diabetes mellitus, liver disease, and others, are well-known to be associated with excessive ROS production. Therefore, agents counteracting excess ROS and/or boosting the antioxidant defenses represent an appealing strategy for the treatment of multiple diseases.

Antioxidant substances could be natural or synthetic. Natural antioxidants are obtained entirely from natural sources and have been used in food, cosmetics, and pharmaceutical industries for some time. On the other hand, synthetic antioxidants are substances created from chemical processes. The current understanding of the complex role of ROS in physiological and pathological processes points to the necessity of developing multifunctional antioxidants, which can maintain oxidative homeostasis, both in health and in disease. In this context, numerous research groups focus on the characterization and application of natural antioxidant agents in different diseases. In addition, a great deal of effort is being conducted to design and synthesize free radical scavenging and antioxidant substances that can diminish excessive ROS production and improve the endogenous antioxidant defenses. Understanding and validating the biological activities of natural and synthetic antioxidant compounds and their molecular mechanisms in counteracting ROS and oxidative stress will provide a solid scientific foundation to the application of antioxidants in the prevention and treatment of multiple diseases.

This special issue encompasses 12 research articles focusing on the usefulness of antioxidants as novel therapeutic approaches to prevent and fight different disease conditions, including phototoxicity, drug-induced liver injury, autoimmune encephalomyelitis, nonalcoholic fatty liver disease, and hypoxia-induced cardiomyocyte injury. The guest editors are pleased to present a compendium of these cutting-edge original research articles as follows:

*Research article*: "Gender difference on the effect of omega-3 polyunsaturated fatty acids on acetaminophen-induced acute liver failure". In this article, Y. Liu et al. investigated the effect of n-3 polyunsaturated fatty acids (PUFAs) on acetaminophen-(APAP-) induced liver damage in male and female *fat-1* mice. The results revealed the sex-differential effect of n-3 PUFA on APAP-induced liver injury in mice. $\beta$-Catenin-mediated

regulation of autophagy represented the essential event for the n-3 PUFA-modulated APAP hepatotoxicity.

*Research article*: "Metabolomic analysis of the ameliorative effect of enhanced proline metabolism on hypoxia-induced injury in cardiomyocytes". Based on previous cardiovascular metabolomics studies showing severe altered proline metabolism after cardiomyocyte hypoxia, J. Wang et al. investigated the ameliorative effect of enhancing proline metabolism by overexpressing proline dehydrogenase (PRODH) on hypoxia-induced injury in cardiomyocytes. The results demonstrated that PRODH was downregulated after myocardial infarction and hypoxia and overexpression of this enzyme reduced ROS and apoptosis levels, an effect that was associated with significant changes in sphingolipid signaling pathways, glutathione disulfide, unsaturated fatty acid biosynthesis, phosphocreatine, aminoacyl-tRNA biosynthesis, and ABC transporters.

*Research article*: "Phloroglucinol strengthens the antioxidant barrier and reduces oxidative/nitrosative stress in nonalcoholic fatty liver disease (NAFLD)". K. Drygalski et al. reported that NAFLD and hydrogen peroxide models are comparable and suitable for assessing hepatic oxidative/nitrosative stress. The results showed that phloroglucinol is an effective nutraceutical in counteracting NAFLD, and its effectiveness is comparable with $\alpha$-lipoic acid and N-acetylcysteine.

*Research article*: "Ascorbic acid: a new player of epigenetic regulation in LPS-*gingivalis* treated human periodontal ligament stem cells". Periodontal disease is an infectious disease that can lead to the progressive destruction of the periodontal ligament tissue as well as bone and tooth loss. In this study, G. Marconi et al. investigated the effects of ascorbic acid in primary culture of human periodontal ligament stem cells (hPDLSCs) exposed to *Porphyromonas gingivalis* lipopolysaccharide (LPS-G). Ascorbic acid exerted a protective effect against oxidative stress and inflammation and modulated miR-210 in an *in vitro* periodontitis model.

*Research article*: "Preclinical evaluation of safety, pharmacokinetics, efficacy, and mechanism of radioprotective agent HL-003". In this study, Y. Liu et al. evaluated the antioxidant and radioprotective properties of the small molecule amifostine derivative HL-003. This compound showed a radical-scavenging activity *in vitro* and exerted protective effect against radiation-induced intestinal injury by promoting the proliferation, differentiation, and regeneration of the intestinal epithelium, protecting DNA from radiation damage, and inhibiting apoptosis in mice.

*Research article*: "Inhibition of calcium oxalate formation and antioxidant activity of carboxymethylated *Poria cocos* polysaccharides". C. Li et al. obtained three carboxymethylated *Poria cocos* polysaccharides through carboxymethylation of the original polysaccharide and studied their antioxidant activity *in vitro*. The carboxymethylated polysaccharides prevented oxalate-induced oxidative damage in human kidney proximal tubular epithelial cells by inhibiting excessive generation of ROS and DNA damage.

*Research article*: "Bu Shen Yi Sui capsule alleviates neuroinflammation and demyelination by promoting microglia toward M2 polarization, which correlates with changes in miR-124 and miR-155 in experimental autoimmune encephalomyelitis". Z. Zha et al. examined the effects of Bu Shen Yi Sui (BSYS) on microglial polarization in mice with experimental autoimmune encephalomyelitis (EAE). The results revealed that BSYS regulated the inflammatory factors, ameliorated neurological function, and suppressed demyelination by promoting M2 polarization of microglia, effects that were correlated with the changes of miR-124 and miR-155 *in vivo*.

*Research article*: "Melatonin alleviates the toxicity of high nicotinamide concentrations in oocytes: potential interaction with nicotinamide methylation signaling". In this study, M. El-Sheikh et al. reported that the administration of melatonin during *in vitro* maturation can protect bovine oocytes against high nicotinamide-induced excess ROS production, DNA damage, and mitochondrial dysfunction. These findings might be attributed to a potential involvement of melatonin in regulating nicotinamide hypermethylation signaling.

*Research article*: "Pharmacological activation of Nrf2 by rosolic acid attenuates endoplasmic reticulum stress in endothelial cells". K. Amin et al. contributed a research article showing that rosolic acid treatment dose-dependently activates Nrf2 and attenuates endoplasmic reticulum stress in endothelial cells stimulated with thapsigargin.

*Research article*: "Comparative studies on the hepatoprotective effect of white and coloured rice bran oil against acetaminophen-induced oxidative stress in mice through antioxidant- and xenobiotic-metabolizing systems". In this study, W. Phannasorn et al. compared the phytoconstituents and antioxidant properties of white rice bran oil (WRBO) and coloured rice bran oil (CRBO) and tested their hepatoprotective effect in APAP-treated mice. CRBO exhibited greater antioxidant potential and attenuated APAP hepatotoxicity induced through enhancement of antioxidants and modulation of APAP metabolism.

*Research article*: "Maternal probiotic or synbiotic supplementation modulates jejunal and colonic antioxidant capacity, mitochondrial function, and microbial abundance in Bama mini-piglets". K. Wang et al. investigated the role of maternal probiotic or symbiotic, supplemented during gestation and lactation, on redox homeostasis, mitochondrial function, and intestinal microbiota in offspring weaned piglets. The study concluded that maternal probiotic or synbiotic supplementation improves the antioxidant capacity and mitochondrial function of weaned piglets by altering the intestinal microbiota.

*Research article*: "Red ginseng oil attenuates oxidative stress and offers protection against ultraviolet-induced photo toxicity". Owing to the beneficial therapeutic effects of ginseng, H.M. Arif Ullah et al. investigated the protective effect of red ginseng extract (RGE) and red ginseng oil (RGO) against APAP hepatotoxicity in mice. Besides, their *in vitro* radical-scavenging efficacies, RGE, and RGO ameliorated liver function markers and DNA oxidative damage in APAP-intoxicated mice. RGO protected 3T3 cells against UV irradiation-induced injury.

The editors anticipate this special issue to be of interest to the readers and expect researchers to benefit in making

further progress in understanding the mechanisms underlying the therapeutic potential of natural and synthetic antioxidants in different diseases.

## Conflicts of Interest

The editors declare that they have no conflicts of interest regarding the publication of this special issue.

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