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DEVELOPMENT PERSPECTIVES OF NEW GENERATION MEDICATIONS BASED ON THE REDOX SYSTEM REGULATORS

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Abstract. This survey paper describes the necessity of the development of new medications influencing the body redox-potential. It supports the most pressing branch of pharmacology, which coincides with logically relevant attempts to shift paradigm of pharmacology from molecular to electronic, quantum-wave. This article covers and logically assorts research results of recent years and opinions of wide range of scientists from various countries. The authors also give their own assessment of the possibility to influence body redox potential. It is reported that some biophysical achievements regarded undoubtedly put a new spin in pharmacology of the biophysical level. These research results devoted to the role of redox-potential in regulation of biological systems are considered to open up new opportunities for pharmacotherapy of pathological conditions by developing medications of the new generation – redox-potential regulators - aimed at the induction of the body protective resources. The paper further reports that elaborate study of redox-potential in providing biological systems regulation has resulted in the detailed investigation of Mexidol benefits. Special attention is paid to the general principle of action of endogenous redox regulators: metabolic, energetic and informational. The article also highlights key issues of the regulation of oxidation-reduction processes in the body and, consequently, the role of reactive oxygen species in physiology and pathology. The paper reasonably concludes with the statement on the necessity to turn pharmacologists' attention not only to improving the existing anti-oxidant preparations, but to developing the redox system regulators, which appear to be medications of the new generation for pathogenic therapy.
Key words: reactive oxygen species, oxygen, reduction-oxidation reactions, redox potential, pharmacotherapy.

Introduction. Use of oxygen to receive energy needed for the life-sustaining activity by substrate oxidation in biological objects is considered to be one of the mainstreams of the living systems evolution [1]. Functioning of the human body as the most highly organized life-form depends on oxygen supply; its deficiency causes multiple pathological conditions. Decrease of energy resources under hypoxia results in multisystemic and multiorganic functional-metabolic changes and, subsequently, death of the whole body.

Oxygen is the leading factor of the biological rhythms control: circadian, seasonal, reproductive, as well as homeostasis, proliferation, differentiation, apoptosis, carcinogenesis, aging, necrosis and some other cellular processes [2-5], and their exact mechanisms can be understood only in the plant cell [6].

Aerobic organisms have oxidative potential, which increases with the increase of tissue blood supply or activation of free-radical particles. Oxygen deficiency, on the contrary, leads to reductive change of potential. Shift of the balance between prooxidants

and anti-oxidants induces oxidative stress characterized by specific changes of the cellular processes: membrane structure is violated due to lipid perioxidation, proteins are oxidated, DNA is damaged, cellular redox potential changes.

There have been recorded instances of more than 200 nosological forms accompanied by oxidative stress: cardio-vascular [7-14], oncological [15], infectious diseases [16, 17], pathologies of the respiratory [18], reproductive [19-21], urinary [22, 23], nervous system, pyoinflammatory processes [24], arthritis of various types, diabetes mellitus, cataract and others [25].

Mitochondrial respiratory chain, microsome electron-transport chain, arachidonic acid metabolism, hypoxanthine-xanthine oxidase reactions, biosynthesis and catecolamine oxidation are reported to be sources of reactive oxygen species (ROS) [26]. Mitochondrias are stated to be the main sources of radicals in a cell [27], therefore these organelles need to be constantly protected from damages induced by oxidative stress. Mitochondrial DNA appears to be the most vulnerable target for ROS. There exist a lot of evidences that its oxidative violation and increasing de-energization of oxygen-dependant cells play the key role in the whole range of "mitochondrial diseases" [28, 29], neurodegenerative pathologies [30, 31], as well as body aging [32]. The final stage of this process is necrosis, due to which a cell as a living system stops existing, since transformation systems of substance and energy flows, permeability of cellular and sub-cellular membranes are violated, ion gradients disappear [1]. Currently, the role of mitochondrias in regulation of proliferation and differentiation processes, apoptosis and cancerous growth is actively investigated. Change of ROS generation rate under influence of mitochondrias may be considered as one of the mechanisms that switch functional activity of a cell [33].

ROS comprises a lot of transitional products of oxygen metabolism producing in the body; they, in turn, having high reactive capacity can lead to violation of practically all structural components of the biological system [2, 33-36]. Increased ROS levels result in initiation of free-radical oxidation – the process of immediate oxygen transfer on substrate with formation of peroxides, ketones, aldehydes inducing reactions of peroxide oxidation. This ancient natural destructive mechanism that has a hold over all the organic compounds is necessary for the following renovation of cells and tissues, their adaptation for the changing environment, body protection against infections, participation in formation of biologically active compounds. This implies the fact that presence of free radicals in a body has specific, physiologically important significance [37].

On the other hand, it is beyond argument that functional properties of some enzymes, carbohydrates, proteins, DNA and RNA are changed under the influence of free-radicals so that a cell loses its regulatory functions [2]. Concurrently there may appear abnormal proteins; secondary destructive processes may be stimulated apart from direct damaging action.

Discussion. The leading role in pathogenesis of radiation damage, inflammatory processes of various localization and origin, development of hyper- and hypoxic conditions, post-ischemic, reperfusion and hyperoxic disorders, wound processes, stress, acute and chronic hepatic diseases, myocardial infarction, strokes, atherosclerosis, carcinogenesis, aging and so on belongs to lipid peroxidation. Influence of free-radicals on structure and functions of biological membranes is one of the most important pathogenic mechanisms in hypoxia.

There is a multilevel physiological system of protection against oxidation agents in a body – the antioxidant system supporting oxidative-antioxidative balance in all organs and systems [38, 39]. The antioxidant system includes the whole complex of enzymes: superoxide dismutase (SOD), catalase, glutathione-dependant peroxidases, transferases etc., as well as a range of cellular metabolites: lipoic, ascorbic, uric acids, tocopherols, carotenoids, flavonoids, polyphenols, carnosine, bilirubin, coenzyme Q10 and other compounds aimed at maintaining the normal reactions of the body in various pathological conditions, including hypoxia [2, 32, 40-50]. Malfunctioning of these systems is stated to be one of the most significant factors in violation of prooxidant-antioxidant balance and oxidative stress development [51, 52]. Some research studies have demonstrated that ROS formation and multicomponent anti-oxidative protection constitute the unified system being in the dynamic balance and having capacity for self-regulation [35]. Due to the associated functioning of the ROS generation and anti-oxidative protection systems oxidation-reduction balance is established in a cell, in other words redox status. Redox potential formation reflecting balance status of the pro- and antioxidant body systems [53] is greatly influenced by protein components of blood plasma, catalase enzyme activity and, possibly, alpha-synuclein level [54].

The importance to maintain such balance for the living system was marked by A. Szent-Györgyi [55] in the mid-XXth century; he considered the balance between electron donors and acceptors to be one of the basic life parameters.

Associated redox system representing combination of redox cycles of carbon, nitrogen, oxygen and sulphur, has been formed during the evolution process [56]. Redox potential of the normally functioning cells is maintained at the constant level and changes only under specific actions [1, 34, 57-59]. In spite of the fact that oxidation-reduction reactions are the basic reactions of the bioenergetic processes and regulate cellular activity as a whole [27], there is no clear understanding of their role in the intra- and extracellular pathogenesis, signaling processes, homeostasis regulation. However, redox homeostasis acquires conceptual significance in some pathological body processes [60].

Redox potential reduction shift forms the basis of triggering hypoxic necrobiosis and damaging specific oxygen-sensitive cells; redox potential oxidation shift forms the basis of developing free-radical necrobiosis and apoptosis of trophic cells [1]. Oxidative and nitrosative stress removes SH-SS balance towards oxidated thiols that causes neurons necrosis and death [61].

Insignificant redox-potential shifts through a biological cycle give an opportunity to rhythmically regulate phases of functional activity of the living systems with resting phases; and its significant shifts lead to activation of cellular death processes. Thus, for example, correlation of reductive and oxidated glutathione levels plays role of a special “switch” from proliferation phase to differentiation phase and further to apoptosis [62].

Redox potential shift has an effect on realization of metabolic processes, work of the signaling transduction system, gene expression, activity of transcription factors [63-66], change of activity and biological full value of both intracellular compartments and a cell as a whole [67]. When changing redox potential status cellular strategy is mostly defined by the status of signal transmitting systems [68]. Redox potential has been demonstrated to be an indicator of cellular functional activity and effectiveness of anti-oxidated protection [69].

Organic substances (vitamins, aminoacids) and compounds of inorganic origin – macro- and microelements - take part in redox potential regulation alongside with oxygen; even insignificant change of concentration of inorganic substances has an effect on the functioning of the whole body [1, 70]

The data obtained on the leading role of redox potential in maintaining the biological system regulation give new opportunities for pharmacotherapy of pathological conditions including hypoxic one. Currently the amount of theoretical, experimental and clinical data is sufficient to create a theory of developing highly effective medications of new generation – redox regulators – based on the study of functional biological multivaluedness of redox-active agents.

The enormous list of modern preparations for chemotherapy is represented by chemical compounds foreign for the biological system, having xenobiotic load on a body and, consequently, causing side effects. Therapeutical effect of any xenobiotic is restricted by the blockage of adaptational body reactions to a damage and replacement of the proper protective resource into the artificial one until its atrophy. Besides, introduction of foreign medications can result in resistance that increases danger of overdose and individual hypersensitivity. Severe drawbacks of modern medications are reported to be a narrow range of pharmacological activity and absence of selectivity towards a biotarget; that is why a positive result in vivo for a foreign compound is accidental; this fact is proved by rare successful cases of numerous chemicals screening.

Synthesis of effective and safe medications – natural participants of enzymatic reactions and metabolism compatible with biological structures and systems, - is possible by applying electrophilic replacement, redox vitamin modification and complex formation. The example of redox vitamin modification appears to be an effective polyfunctional preparation – mexidol – vitamin B_6 modification (redox oxypyridine active centre) with succinate [71].

Analysis of numerous investigations of this medication allows concluding that vitamin B_6 easily entering a cell through its own natural canals transfers a succinate; this makes mexidol an irreplaceable pathogenetic preparation in complex therapy of post-hypoxic conditions [72, 73]. Vitamin B_6 as an active redox agent participates in the regulation of oxidation-reduction processes in cytosol and membrane, and a succinate metabolite – succinic acid – reactivates cell respiration. Due to such synchronic tandem cells living activity remains unchanged and a chance to restore cellular functional activity under oxygen deficiency increases.

Impact of succinate on the energy exchange has been studied more in details for all substrates of the Krebs cycle [74]. Predominant use of succinate is natural cell protection against hypoxia. At that,

replenishment of the substrate fund may occur as a result of the Krebs cycle reactions, both – linear and reverse. Such a peculiarity of oxidative phosphorylation provides an opportunity to reverse reaction at the di-carbon stage of the Krebs cycle with transition of fumarate into succinate and increasing amount of the latter. Mechanism of inversive fumarate transformations during the Krebs cycle explains the efficient use of fumarate-containing preparation – sodium fumarate, mafusol, polyoxifumarin, konfumin, as well as the complex fumarate + Hydroxyethylstarch, which is successfully passing through the last stage of pre-clinical trials [75, 76]. Preparations of this group have come to stay in the program of fumarate-containing solutions for infusions applied in Accident and Emergency Departments of healthcare facilities in the Russian Federation and CIS-states when delivering medical care to the injured in military conflicts, natural and technological disasters [77].

Currently there has been shown an opportunity of redox potential pharmaco-correction of heart failure caused by ischemic heart disease with adenosine containing reduced NAD form [78]; there have been revealed pre-conditions for Histochrom application in complex therapy of venous retinal occlusions associated with changes of the redox system [79].

Redox regulators take the exceptional position among biomolecules, because only redox-active substances are able to transfer electrons intermolecularly. Since charge redistribution is considered to be a basis of a biochemical reaction, then only redox-active elements and molecules specific for the given enzyme play the functional role. This explains synchronization of biological processes occurring at all levels of the systemic organization influenced by associated redox-factors. At that, the significance of the unique organization of a protein molecule or its active polypeptide part is evident.

An attempt to change redox potential of the body liquid media with ionized liquid having either positive or negative potential has been made in the Voronezh N.N.Burdenko State Medical University [80, 83]. Some research studies performed prove safe application of fluids with various redox potential, establish therapeutic range of the redox potential parameter in millivolts [81, 82].

Variety of biological systems, numerosity of active particles and secondary messengers, complexity of the inflammatory reaction mechanism and variety of factors influencing it do not allow creating a precise picture of mechanisms, which realize protective potential of safe medications. However, universe character of their participation in these mechanisms as a redox potential agent supports not only reasonability but also the necessity of creating such agents.

Redox agents perform an antioxidant function as constituents of the physiological antioxidant system, however, the fact of even greater importance is that they provide functional enzymes activity as co-enzymes, co-substrates and co-factors, i.e. reveal prooxidant activity. More than that, redox agent activity is defined by the redox environment, mainly, protein having signaling transduction.

General principle of endogenic redox regulators impact is aimed at three biological flows: metabolic, energetic and informational; their synchronic interaction at all levels of organization of the living system is achieved due to redox factors incorporation into enzymatic processes. Simultaneously they act as sensors responding to changes of one of the most important indicators of the biological system – redox potential. A received signal is directly or indirectly transformed into activity shift of a specific enzyme.

Currently redox-sensitive elements of the intracellular signal-transmitting systems (p 38 MAP kinase, JNK, transcription factors and proteins of Bcl-2 family) are shown to be molecular targets for therapeutic correction of the apoptotic program violation under oxidative stress [68].

In the extreme (pathological) situation associated with hypoxia anti-oxidants are able to reveal their own protective function acting as an electron buffer. Redox-active agents, on the contrary, produce induction and mobilization of all protective resources at any level of the biological system demonstrating not only anti-oxidant, but pro-oxidant activity as well. The problem to be studied is how to trigger these processes and further regulate them.

If a danger of stress-reaction is insignificant and the amount of operative protective resource is sufficient enough to eliminate its consequences, then participation of endogenic redox regulators may be considered as manifestation of their preventive potential.

Different situation occurs if the amount of protective resource is insufficient and it is necessary to mobilize specific protective proteins, information on which is kept in the genetic material. It is the medication based on modified signaling molecules of proteins that should participate in the mechanisms of induction and mobilization of protective resource. Such varieties of redox-active signaling molecules performing the role of the protective function trigger may claim to be highly effective medications.

Development of organic complexes of biometals seems to be the most universal. In this case organic bioligand being a natural redox-active agent of an enzyme allows an element to be the most effectively included in the metabolic mechanism. Such complex compounds of transitional biometals may reproduce chemical behaviour of metalo-enzymes in a cell. The role of these complexes is restricted by the participation of electrons and redox-reactions typical for this enzyme in the processes of transport. Low-molecular compounds with metals, for example, zink sulfate or gluconate, cannot be referred to the category of redox regulators, since absence of a relevant ligand in their composition deprives these compounds of substrate specificity. Taking into account high level of biological activity of essential bioelements their reliable and fast delivery by transport proteins with easier release appears to be a warrant of high effect.

Conclusion. Thus, any violation of homeostasis results in pathological conditions causing violation of energy production, storage and utilization. Redox-potential is considered to be the basic indicator of metabolic cell status integrating uncountable number of oxidation-reduction reactions. The data available on the leading role of redox-potential changes in providing the biological systems regulation give new opportunities for pharmacotherapy of pathological conditions including hypoxic ones. Development of medications – redox system regulators – aimed at the induction of proper protective body resource appears to be strategic concern of creating new generation pathogenic therapy agents.

References

1. Shilov V.N. *Molecular mechanisms of structural homeostasis* (Moscow, «Intersignal», 2006), 288 p.(In Russian) [eLIBRARY]

2. Gus'kov E.P., Shkurat T.P., Varduni T.V., Mashkina E.V., Pokudina I.O., Shimanskaya E.I., Gus'kov G.E., Belichenko N.I., Aleksandrova A.A. *Genetics of oxidative stress* (Rostov n/D: Izd-vo SKNTS VSHH YUFU, 2009), 156 p. (In Russian) [eLIBRARY]

3. Ren F.L., Wang K., Zhang T., Jiang J.W. New insights info redox regulation of cell self-renewal and differentiation. *Biochimica et biophysica acta-general subjects*. 2015, № 1850(8): pp.1518-1526. [Full text]

4. Lee M.J., Kao S.H., Hunag J.E., Sheu G.T., Yeh C.W., Hseu, Y.C., Wang C.J., Hsu L.S. Shikonin time-dependently induced necrosis or apoptosis in gastric cancer cells via genera-tion of reactive oxigen species. *Chemico-Biological Interactions*. 2014, № 211, pp. 44-53. [Full text]

5. Kim Y., Jeong I.G., You D., Song S.H., Suh N., Jang S.W., Kim S., Hwang J.J., Kim C.S. Sodium meta-arsenite induces reactive oxigen species-dependent apoptosis, necrosis, and autophagy in both androgen-sensitive and androgen-insensitive prostate cancer cells. *Anti-Cancer Drugs*. 2014; 25: pp. 53-62. [Full text]

6. Schmidt R., Schippers Jos H.M. ROS-mediated redox signaling during cell differentiation in plants. *Biochimica et biophysica acta-general subjects*. 2015; 1850(8): pp. 1497-1508. [Full text]

7. Bagchi D., Sen C.K., Ray S.D., Das D.K., Bagchi M., Preuss H.G., Vinson J.A. Molecular mechanisms of cardioprotection by a novel grape seed proanthocyanidin extract. *Mutat Res*. 2003; pp. 523–524. [Full text]

8. Elahi M.M., Kong Y.X., Matata B.M. Oxidative stress as a meditator of cardiovascular disease. *Oxid Med Cell Longev*. 2009, № 2 (5), pp. 259-69. [Full text] Lakshmi S.V., Padmaja G., Kuppusamy P., Kutala V.K. Oxidative stress in cardiovascular disease. *Indian J Biochem Biophys*. 2009, № 46 (6), pp. 421-440. [Full text]

9. Hirooka Y., Sagara Y., Kishi T., Sunagawa K. Oxidative stress and central cardiovascular regulation. *Circ J*. 2010, № 74(5), pp. 827-835. [Full text]

10. Hirooka Y. Pathogenesia of hypertension and therapeutic aspects. *Hypertens Res*. 2011, №34(4), pp. 407-412. [Full text]

11. Fort-Gallifa I., Garcia-Heredia A., Hernandez-Aguilera A., Simo J.M., Sepulveda J., Mar-tin-Paredero V., Camps J., Joven J. Biochemical indices of oxidative stress and inflamma-tion in the evaluation of peripheral artery disease. *Free Radical Biology and Medicine*. 2016, № 97, pp. 568-576. [Full text]

12. Tangvarasittichai S., Pingmuanglaew P., Tangvarasittichai O. Association of Elevated Se-rum Lipoprotein(a), Inflammation, Oxidative Stress and Chronic Kidney Disease with Hypertension in Non-diabetes Hypertensive Patients. *Indian Journal of Clinical Biochemistry*. 2016, №31(4), pp. 446-451. [Full text]

13. Wang D.W., Wang J., Liu Y.T., Zhao Z., Liu Q. Roles of Chinese herbal medicines in ischemic heart diseases (IHD) by regulating oxidativestress. *International Journal of Cardiology*. 2016, № 220, pp. 314-319. [Full text]

14. Pashov A.I., Tskhay V.B., Grebennikova E.K., Sivova E.N. Oxidative stress and glutathione redox-system in carcinogenesis. *Mother and baby in Kuzbass*. 2012, № 3, pp. 3-8. (In Russian) [Full text]

15. Dzhikiya I.V., Rizhvadze M.A., Dzhangidze M.A. Oxidation-reduction blood potential and consistency of the energy supply system in case of cytomegalovirus infection in the pregnant women. *Georgian medical news*. 2006, №5(134), pp. 28–31. [Full text]

16. Egorova Y.V., Nesterov A.S. Basic redox-system findings in women with urogenital chlamidiosis. *International Journal of Applied and Fundamental Research*. 2013, № 8-3, pp. 20-23. (In Russian) [Full text]

17. Zhou M.X., Wei X., Li A.L., Wang A.M., Lu L.Z., Yang Y., Ren D.M., Wang X.N.,Wen X.S., Lou H.X., Shen T. Screening of traditional Chinese medicines with therapeutic po-tential on chronic obstructive pulmonary disease through inhibiting oxidative stress and in-flammatory response. *BMC Complementary and Alternative medicine*. 2016. [Full text]

18. Bozhedomov V.A., Gromenko D.S., Ushakova I.V., Toroptseva M.V., Galimov S.N., Aleksandrova L.A., Teodorovich O.V., Sukhikh G.T. Oxidative stress of sperm cells in the pathogenesis of male infertility. *Urology*. 2009, № 2, pp. 51–56. (In Russian) [eLIBRARY] [Full text]

19. Aitken R., Gibb Z., Baker M. et al. Causes and consequences of oxidative stress in spermatozoa. *Reproduction, Fertility and Development*. 2016, № 28(2), pp. 1–10. [Full text]

20. Galimov S.N., Abdullina A.Z., Kidrasova R.S., Galimova E.F. Content of dioxins and status of the glutathione system in ejaculate in case of male infertility. *Kazan Medical Journal*. 2013, №94(5), pp. 658-661. (In Russian) [eLIBRARY] [Full text]

21. Osikov M.V., Telesheva L.F., Ageev Y.I., Cherepanov D.A., Fedosov A.A. Pathophysiological aspects of innate immunity changing and correction in chronic renal failure. *Modern Problems of Science and Education*. 2013, №5, pp. 274-286. (In Russian) [eLIBRARY] [Full text]

22. Kazmirchuk A.V., Telesheva L.F., Bychkovskikh V.A., Osikov M.V. Role of the immune status and redox potential in the pathogenesis of secondary pyelonephritis under urinary stone disease. *Modern Problems of Science and Education.* 2016, № 3, pp. 65. (In Russian) [Full text]

23. Gavrilyuk L.A., Pokhilenko A.V. Influence of anti-oxidant therapy on the status of enzymatic glutathione redox system with phlegmons. *Scholarly Discussion: medical issues*. 2016, № 3 (34), pp. 6-12. (In Russian) [Full text]

24. Men'shhikova E.B., Zenkov N.K., Lankin V.Z., Bondar' I.A., Trufakin V.A. Oxidative stress. *Pathological conditions and diseases: monograph*. Novosibirsk: ARTA, 2008, pp. 284. (In Russian) [eLIBRARY] [Full text]

25. Tregubova I.A., Kosolapov V.A., Spasov A.A. Antioxidants: current status and perspectives. *Achievements of Physiological Sciences*. 2012, № 43(1), pp. 75-94. (In Russian) [Full text]

26. Li P.Y., Zhang D.Y., Shen L.X., Dong K.L., Wu M., Ou Z.,Shi D. Redox homeostasis protects mitochondria through accelerating ROS conversion to enhancehypoxia resistance in cancer cell. *Nature Publishing Group*. 2016, № 6. [eLIBRARY]

27. Schon, E. A., DiMauro, S. & Hirano, M. Human mitochondrial DNA: roles of inherited and somatic mutations. *Nature Rev. Genet.* 2012, № 13, pp. 878–890. [Full text]

28. Gorman G.S., Schaefer A.M., Ng Y., Gomez N., Blakely E.L., Alston C.L., Feeney C., Horvath R., Yu-Wai-Man P., Chinnery P.F., Taylor R.W., Turnbull D.M., McFarland. Pre-valence of Nuclear and mitochondrian DNA Mutations Related to Adult Mitochondrian Disease. *Annals of Neurology*. 2015, № 77(5), pp. 753-759. [Full text]

29. Chen Y.C., Liu C.S., Parker W.D., Chen H.Y., Beach T.G., Liu X.H., Serrano G.E., Lu Y.F., Huang J.J., Yang K.F. Mitochondrian DNA Rearrangement Spectrum in Brain Tissue of Alzheimer's Disease: Analysis of 13 Cases. *Plos One*. 2016, №11(6).

30. Pyle A., Anugrha H., Kurzawa-Akanbi M., Yarnall A., Burn D., Hudson G. Reduced mito-chondrian DNA copy number is a biomarker of Parkinson's disease. *Neurobiology of Aging*. 2016, № 38. [Full text]

31. Otten A.B., Smeets H. Evolutionary defined role of the mitochondrial DNA in fertility, disease and ageing. *Human Reproduction Update*. 2015; 21(5), pp. 671-689. [Full text]

32. Martinovich G.G., Cherenkevich S.N. *Oxidation-reduction processes in cells*. (Minsk: BGU, 2008), 159 p. (In Russian) [eLIBRARY] [Full text]

33. Shanin Y.N., Shanin V.Y., Zinov'ev E.V. *Antioxidant therapy in clinical practice*. (Saint Petersburg: ELBI-SPb; 2003), 128 p. (In Russian)

34. Zenkov N.K., Lankin V.Z., Men'shhikova E.B. *Oxidative stress: biochemical and pathophysiological aspects*. (Moscow: Nauka. Interperiodika, 2001), 343 p. (In Russian) [eLIBRARY]

35. Sazontova T.G., Arkhipenko Y.V. Balance significance between prooxidants and antioxidants – equal participants of metabolism. *Pathological physiology and experimental therapy*. 2007, № (3): pp. 2-18. (In Russian) [PubMed]

36. Ulashchik V.S. Active oxygen forms, antioxidants and therapeutic physical factors effect. *Issues of Resort Medicine, Physiotherapy and Physical Therapy*. 2013, № (1), pp. 60-69. (In Russian) [eLIBRARY]

37. Novikov V.E., Levchenkova O.S. New directions of search for medications with antihypoxic activity and targets of their action. *Experimental and clinical pharmacology*. 2013, № 76(5), pp. 37-47. (In Russian)

38. Statsenko M.E., Turkina S.V., Kosivtsova M.A. Opportunities of mexicor when using it as a constituent of the combined therapy in patients with ischemic heart disease and diabetes type II. *Clinical medicine*. 2013, № (5), pp. 59-64. (In Russian) [eLIBRARY]

39. Gorozhanskaya E.G. Free radical oxidation and mechanisms of antioxidant protection in a normal cell and under tumors. *Clinical Laboratory Diagnostics*. 2010, №6, pp. 28–44. (In Russian) [Full text]

40. Kalinina E.V., Chernov N.N, Novichkova M.D. Role of glutathione, glutathione-transferase and glutaredoxin in regulation of redox-dependant processes. *Achievements of biological chemistry*. 2014, № (54), pp. 299-348. (In Russian) [Full text]

41. Koyu A., Ozguner F., Caliskan S., Karaca H. Preventive effect of vitamin E on iron-induced oxidative damage in rabbit. *Toxicol. Ind. Health*. 2005, № 21, pp.239–242.

42. Aycicek A., Iscan A., Erel O., Akcali M., Ocak A.R. Oxidant and antioxidant parameters in the treatment of meningitis. *Pediatr. Neurol*. 2007, №37(2), pp.117–120. [Full text]

43. Nadeem A., Masood A., Siddiqui N. Oxidant-antioxidant imbalance in asthma: scientific evidence, epidemiological data and possible therapeutic options. *Ther. Adv. Respir. Dis.* 2008, №2, pp.215–235.

44. Hong Z., Hailing L., Hui M., Guijie Z. Effect of vitamin E supplementation on develop-ment of

reproductive organs in Boer goat. *Anim. Reprod. Sci*. 2009, № 113, pp. 93–101. [Full text]

45. Ostman B., Michaelsson K., Helmersson J., Byberg L., Gedeborg R., Melhus H., Basu S. Oxidative stress and bone mineral density in elderly men: antioxidant activity of alpha-tocopherol. *Free Radic. Biol. Med*. 2009, № 47, pp. 668–673. [Full text]

46. Lee S., Park Y., Zuidema M.Y., Hannik M., Zhang C. Effects of interventions on oxidative stress and inflammation of cardiovascular diseases. *World J. Cardiol*. 2011, № (1), pp.18-24.

47. Allen E.M., Mieyal J.J. Protein-Thiol Oxidation and Cell Death: Regulatory Role of Gluta-redoxins. *Antioxidants & Redox Signaling.* 2012, № (17), pp.1748-1763.

48. Board P.G., Menon, D. Glutathione transferases, regulators of cellular metabolism and physiology. *Biochimica et Biophysica Acta*. 2013, pp. 3267-3288. [Full text]

49. Lillig C.H., Berndt C. Glutaredoxins in thiol/disulfide exchange. *Antioxidants & Redox Signaling.* 2013, № 18, pp.1654-1665.

50. Bonnefoy M., Drai J., Kostka T. Antioxidants to slow aging, facts and perspectives. *Presse Med.* 2002, №31, pp. 1174–1184.

51. Solov'eva E.Y., Chipova D.T. From concept of oxidative stress to modulation of cellular signaling. *S.S.Korsakov Journal of Neurology and Psychiatrics*. 2015, №115(8), pp. 105-111.(In Russian)

52. Andreev V.N., Evseev A.K., Garaeva G.R., Gol'din M.M. Comparison of redox-potential and blood serum anti-oxidative activity. *Molecular medicine*. 2013, № 4, pp.37–40. (In Russian) [eLIBRARY]

53. Cherenkov I.A., Sergeev V.G., Ivanova I.L., Shunaylova N.YU., Raevskikh K.S., Popova M.V. Mechanism of formation of plasms redox potential in patients with Parkinson's disease. *Health, demography, ecology of Finno-Ugric ethnic groups*. 2015, № 4, pp. 94-96. (In Russian) [eLIBRARY]

54. Szent-György A. *Bioelectronics. Research in the field of cellular regulation, protective mechanisms and cancer*. (Moscow: Mir, 1971). (In Russian)

55. Tereshina E.V., Laskavy V.N., Ivanenko S.I. Four components of conjugated body redox system: carbon, nitrogen, sulphur, oxygen. *Biochemistry*. 2015, № 80(9), pp.440-1455. (In Russian) [Full text]

56. Lamb H., Stammers D., Hawkins A. Dinucleotide-Sensing Proteins: Linking Signaling Networks and Regulating Transcription. *Sci. Signal*., 2008, №1, pp. 38. [Full text]

57. Oka Sh.-I., Hsu Ch.-P., Sadoshima J. Regulation of Cell Survival and Death by Pyridine Nucleotides. *Circ. Res*. 2012, № 111, pp. 611–627. [Full text]

58. Rael L.T., Bar-Or R., Mains C.W., Slone D.S., Levy A.S., Bar-Or D. Plasma Oxidation-Reduction Potential and Protein Oxidation in Traumatic Brain Injury. J. *of neurotrauma*. 2009, № 26, pp. 1203–1211. [Full text]

59. Moyseyonok A.G., Buko I.V., Gorudko I.V., Konstantinova E.E., Tsapaeva N.L., Mrochek A.G. Correlation of findings of systemic inflammation, oxidative stress and glutathione redox-status in patients with ischemic heart disease and diabetes type II. *Arterial Hypertension*. 2013, № 19(4), pp. 356-366. (In Russian) [Full text]

60. Gorbacheva S. V., Belenichev I. F. Genome response and the status of glutathione system in the cortex of rats with experimental violation of cerebral circulation on the background of thiol-containing anti-oxidant therapy. *Modern Medicine: Challenging Issues: Proceedings of the XLVIII-XLIX International Scientific Reseach Conference*. (Novosibirsk: SibAK. 2015; № 10-11(43)). (In Russian) [eLIBRARY]

61. Kalinina E.V. Chernov N.N., Novichkova M.D. Role of glutathione, glutathione-transferase and glutaredoxin in regulation of redox-dependant processes. *Achievements of Biological Sciences*. 2014, № 54, pp. 299–348. (In Russian) [Full text]

62. Oktyabr'skiy O.N., Smirnova G.V. Redox regulation of cellular functions (review). *Biochemistry*. 2007, № 72(2), pp. 158-175. (In Russian) [eLIBRARY]

63. Akhmadullina G.K., KHaybullina Z.G., Gaysina A.F., Travnikov O.Y., Galimova S.S. Lipoic acid in the correction of redox potential of sperm plasma pyridine nucleotides under infertility. *Medicus*. 2016, № 2 (8), pp. 113-115. (In Russian) [eLIBRARY]

64. Montero A.J., Jassem J. Cellular redox pathways as a therapeutic target in the treatment of cancer. *Drugs*. 2011, № 71(11), pp. 1385-1396. [Full text]

65. Gegotek A., Skrzydlewska E. CNC propeins in physiology and pathology. *Posthepy higienny i medycyny doswiadczalnej*. 2015, № (69), pp. 729-743.

66. Goroncharovskaya I.V., Makarov M.S., Kolesnikov V.A. Redox potential as a characteristic feature of thrombocytes living activity. *Achievements in Chemistry and Chemical Technologies.* 2015, № 3(162), pp. 35-37. (In Russian) [Full text]

67. Chasovskikh N.Y. Role of JNK and p38 protein-kinases in regulation of mononuclear blood leucocyte apoptosis under oxidative stress. *Bulletin of Siberian Medicine*. 2008, № 3, pp. 38-43. (In Russian) [Full text]

68. Rhieu S.Y., Urbas A.A., Bearden D.W., Marino J.P., Lippa K.A., Reipa V. Probing the Intracellular Glutathione Redox Potential by in-cell NMR Spectroscopy. Angew. *Chem. Int. Ed. Engl*. 2014, № 53(2), pp. 447-450. [Full text]

69. Romero-Canelón I., Sadler P.J. Next-generation metal anticancer complexes: multitargeting via redoxmodulation. *Inorg. Chem*. 2013, № 52(21), pp. 12276-12291. [PubMed]

70. Voronina T.A. Mexidol: range of pharmacological effects. *Journal of Neurology and Psychiatrics*. 2012, №12, pp. 86–90. [eLIBRARY] [Full text]

71. Verizhnikova E.V., Doroshenko L.M., Mil'tsin A.S., Zakharova N.B. Polyprotective action of mexidol in patients with multi-organ dysfunction. *Bulletin of Experimental Biology and Medicine*. 2012, №1, pp.109–113. (In Russian)

72. Shchul'kin A.V. Influence of mexidol on the development of neurons excitotoxicity phenomenon in

vitro. *S.S.Korsakov Journal of Neurology and Psychiatrics*. 2012, № 2, pp. 35–39. (In Russian)

73. Slepneva L.V., Khmylova G.A. Mechanism of energy exchange violation in hypoxia and possible ways of its correction using fumarate-containing solutions. *Transfusiology*. 2013, № (2), pp. 36–39. (In Russian) [Full text]

74. Selivanov E.A., Slepneva L.V., Gerasimova M.L., Alekseeva N.N., Khmylova G.A. Efficient application of fumarate-containing preparations with polyfunctional action in the emergency infusion therapy. *Reporter of I.I.Mechnikov Saint Petersburg State Medical Academy*. 2006, № 7(2), pp. 150–153. (In Russian) [eLIBRARY]

75. Sukhomlin A.K., Ivanov A.YU., Slepneva L.V., Alekseeva N.N., Khmylova G.A., Verbitskiy V.G. Past, present and future of infusive fumarate-containing anti-hypoxic drugs in the therapy of urgent and critical conditions. *Journal of International Medicine*. 2016, № 1(18), pp. 60–69. (In Russian) [Full text]

76. Sofronov G.A., Selivanov E.A., Khanevich M.D., Fadeev R.V., Giparovich M.A., Yusifov S.A., Stolyarov I.K., Pshenkina N.N. Application of anti-hypoxic infusion solutions in surgery. *Reporter of N.I.Pirogov National Medico-Surgical Centre*. 2011, № 6(1), pp. 87–90. (In Russian)

77. Donetskaya O.P., Tulupova V.A., Shul'deshova N.V., Fedorova M.M. Pharmacocorrection of plasma redox potential and endothelium dysfunction in heart failure resulted from ischemic heart disease. *Cardiovascular Therapy and Prevention*. 2012, № 11(1), pp. 54-58. (In Russian) [Full text]

78. Budzinskaya M.V., Mikhaylova M.A., Balatskaya N.V. Pre-conditions for application of Histochrom preparations under redox system disbalance caused by venous retinal occlusions. *Efficient Pharmacotherapy*. 2013, № 23, pp.36-40. (In Russian)

79. Reznikov K.M. *Role of body water segment in the processes of its life activity: multi-author monograph*. (Voronezh, 2014), 249 p. (In Russian) [eLIBRARY]

80. Kolesnichenko P.D., Reznikov K.M. Influence of liquids with various oxidation-reduction potential on the gastro-intestinal tract. *Systemic Analysis and Management in Biomedical Systems*. 2012, Vol.11, № 1, pp. 55-60. (In Russian) [eLIBRARY]

81. Reznikov K.M., Levchenko Y.A., Levchenko P.V., Fateev A.L. *Salt-water body exchange and renal function under impact of electro-activated water solutions of sodium chloride for therapeutic purpose. Monograph*. (Voronezh: VGMA, 2011), 137 p. (In Russian) [eLIBRARY]

82. Reznikov K.M., Brezdynyuk A.D., Latysheva Y.N. *Safe application of electro-activated sodium chloride water solutions for therapeutic purpose. Monograph*. (Voronezh: VGMA, 2010), 144 p. (In Russian)

83. Mukhina D.Y., Kolesnichenko P.D. Impact of ionized water on the isolated heart parameters of a rat when simulating ischemia-reperfusion. *Journal of Research Articles "Health and Education in the XXI century"*. 2016, Vol. 18, № 1, pp. 312-315. (In Russian) [eLIBRARY] [Full text]

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