

Symposium “อนุมูลอิสระและสารต้านออกซิเดชันในการเกิดและการป้องกันโรค และเสริมสุขภาพ”

## Roles of Free Radicals in Health and Diseases with Special Reference to Cancer

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All aerobic organisms are evolved with cellular respiration using molecular oxygen as final electron acceptor, where mitochondria are the powerhouse generating high energy phosphate compounds, ATP. The inevitable electron leakage from the electron transport chain in mitochondria is one of major sources of reactive oxygen species (ROS) formed in the cell. ROS is also generated by other systems including NADPH oxidases (NOXs), xanthine oxidases (dehydrogenase) and etc. The ROS formation is not simply the waste products from cellular metabolism, but in many conditions it is purposefully formed to serve many special functions, for instances, for defending invading microorganisms in phagocytic cells, and importantly serving as intracellular signaling molecules. In contrast, uncontrolled formation of ROS produces deleterious effects on biomolecules such as lipid peroxidation, protein oxidation and DNA damage which lead to cell dysfunction and cell death. A number of diseases are associated with oxidative stress, such as, cardiovascular disease, diabetes, metabolic syndrome, ageing and various neurodegenerative disorder and cancer. The double edged roles of ROS are finely modulated by cellular antioxidant systems, where Nrf2-ARE (nuclear factor erythroid 2-related factor 2 – antioxidant response element) signaling pathway plays prominent role in

regulating ROS and redox homeostasis. Nrf2-ARE signaling functions as stress sensor and responses by upregulation of variety of antioxidant, cytoprotective and xenobiotic metabolizing genes as an adaptive survival response. A number of phytochemical products, for instances, curcumin, sulforaphane, luteolin and isothiocyanates, exert cardioprotective and cancer chemopreventive effects through activation of Nrf2-ARE system. On the other hand, not only normal cells employ Nrf2-ARE to protect themselves, some cancer cells also evolve to exploit this system for their own cytoprotection and their very existence of immortality. Modulation of cellular ROS and redox homeostasis is a current fascinating research area where it involves with numerous health aspects.

**Key words:** Reactive oxygen species, Free radical, Cellular signal transduction, Nrf2, Antioxidant, Cytoprotection, Phytochemical

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### Roles of Oxidants and Antioxidants in Health and Diseases of the Brain

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Although many evidences suggest that reactive oxygen species (ROS) are involved in a number of diseases, they are also acting as mediators of several normal physiological processes such as regulating the vascular tone by smooth muscle relaxation and inflammatory response. In the brain, ROS, including NO and H<sub>2</sub>O<sub>2</sub>, have roles in modulating synaptic and non-synaptic communication between neurons and glia. In addition, ROS could modify the myelin basic protein in the brain and induce synaptic long-term potentiation which is a form of activity dependent synaptic plasticity and memory consolidation. However, with excessive, activated ROS, the results of membrane damage, changes cell structure and function, lipids denaturation, and structural damage to DNA could be seen. The brain is an organ that especially susceptible to the damaging effects of ROS, since the brain, is a major oxygen metabolizer (produce more ROS) and has relatively

inadequate protective antioxidant mechanisms. Thus, many neurodegenerative disorders (including Alzheimer's disease, Parkinson's disease, and stroke-related brain damage), neuropsychiatric disorders (including depression and bipolar disorder) and developmental disorders (including autism) are suggested to be linked to oxidative stress. Many studies now highlighted the importance of antioxidative defenses in those brain disorders. Although it is still unclear whether these responses are beneficial, antioxidants could probe pathological pathways associated with neurodegeneration and psychiatric disorders.

**Key words:** Reactive oxygen species, Antioxidants, Brain functions, Brain disorders





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# Oxidative Stress and Endothelial dysfunction in Metabolic Syndrome and Cardiovascular Diseases

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Metabolic syndrome (MetS) is characterized by a cluster of cardiovascular risk factors, including central obesity, hyperglycemia, dyslipidemia and hypertension, which are highly associated with increased morbidity and mortality of cardiovascular diseases (CVD). MetS has become a serious public health problem as prevalence and incidence are increasing along with the worldwide rise in rates of obesity and sedentary lifestyles. A growing body of evidence suggests that increased oxidative stress to adipocytes is central to the pathogenesis of CVD in MetS. Excessive oxidative stress to adipocytes causes dysregulated expression of inflammation-related adipocytokines in MetS, which contributes to obesity-associated vasculopathy and cardiovascular risk primarily through endothelial dysfunction. Impaired endothelial nitric oxide synthase (eNOS) activity as well as enhanced the production of reactive oxygen species (ROS) results in diminished nitric oxide (NO) bioavailability and the consequent pro-atherogenic alterations. Additionally, intrinsic properties of the injured endothelium result in vasoconstriction, smooth

cell proliferation, coagulation disorders, leukocyte aggregation, thrombosis, and vascular inflammation predisposing to atherosclerosis. The most important vascular superoxide anion sources include the nicotinamide dinucleotide phosphate (NADPH) oxidase (NOX), xanthine oxidase, mitochondria, and NOS uncoupling. Thereby, reduction of oxidative stress in the vascular tissue should be, in general, beneficial to not only vascular function, but also to the prognosis of patients with MetS and CVD. In line with this concept, attention has been focused on strategies that enhance the removal of ROS using either antioxidants or drugs that enhance endogenous antioxidant defense, thereby reducing oxidative stress related to MetS and lessening the cardiovascular risk.

**Key words:** Antioxidants, Cardiovascular diseases, Endothelial dysfunction, Metabolic syndrome, Nitric oxide, Oxidative stress, Reactive oxygen species





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## The Role of Antioxidants in the Inhibition of Photoaging: Studies of Phytochemicals as Promising Photoprotective Agents

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Photodamage of the skin caused by ultraviolet radiation (UVR) is implicated in pathogenesis of skin aging, which has become crucial dermatological problems affecting quality of life and caused high cost of skin care in Thailand. Biological responses of the skin to UV irradiation, which are the hallmarks of skin aging, include dyspigmentation caused by abnormal melanogenesis, cell death, and activated matrix metalloproteinase-1 (MMP-1), a major proteolytic enzyme which is contributed to collagen degradation. UVR-mediated stimulation of tyrosinase, the key and the rate-limiting enzyme of melanin synthesis, in melanocytes can cause hyperpigmentation in aging skin. Additionally, induction of MMP-1 expression and activities by UVR in keratinocytes and/or fibroblasts leads to a progressive loss of the skin's physiological and structural integrity. Oxidative stress induced by UVA has been proposed to play an important role in premature aging of the skin. Thus, enhancing capacity of antioxidant defenses including glutathione (GSH)-related enzymes such as  $\gamma$ -glutamate cysteine ligase ( $\gamma$ -GCL) and glutathione S-transferases (GST) to counteract oxidative stress would represent a promising strategy for inhibition of photoaged skin. Natural and synthetic antioxidants including phenolic compounds have gained remarkable attention as potential photoprotective agents, although redox mechanisms at the molecular level underlying their inhibitory effects against photodamaged

skin remain unclear. Phytochemicals including antioxidant phenolics, in particular, caffeic acid (CA), ferulic acid (FA) and gallic acid (GA), have been identified as common active ingredients in several medicinal herbs. In order to develop natural products possessing antioxidant properties as effective photoprotective agents against skin aging, we have explored antioxidant mechanisms by which phytochemicals inhibit UVA-mediated melanogenesis in B16 melanoma cells and MMP-1 upregulation in keratinocyte HaCaT cells. Our findings showed that all testing phenolic compounds inhibited induction of melanogenesis and MMP-1 in association with enhancement of antioxidant defense system including cellular GSH and antioxidant enzymes in irradiated cells. Our study suggests that upregulation of endogenous antioxidants could be the mechanism by which phytochemical phenolics suppressed UVA-stimulated hyperpigmentation and MMP-1 expression. Upregulation of antioxidant defense system by natural products would thus represent a promising opportunity for development of prototypical photoprotective agents for inhibition of premature skin aging.

**Key words:** Photoaging, ultraviolet, melanocytes, keratinocyte,  $\gamma$ -glutamate cysteine ligase, glutathione, phytochemicals