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Chapter 1

Introductory Chapter: Basics of Free Radicals and Antioxidants

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Additional information is available at the end of the chapter

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1. Historical Aspect

Do you know the scientist who had discovered the free radical? It was a stunning Professor of Chemistry named Moses Gomberg in 1900 at Michigan State University. In June 25, 2000, after a century the discovery was commemorated by the American Chemical Society as a National Historic Chemical Landmark in a ceremony at the University of Michigan, Michigan [1]. Earlier evidence by a British Chemist Fenton also suggests that hydrogen peroxide which reacts with ferrous sulfate results in violet color which is nothing but oxidation of tartaric acid upon addition of alkali. This is the basis of production of hydroxyl radical, and the reaction is called as Fenton reaction [2].

2. Free Radicals

The most common definition of free radicals is "molecules or molecular fragments containing one or more unpaired electrons in atomic or molecular orbitals" [3]. Free radicals are uncharged, very reactive, and short-lived molecules. Human beings contain 10,000–20,000 free radicals which attack each and individual cell of our body. Many of these radicals are beneficial in that they work for immune cells responsible for killing bacterial cells and toning of smooth muscles, which in turn regulate the normal working of blood vessels and internal organs. Uncontrolled generation of free radicals in our body may lead to various ill effects such as autoimmune diseases, heart and neurodegenerative diseases, cancers, etc. [4].

Now, coming to their very existence, one should know the basics. The free radicals are produced during ATP generation through mitochondria. They are generally divided into two

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well-known entities: reactive oxygen species (ROS) and reactive nitrogen species (RNS). ROS and RNS collectively form all the radical and non-radical (oxidants) entities. Radicals are more reactive and less stable than their non-radical counterparts. Non-radical derivatives or oxidants can be easily converted into free radicals by various reactions in living organisms [5].

Oxidative phosphorylation occurring in mitochondria is a nonenzymatic process which results in the production of ROS and RNS. For example, excess generation of hydroxyl radical and peroxynitrite causes damage to cell membranes and lipoproteins, and the process referred to as lipid peroxidation. This results in the formation of mutagenic and cytotoxic compounds such as malondialdehyde (MDA) and other diene derivatives. ROS/RNS affects proteins which may lead to the loss of enzyme activity and structural deformity. These species attack DNA, thus affecting the functional growth and formation of oxidative lesions which can lead to mutagenesis. The body has various enzymes and antioxidants to combat the damage incurred by oxidative stress [6, 7].

3. Antioxidants

Antioxidants are chemicals that bind with free radicals and nullify their effect from causing damage to biological molecules. Endogenous antioxidants are produced by our body which is used to combat various free radicals. However, most of them are obtained from external sources, primarily through diet called as exogenous antioxidants or dietary antioxidants. Major sources of this class of antioxidants are brightly colored vegetables, fruits, and grains. Other very effective sources are berries, green tea, and dark chocolate. Nowadays, many oral supplements are available in the market labeled as dietary antioxidants.

Antioxidants bind with free radical by giving up their own electrons. These results in the termination of oxidative chain reactions, and the free radicals are no longer able to attack the cell. Antioxidant attains free radical state after donating its electron. It can accommodate the change in electrons without becoming reactive, and that's why they are not harmful. There are two lines of antioxidant defense inside the cell. Vitamin E, beta-carotene, and coenzyme Q constitute the first line which is found in the fat-soluble cell membrane. Vitamin E is considered as the most potent chain-breaking antioxidant within the cell membrane. The water-soluble antioxidant is present inside the cell. These are vitamin C, superoxide dismutase (SOD), glutathione peroxidase, and catalase [8].

4. Role in Diseases

Despite the antagonistic role played by various antioxidants, the free radical damage has been implicated in various degenerative conditions such as cardiovascular diseases, neurological disorders, diabetes, ischemia-reperfusion injury, and aging. These diseases may be divided into two groups: (i) the first group includes cancer and diabetes which occurs due to impairing glucose tolerance in which the condition is better known as "mitochondrial oxidative stress" and (ii) the second group is characterized by inflammatory oxidative conditions leading to atherosclerosis

and chronic inflammation. Aging is also a form of the deleterious effect of free radical damage (protein oxidation, lipid peroxidation). Mutation of DNA is a crucial step in carcinogenesis, and elevated levels of DNA lesions are found in many tumors, strongly correlating the oxidative damage in the etiology of cancer. ROS-induced changes are found in various diseases of the heart such as cardiomyopathies, ischemic heart disease, hypertension, atherosclerosis, and heart failure [9].

Free radicals induced cell damage that is found in many autoimmune diseases. Oxidative injury and inflammatory status were proven by raised levels of isoprostanes and prostaglandins in serum and synovial fluid compared to controls [10]. Increased oxidative stress has been proposed as one of the major factors causing hyperglycemia which in turn trigger various diabetic conditions [11]. Oxidative damage advances with age, and this is the reason that it is considered as one of the causative factors in various neurological disorders such as Alzheimer's and Parkinson's diseases [4].

5. Book Overview

In this book, we have tried to incorporate themes and concepts which eventually give the insights into the role of antioxidants in combating various disorders caused by free radical damage. In one of the chapter the author discusses the unique property of essential oil extracted from *Coleus zeylanicus* using the bioautography technique. It reveals the antimicrobial and antioxidant properties of oil from *Coleus zeylanicus* which further increases upon exposure to salinity stress condition.

A novel concept of immune-spin trapping combined with molecular magnetic resonance imaging is also explored in this book. This would give the readers an insight to detect free radicals *in vivo* formed in different tissues. Various therapeutic agents can also be traced to their role in free radical generation and quenching.

The very motive of including a chapter on ethnic aspects of oxidative stress-induced TIDM is that the racial variability was not studied and there is no conclusive evidence about lipid peroxidation and antioxidant defense system in patients of a region. Their comparative study recommends a highly significant approach to this aspect.

Scavenging effect of dimethylformamide (DMF) in cerebral ischemia (CI) is also analyzed. The results and discussion will lead to future research and more clinical trials to establish DMF as an antioxidant in CI.

The role of physical exercise on oxidative stress and vascular diseases is reviewed extensively. Generation of oxidants and simultaneously antioxidants during physical exercise which is in turn responsible for its prevention is summarized.

The recent findings in free radical-induced damage in aging and how antioxidants are employed as an anti-aging agent in the preclinical model are discussed in the book. This would give an idea of their therapeutic potential. Micro-RNAs (miRNAs) are the novel regulators of gene expressions which induce aging process. In the chapter of miRNAs in the regulation of hyperglycemia-induced oxidative stress and cellular senescence, authors explain the critical role of miRNAs in age-related disorders which could open the front of new findings in geriatrics.

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