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Foreword

**DEVELOPMENT OF THE RESEARCH
OF ANTIOXIDANT DEFENSE SYSTEM IN SERBIA
RAZVOJ ISTRAŽIVANJA ANTIOKSIDACIONE ZAŠTITE U SRBIJI**

Radoslav V. ŽIKIĆ and Zorica S. SAIČIĆ

Faculty of Sciences, Kragujevac
Institute for Biological Research “Siniša Stanković”, Beograd,
Serbia and Montenegro

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INTRODUCTION

Appearance of free oxygen and aerobic way of life on the planet enabled the organisms to use significantly higher quantities of energy in comparison to exclusively anaerobic way of life in the past. It was the driving force of evolution and the living beings, first those who lived in water, directed themselves to expansive development, both in the number of species and biomasses. Gradual increase of the quantity of oxygen in the atmosphere enabled the formation of ozone protective layer and the layer became efficient enough 540 million years ago and enabled the living beings to move to the land and accommodate to completely different ecological environmental conditions. This was a new and extremely turbulent stage in the evolution of living beings. However, oxygen did not only contributed the progress of the evolution, but together with its metabolically products, i.e. **reactive oxygen species (ROS)** caused different kinds of damages in cells, tissues and organs, in that way, it caused structural and functional disorders,

such as diseases and death. That was a high price that aerobic organisms had to “pay” for the energetic “comfort” they got. The dangers that the living beings encountered after the formation of oxygen, can be called the first ecological catastrophe. A great number of organisms could not survive, while the others continually developed a complex **antioxidant defense system (AOS)** which consists of enzymatic and non enzymatic components. Due to the evolutionary development of defense mechanisms, aerobic organisms were able to use oxygen as a final acceptor of electrons and to protect themselves from both its harmful effects and its reactive metabolites.

Antioxidant defense system efficiency in eliminating toxic reactive oxygen species is a basis for a normal functioning of every aerobic organism. However, due to ageing and other disorders, antioxidant defense system becomes less efficient and initial disorders develop into diseases and ultimately death. The question is: can antioxidant defense system enables the survival of aerobic forms of life in the biodiversity in conditions of different way of life and global environmental pollution.

Living organisms form a variety of reactive species, not only of oxygen, but also of other chemical elements (N) and molecules. They also, have a significant role in the functioning of biological systems. The disturbed balance between reactive oxygen species formation and other elements reactive forms formation on one side and the formation of antioxidant defense systems on the other side, cause oxidative stress (HALLIWELL and GUTTERIDGE, 1999). Oxidative stress causes development of a variety of potential damages, intensifies the process of ageing and the development of different diseases and death of organisms (SIES, 1991; SCOTT, 1995).

Lately, scientists have been more and more aware of the role of reactive species in cell differentiation, signal transfer, metabolism regulation and intercellular communication. It has become clear, that the effects of reactive species are more complex than cell, tissue and organ damages. Discovery that nitrogen-oxide NO acts as a neurotransmitter, vasodilatator and molecule with specific roles in the immune system, made these hypotheses more acceptable.

Discovery of “erythrocuprein” which was isolated from human erythrocytes in 1964. years, proved its role in eliminating superoxide anion radicals. Since then, scientists have intensively investigated this phenomenon all over the world and the results have been published in a large number of works, more than 5000 a year (MCCORD and FRIDOVICH, 1969). In that way, many questions on the function and regulation of antioxidant defense system in aerobic organisms have been solved. It was determined that many elements acting in the mechanisms of antioxidant defense system are similar to and sometimes identical with elements of detoxification system.

INVESTIGATION OF REACTIVE OXYGEN SPECIES AND ANTIOXIDANT DEFENSE SYSTEM IN SERBIA

First investigations of reactive oxygen species were carried out on the Department of Physiology (the former name was Department of Endocrinology and Metabolism) on the Institute for Biological Research "Siniša Stanković" in Belgrade. Academician VOJSLAV M. PETROVIĆ conducted the department. Dr TATJANA IVANOVNA GUDZ, who worked at Institute of Biophysics "Lomonosov" University in Moscow, visited the Institute and significantly contributed the initiation of ROS and AOS investigation, and connected them with the metabolism of thyroid hormones and catecholamine. Academician VOJSLAV M. PETROVIĆ's laboratory investigated the problems for many years. First, internationally accepted researches in this area were published in 1981. year (PETROVIĆ, V. M., GUDZ, T. I. and SAIČIĆ, Z. S.) and in 1982. year (PETROVIĆ, V. M., SPASIĆ, M.B., SAIČIĆ, Z.S., MILIĆ, B. and RADOJIČIĆ, R. M.). Later on, they widened investigations to all AOS components. The results were very attractive to international and domestic scientists, and according to SCI (Science Citation Index), they were cited a lot and that was a basis for cooperation with other scientific teams.

Investigation of the position and role of free radicals and free-radical reactions signal transfer, metabolism regulation: assessment of their connection to current problems of toxicology and pharmacology, as well as, the protective role of antioxidants, became the topic of many doctorates in this country: Dr RADOSLAV V. ŽIKIĆ, Faculty of Science, Kragujevac, 1986; Dr MIHAJLO B. SPASIĆ, Faculty of Chemistry, Belgrade, 1986; Dr RATKO M. RADOJIČIĆ, Faculty of Biology, Belgrade, 1986; Dr BILJANA BUZADŽIĆ, Faculty of Biology, Belgrade, 1990; Dr ZORICA S. SAIČIĆ, Institute of Biology, Belgrade, 1991. In that way, these very popular researches were carried out in this country. Investigation of molecular and physiological processes in various experimental conditions attracted international scientific public. As a result of the investigation, team members were provided improving courses abroad, established international cooperation with Professor A. M. MICHELSON (Chemin du Puech, Labeaume, France), Professor BARRY HALLIWELL (Neurodegenerative Research Centre, University of London Kings College, UK) and Professor JOSEPH F. WEISS (Office of International Health Programs, Department of Energy, Germantown, Maryland, USA). This cooperation brought to the redirection of the investigations toward molecular and physiological aspects of research and the scientists concentrated their research on both fundamental research and on its application in medicine and pharmacy.

Investigations of ROS and AOS were carried out successfully during the last decade of 20th century. The research mostly concentrated on the place and role of free radicals and free-radical reactions in the process of signal transduction and metabolism regulation; on the possibility to increase the efficiency of antioxidant defense systems by application of different hormones; on the disturbance of free-radical balance; on the application of exogenous antioxidants in pathophysio-

logical states and on the role of preventive application of antioxidants and their therapeutic and protective role.

Cooperators who took part in the investigations, carried out at the Institute for Biological Research "Siniša Stanković", during the last decade of 20th century were: BLAGOJEVIĆ, D., KORAC, B., NIKOLIĆ, A., BOŽIĆ, I., MIJALKOVIĆ, D., SIMOVIĆ, M. O., ŽUNIĆ, Z., JOVIĆ, M., ZIROJEVIĆ, T., DUSINOVIĆ, S., MILJEVIĆ, Č., VELKOVSKI, S., and so on.). Some colleagues from The Clinics for Neurology, KBC, Belgrade, took part in the investigations: APOSTOLSKI, S., and MARINKOVIĆ, Z.). The investigations were partly concentrated on neurological diseases and supplementation of antioxidants as a method of therapy and they partly had fundamental character.

At the beginning of the 20th century researchers from the Institute for Biology, The Faculty of Science in Kragujevac started to investigate the role of toxicants (heavy metals and pesticides), antioxidants (vitamins E and C, olive oil and selenium), and changed ecological conditions (hypoxia and hyperoxia) on the system of antioxidant defense that various species developed. The team formed here (ŽIKIĆ, R. V. and ŠTAJN, A. Š.) cooperated with colleagues from the department for Animal Physiology at the Faculty of Biology in Poznan, Poland. Professor K. ZIEMNICKI conducted the department. We also established a successful cooperation with the Institute for Experimental Hematology, at the Faculty of Medicine in Kragujevac. The institute was conducted by Professor KOSTIĆ, M. M. Here we started a complex investigation of the energetic metabolism of blood elements and antioxidant defense system. Other investigators joined the mutual project of the two faculties and they were: OGNJANOVIĆ, B. I., MALETIĆ, S. D., JAKOVLJEVIĆ, V., PAVLOVIĆ, S. Z., BABIĆ, G., DRAGIĆEVIĆ-DJOKOVIĆ, LJ., PETRONIJEVIĆ, N., PETRONIJEVIĆ, M. and MARKOVIĆ M. They investigated different aspects of antioxidant defense system functioning at experimental animals and people.

Investigations of ROS and AOS at the Faculty of Medicine in Niš started at the Laboratory for Immunology at the Institute of Nephrology and Chemodialysis (SAVIĆ, V., NAJMAN, S., SAVIĆ, D., KAMENOV, B., JOVIĆ, T., VLAHOVIĆ, P., MILIĆ, V., STOILJKOVIĆ, S., STANKOVIĆ, Z., BAKIĆ, S. and ANTOVIĆ, S.) Soon, a number of researchers joined the investigations: PAVLOVIĆ, D., KORAČEVIĆ, D., BJELAKOVIĆ, G., DORDEVIĆ, V., KOCIĆ, G., KOCIĆ, R., CVETKOVIĆ, I., JELENKOVIĆ, A., VLAHOVIĆ, P., STOJANOVIĆ, I., STAMENKOVIĆ, I., JEVTOVIĆ, T., RADENKOVIĆ, S., MIKIĆ, D., TAMBURIĆ, V., VOJINOVIĆ, J., ČOŠIĆ, V., ZVEZDANOVIĆ, L., STEFANOVIĆ, V., NIKOLIĆ, J., MILJEVIĆ, M., TADIĆ, S., DELJANIN-ILIĆ, M., ILIĆ, S., ŽIVIĆ, S., MILENOVIĆ, M., SOKOLOVIĆ, D. and ĐINDIĆ, B. In cooperation with the Clinical Center these researches are included in the education of the students of medicine. The researchers first established an international cooperation with the colleagues from Sent Louis Hospital in Paris, France (NAJMAN, S.) and then with the colleagues from the Institute for Biophysics, The Faculty of Medicine, Sophia, Bulgaria (PAVLOVIĆ, D). The investigations carried out in Niš included experimental animals in *in vitro* investigations, clinical and *in*

vitro examination and clinical investigations. The investigations were partly directed to antioxidant defense system in animals (MILADINOVIĆ, D., NAJMAN, S., RANDJELOVIĆ, N., GAŠIĆ, O., SAVIĆ V. and PEKIĆ B.).

Investigations of ROS and AOS at Military Medical Academy in Belgrade were initiated at the Institute for Medical Research during the mid nineties. They concentrated on the phagocyte activity of a mouse after it had been thermally injured (NAJMAN, S., RADOJIČIĆ, Č., DUJIĆ, A., NANUŠEVIĆ, N., JOKOVIĆ, B. and LAKO, B.). Researchers in other areas joined the investigations later on and established a successful cooperation with the colleagues from Military Technical Institute (MILOVANOVIĆ, S., DOBRIĆ, S., VASILJEVIĆ, I., NINKOVIĆ, M., BOKONJIĆ, D., SIMOVIĆ, M. O. and SELAKOVIĆ, V.), as well as, with the colleagues from other institutes in the country and abroad.

In the Institute for Nuclear Research "Vinča" researchers started investigations of ROS and AOS at the beginning of the nineties of 20th century (KANAZIR, D., MARTINOVIĆ, J., PAJOVIĆ, S., KASAPOVIĆ, J., PEJIĆ, S. and RADOJIČIĆ, M.). They established cooperation with their colleagues from the Institute for Oncology and Radiology and investigated malign breast diseases. Later on, the investigation concentrated on different aspects of the disease (STANKOVIĆ, J., BOROJEVIĆ, N. and RADOŠEVIĆ-JELIĆ, LJ.).

Investigations of ROS and AOS at the Institute of Chemistry in Belgrade started at the beginning of the nineties in 20th century. The results of the investigations (VUČETIĆ, J. and VRVIĆ, M.) were in 1987. year applied on the production of "Ferksevit" the supplementation produced in cooperation with "Galenika" the factory of pharmaceutical products. In this country, this represented the first successful step toward the implementation of selenium as an antioxidant. Academician GAŠIĆ, A. and his colleagues investigated antioxidants at aquatic organisms. After this, other researchers joined the investigations: (ČEKOVIĆ, Z., SAIČIĆ, R. N., NIKETIĆ, V., TOMAŠEVIĆ, N., STOJANOVIĆ, S. etc.)

During the mid nineties of 20th century investigations of antioxidants were initiated at the Faculty of Medicine in Belgrade (MRŠULJA, B., DJURIČIĆ, B., MIMIĆ-OKA, J., SIMIĆ, T. etc) and they were expanded to different aspects of oxidative and antioxidant status. Other researchers joined the project too.

Researchers at the Multi Center in Belgrade investigate the phenomenon of ROS and AOS at plants (spruce) in conditions of increased pollution (VUČINIĆ, Z., RADOTIĆ, K., and RADENKOVIĆ, L.)

In Department for the Physiology and Biochemistry at the Faculty of Biology in Belgrade at the end of the nineties researchers started the investigations of the effects of hormones and other factors on ROS and AOS at the experimental organisms (RADOJIČIĆ, R., DAVIDOVIĆ, V., CVIJIĆ, G., DJURAŠEVIĆ, S. etc).

At the end of the nineties, researchers initiated investigations of ROS and AOS at insects and fish at the Department of Biology, the Faculty of Science in Novi Sad (LAJŠIĆ, G. and DJUKIĆ, N.). They also determined their status and the way they change under the influence of different pollutants. Later, they expanded the investigations on the supplementation of antioxidants (JOVANOVIĆ-GALOVIĆ,

A.). Together with the colleagues from the Institute in Kamenica (BOGDANOVIĆ, G.) they investigated antioxidants found in black grape. Soon, at the same Institute, they started the investigation of the therapeutical effects of antioxidants (NIKOLIĆ, V.).

Researchers at the Institute for Corn investigate antioxidants found in corn (SREDOJEVIĆ, S., DRAGIČEVIĆ, V., etc).

This short review of investigations of ROS and AOS in Serbia cannot provide a complete picture of the research, but one review that is more complex would take a lot of time and space. Yet, *it can be concluded*, that a great number of researchers from different institutes and fields are included in the investigation of ROS and AOS. The investigations started more than 25 years ago and have been concentrated on different aspects and mechanisms at animals, plants and people.

Investigations of the systems of oxidative damages protection at aerobic organisms included the following species:

Plants (*Asragalus onobrychis* var. *Chlorocarpus*; grape seeds, *Vitis Vinifera*; spruce and corn);

Insects (bean weevil, *Acanthoscelides obtectus* Say; gypsy moth, *Lymantria dispar*; corn borer, *Ostrinia nubilalis*);

Mollusks (mussel, *Mytilus galloprovincialis*);

Crabs (sea crabs: shrimp, *Parapaeneus longirostris*);

Fishes (fresh water fishes: crucian carp (*Carassius auratus gibelio* Bloch; carp, *Cyprinus carpio* L.; barbel, *Barbus barbus*; bream, *Abramis Balerus*; sturgeon, *Acipenser ruthenus* and sea fishes: grey mullet, *Liza romada*; hake, *Merluccius merluccius*; surmullet, *Mullus barbatus* and gurnard, *Triglalucerna*);

Amphibians (frog, *Rana esculenta* L.);

Rodents (ground squirrels, *Citellus, citellus*; rats: *Rattus rattus*, *Rattus norvegicus*, *anemic Belgrade (b/b)*; laboratory rats: *Mill Hill hybrid hooded*, *Wistar albino*, *Dark August* and *Albino Oxford*).

Besides investigations on animals, researchers also investigated ROS and AOS at people in many laboratories. They investigated amyotrophic lateral sclerosis (ALS), epilepsy, schizophrenia (positive and negative), atherosclerosis, Parkinsons disease, stomach cancer, colon cancer, lungs cancer, breast cancer, psoriasis, different kidney diseases, endemic nephropathy, liver diseases, hypertension, multiplex sclerosis, meningitis, ischemic cerebrum-vascular insult, hyperthyroid, diabetes, glaucom, changes on blood vessels, asthma, and so on).

A part of the investigations of ROS and AOS in some organs and tissues was directed toward the molecular and physiological assessment of the environmental conditions.

Republic and State Ministry for Science financially supported major part of the investigation and thus many researchers were included in many fundamental and applied projects. Results of the investigations were published in a number of scientific issues and many scientific works of international and national importance, as well as, in congress publications of international and national importance. The results attracted attention of international and national scientists and according to SCI (Science Citation Index) they are considered to be highly cited.

A parts of the research were published in **monographs** of the national importance. They are:

- 1) Toksikološki značaj zaštite od oksidacionih oštećenja (2000): ŽIKIĆ, V. RADOSLAV, ŠTAJN, Š. ANDRAŠ, SAIČIĆ, S. ZORICA, SPASIĆ, B. MIHAJLO i Milovanović, R. SLOBODAN. Prirodno-matematički fakultet, Kragujevac, str. 1-150;
- 2) Biohemija slobodnih radikala (2000): ĐORĐEVIĆ, B. VIDOSAVA, PAVLOVIĆ, D. DUŠICA I KOCIĆ, M. GORDANA. Medicinski fakultet u Nišu, str. 1-308.
- 3) Biomarkeri: detekcija, struktura i funkcija (2000): IVANIŠEVIĆ-MILOVANOVIĆ, OLIVERA, IVANOVIĆ, VESNA, PAJOVIĆ, B. SNEŽANA, KONSTANTINOV, KOSANA I MLADENOVIĆ-DRINIĆ, SNEŽANA. VELARTA, Beograd, str. 1- 229.

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