The Modulation of Beneficial and/or Harmful Effects of Free Oxygen Radicals in the Context of Molecular Mechanisms Regarding Drug – PART I

Gjumrakch Aliev¹,²,³,⁴,*

¹Sechenov First Moscow State Medical University (Sechenov University), 8-2, Sechenov, Russia; ²Institute of Physiologically Active Compounds Russian Academy of Sciences, Chernogolovka, 142432, Russia; ³Research Institute of Human Morphology, Tsyurupy Street, Moscow, 117418, Russia; ⁴GALLY International Research Institute, 7733 Louis Pasteur Drive, #330, San Antonio, TX 78229, USA

Abstract: This special issue of Current Topic in Medicinal Chemistry (CTMC) covers outcomes and ideas for future molecular modifications leading to the novel derivatives with better constructive pharmacological potential for treatment of the different human disorders but also may considering anatomical features of the underlying tissues, and non-chemical based treatment strategies.

Reactive oxygen species (ROS) are key mediators of cell biology and its over-production enhances oxidative damage of macromolecules involved in prevalent chronic diseases. In the last decade, an increasing number of studies have demonstrated the involvement of ROS in a number of disorders especially during the development and maturation of cardio- and cerebrovascular diseases, diabetes, inflammation, neurodegeneration, and cancer. Moreover, it has been reported that antioxidant agents in different sources such as fruits and medicinal plants reduce harmful ROS levels by several complementary effects including free oxidative radical concentration, prevention of lipid peroxidation, chelation of metal ions, and inhibition of oxidative chain reactions.

In the past several years, the field of free radical biology, medicinal chemistry, clinical science, and pharmacology has received tremendous attention. ROS, especially intermediate products of ROS such as reactive nitrogen species (RNS) and their derivatives are continuously generated by tissues and cells through various endogenous systems, including their anatomical position and exposure to different physiochemical conditions, and/or pathological states. In addition, intermediate products of ROS such as reactive oxygen species (RONS) are also produced as metabolic by products in almost all diseases. Over-generation of RONS within living cells are due to the mitochondrial electron transport system, NADH oxidase, and cytochrome P450; which all play a pivotal role during the development of human diseases where cell differentiation, mutation, transformation, normal cell homeostasis and signaling pathway interruption occurs. The accumulating bodies of evidence and ongoing research have gained enormous attention due to their widespread application in the diverse fields of biology and medicine including the pathogenesis and new treatment strategies against neurodegeneration, metabolic disorders and cancer treatment, wound healing, sterilization of surfaces, and blood coagulation. Oxidative stress, arising as a result of an imbalance between ROS or called unwanted free radicals production and impairment on the antioxidant defenses, is associated with damage to a wide range of molecular species including lipids, proteins nucleic acids and DNA.

This special issue attempted to put together the latest basic and clinical research on the potential biological application of chronic ROS induced tissues and cells damage that initiates and then becomes a permanent failure of normal tissues and cell homeostasis where those outcomes manifest as disease. This includes research on ROS induced oxidative stress within biological systems and applications to prevent as well as treat various diseases to improve metabolic activities and immune function, leading to cellular survival and cellular longevity with and without drug intervention. Moreover, articles are included with describe how increases in cellular antioxidant levels act as free radical scavengers in the intracellular and extracellular environment to lower ROS levels and relieve oxidative stress by modulations of internal defense mechanisms without external pharmacological interventions. Future determination of how free radicals effect interruption of cellular homeostasis during the development and maturation of neurodegenerative diseases, cancer and others that opens new ways of not only expanding current knowledge about human diseases but also the implications of different strategies for the discovery of targeted therapies. Finally new and modern techniques including atomic force microscopy, gene expression visualization, anatomical features of the brain are also able to bring new information to make better targets for the pharmacological and nonpharmacological interventions in the near future.

*Address correspondence to this author at the GALLY International Research Institute, San Antonio, TX 78229, USA; Tel: +1-440-263-7461; +7-964-493-1515; E-mails: aliev03@gmail.com, cobalt55@gallyinternational.com
Viswanadha Vijaya Padma groups (Prasath Manogaran, Narasimha Murthy Beeraka, Viswanadha Vijaya Padma) [1] present a critical analysis on the cytotoxic protective and anti-cancer potential of bisbenzylisoquinoline alkaloids from *Nelumbo nucifera*. Natural product therapy has been gaining therapeutic importance against various diseases including cancer. The failure of chemotherapy due to its associated adverse effects promoted adjunct therapy with natural products. Phytochemicals exert anticarcinogenic activities through regulation of various cell signaling pathways such as cell survival, inflammation, apoptosis, autophagy, and metastasis. The ‘small molecule–chemosensitizing agents’ from plants induce apoptosis in drug-resistant and host-immune resistant cancer cells in *in vitro* as well as *in vivo* models. For example, alkaloids from *Nelumbo nucifera*, *liensinine*, *isoliensinine*, and *neferine* exert antancer activity through enhanced ROS generation, activation of MAP kinases, followed by induction of autophagy and apoptotic cell death. Likewise, these alkaloids also exert their cytotoxic action against cerebrovascular stroke/ischemic stroke, diabetes, and chemotherapy-induced cytotoxicity. Therefore, the present review elucidates the pharmacological activities of these bisbenzylisoquinoline alkaloids which include the cytotoxic, anticancer, and chemosensitizing activities against various diseases such as cardiovascular disease, neurological disease and cancer.

Maria JE Visser and Etheresis Pretorius [2] summarized recent events using Atomic Force Microscopy for the Characterization of Amyloid Protein Structure in Pathology. It has been widely reported that proteins are versatile macromolecules that perform a variety of functions and participate in virtually all cellular processes. The functionality of a protein greatly depends on its structure and alterations may result in the development of disease states. Most well-known of these are protein misfolding disorders such as include Alzheimer’s and Parkinson’s diseases as well as type 2 diabetes mellitus where soluble proteins transition into insoluble amyloid fibrils. Atomic force microscopy (AFM) is capable of providing a topographical map of proteins of interest and/or its aggregates, as well as probing the nanomechanical properties of a sample. Moreover, AFM requires relatively simple sample preparation, which presents the possibility of combining this technique with other research modalities, such as confocal laser scanning microscopy, Raman spectroscopy and stimulated emission depletion microscopy. In this review, Maria JE Visser and Etheresis Pretorius discussed the basic principles of AFM, followed by a brief overview of how it has been applied in biological research. The focus of the review is specifically on AFM as a characterization method to study protein structure at the nanoscale in pathophysiological conditions, considering both molecules implicated in disease pathogenesis and the plasma protein fibrinogen. In conclusion, AFM is a user-friendly tool that supplies multiparametric data, rendering it a most valuable technique.

Glioblastoma is a highly aggressive and invasive brain tumor. Targeting glioblastoma stem cells has become one of hottest areas in cancer research with potential implications as a new and successful treatment option. The review presented by V. Tarasov and co-workers [3] determined the feasibility of targeting glioblastoma stem cells from concept to clinical trials based on the critical analysis of the recent literature. This study shows that current treatment options do not prolong overall survival significantly because the disease is highly prone to relapse. Therefore, research to find new therapies are of paramount importance. It was discovered that glioblastomas contain a population of cells with stem-like properties and that these cells may be responsible for tumor recurrence. This group also discussed potential treatment strategies to target cancer stem cells in glioblastoma with the focus on clinical perspectives. Several fundamental issues related to the research are highlighted as well.

Breast plastic surgery is a rapidly evolving field in medicine. The modern view of surgical trends reflects the desire to minimize complications and introduce advanced technologies, which always will be priorities for surgeons. Reconstructive surgery, a branch of plastic surgery focusing on restoration of lost functional and aesthetic component, seeks to enhance psychological rehabilitation and improve quality of life, as well as aesthetic recovery. The review entitled “The use of fibrin-based tissue adhesives for breast in reconstructive and plastic surgery” by Kuo Chen and co-investigator [4] addresses the action of fibrin agents and their effects on the quality of surgical homeostasis. As described by Kuo Chen and coworkers, the fundamental goals for the surgeon are to perform a minimally traumatic intervention and to prevent any form of complication. Achieving complete homeostasis is an intraoperative necessity. Timely prevention of bleeding and hemorrhagic phenomena can affect not only the outcome of the operation, but also the incidence of postoperative complications. Topics include the integrity of microvascular anastomosis, tissue adhesion, and the incidence of seromas and hematomas associated with fibrin glue usage. The literature on fibrin adhesives with respect to prevention of postoperative complications, and the effectiveness with active drainage also are analyzed.

Our knowledge regarding structural features of different tissues especially the brain still has many unknowns. Paper presented by Vladimir N. Nikolenko and co-workers [5] attempted to put together all of available literature sources regarding anatomical features of the Posterior Perforated Substance: a Brain Mystery Wrapped in an Enigma. There is a dearth of published information on the posterior perforated substance as compared to the anterior perforated substance. This group managed to glean facts about the posterior perforated substance that can serve as a landmark for surgical operations as well as future drug targets in the adjacent regions of the midbrain and the vessels passing through it. Moreover, posterior perforated substance contains the interpeduncular nucleus responsible for the mental state of the individual. This article helps 1) to describe the topography of the blood vessels supplying the posterior perforated substance area from the surgical point of view; and 2) to investigate the functions of the interpeduncular nucleus. This group assembled and analyzed results from source databases by Elsevier, NCBI MedLine, Scopus, Research Scholar, Google, and Embase. Each article was analyzed in detail for practically useful information about the posterior perforated substance. Critical analysis showed that the P1-segment perforating branches of the posterior cerebral artery supply the posterior perforated substance. This area is especially vulnerable in the case of cerebrovascular pathologies such as stroke, neurodegenerative diseases and vascular dementia. The posterior communicating artery can block the surgeon’s view and impede maneuverability of the tool in the area of the posterior perforated substance, which may
be addressed using the separation technique, which can lead to positive results. In addition, the medial habenula-interpeduncular nucleus in the posterior perforated substance is associated with various addictions and psychiatric conditions. Therefore the posterior perforated substance area is of great interest for surgical intervention. Future studies of the interpeduncular nucleus inform the development of drugs to affect different types of dependencies and some mental, neurodegenerative and cerebrovascular disorders.

Report by Iván Carrera, Olaia Martínez and Ramón Cacabelos [6] summarized recent evidence regarding possible neuroprotection with natural antioxidants and nutraceuticals in the context of brain cell degeneration, especially using the epigenetic connection pathway. Bioactive antioxidants present in selected plants are known to provide the first line of biological defense against oxidative stress. In particular, soluble vitamin C, E, carotenoids and phenolic compounds have demonstrated crucial biological effects in cells against oxidative damage, preventing prevalent chronic diseases, such as diabetes, cancer and cardiovascular disease. The reported wide range of effects include anti-aging, anti-atherosclerosis, anti-inflammatory and anticancer activity are now studied against degenerative pathologies of the brain. In order to explore the potential antioxidant sources in functional foods and nutraceuticals against neurodegeneration, the present review highlights oxidant sources in functional foods and nutraceuticals against neurodegeneration providing a comprehensive assessment of antioxidant activity at chemical and cellular levels. The effects of the different bioactive compounds and their antioxidant activity through an epigenetic point of view are also discussed.

The diverse topics which are highlighted in the current issue of the CTMC are able to provide new information regarding our knowledge in the context of cancer, chronic inflammation, neurodegeneration, ROP, and also a new way of understanding disease pathophysiology and affording more successful treatment options in the near future.

ACKNOWLEDGEMENTS

This research was supported within the framework of the grant provided by CSP Ministry of the Health Russian Federation, and by the IPAC RAS State Targets Project # 0090-2019-0005; the Russian Academic Excellence Project “5-100” for the Sechenov University, in Moscow, Russia, also provided support for the research.

REFERENCES