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# EFFECT OF CHELATES OF MINERAL ELEMENTS ON ADAPTIVE PROCESSES IN THE ORGANISM UNDER OXIDATIVE STRESS

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***Abstract.*** *A review of literary sources shows the prevalence of the problem of the development of oxidative stress as a side effect of many pathological processes in animals and humans. It is essential to develop ways and means of its prevention and correction since its correction can be a non-specific therapy in developing many pathological processes.*

*The development of oxidative stress caused deviations in redox processes, the permeability of cellular membranes, and their integrity. Overcoming the effects of oxidative stress requires bio-preparations with high bioavailability, which can stimulate the body's natural antioxidant defense system and neutralize the toxic effects of xenobiotics. Reducing the manifestation of oxidative stress is often adapting the body's natural antioxidant protection system to increase the supply or formation of reactive oxygen species and free radical oxidation products.*

*Macro- and microelements are absorbed by the body of animals and humans mainly through the digestive system. To correct deficiencies of certain elements, mineral, and vitamin-mineral supplements used in the diet, and drugs for parenteral administration - under acute deficiency.*

*Chelates of chemical elements are increasingly used in therapeutic practice, as they are characterized by higher bioavailability compared to organic and inorganic salts of the same elements.*

*The use of compounds with higher bioavailability makes it possible to introduce a smaller amount of the drug in terms of metal, which will avoid the irritating effect and improve the organoleptic indicators, preserving or even enhancing the therapeutic effect. Chelates have a lower irritating effect at the same concentrations as in saline solutions.*

*Therefore, the study of the biochemical mechanisms of action of the drug (in particular, in the correction of oxidative stress) is an urgent issue that prompts us to study it to develop a drug with high bioavailability and confirm its effectiveness.*

***Key words:*** *bio-preparations, chelate, magnesium, phosphorus, oxidative stress.*

## *Introduction.*

It is known that the production of reactive oxygen species (ROS) increases with the development of many pathological processes in the body of animals and humans (Hybertson, B. M., Gao, B., Bose, S. K., & McCord, J. M., 2011). ROS cause the formation of free radicals and the development of oxidative stress when the amount of ROS formation is greater than the speed of their neutralization and is accompanied by a violation of redox processes, the permeability of cell membranes, and their integrity (Tarallo, A.et al., 2021).

Oxidative stress occurs as a result of a wide range of pathological processes: infection, inflammation, stress, xenobiotic poisoning, etc. Therefore, it is important to develop methods and means of its prevention and correction (Melov, S., 2002). The development of drugs made based on available raw materials and effective methods of their application requires a fundamental study of the body's adaptation mechanisms to the action of oxidative stress (Barnes, P. J., 2020).

The antioxidant defense system (ADS) is responsible for the neutralization of ROS and free radicals in the body, which includes the enzymes superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase, and glutathione tripeptide together with cofactors (Barnes, P. J., 2020).

Magnesium participates (as a cofactor) in more than 300 catalytic reactions, due to which it is involved in energy, protein, lipid, and other exchanges (Morais, J. B. et al., 2017). Studies indicate a direct relationship between the content of magnesium in the body and glutathione, as well as the activities of AOZ enzymes (Kaliaperumal, R. et al., 2021). Since glutathione is involved in the detoxification of toxic metabolites, magnesium, which is necessary for its synthesis, exhibits pronounced antioxidant properties (Chen, Y. et al., 2019). It should be noted that preparations containing phosphorus combined with organic radicals are used as a source of organic phosphorus to enhance metabolic processes (Hax, L. T. et al., 2019; Nuber, U. et al., 2016). They are characterized by a high metabolic rate and low toxicity. Studies show that such phosphorus-containing drugs are not cumulative, and their use ensures the supply of phosphates to metabolic pathways, which are subsequently used for phosphorylation and the formation of macroergic compounds (Kreipe, L. et al., 2011; Rollin, E. et al., 2010).

The combined magnesium and phosphorus preparation based on casein "Biophosphomag" (hereinafter the preparation) is chemically composed of artificially phosphorylated cow's milk casein as a ligand that chelates magnesium ions. The drug was created as a complex with a high therapeutic and preventive, adaptogenic, and stimulating effect, while it was made based on available raw materials (Калачнюк Л. Г. та ін., 2020, a, b).

Chelates of chemical elements are increasingly used in therapeutic practice, as they are characterized by higher bioavailability compared to organic and

inorganic salts of the same elements (Grande, A. et al., 2020; Jahanian, R., & Rasouli, E., 2015).

***Purpose of article.*** Therefore, the study of the biochemical mechanisms of action of the drug (in particular, in the correction of oxidative stress) is an urgent issue that prompts us to study it to develop a drug with high bioavailability and confirm its effectiveness.

## *Chelates of mineral elements and their application.*

Macro- and microelements are absorbed by the body of animals and humans mainly through the digestive system. To correct deficiencies of certain elements, mineral and vitamin-mineral supplements are used in the diet, and in the case of acute deficiency, drugs for parenteral administration are used (Breymann, C., 2017; Fong, J., & Khan, A., 2012). The lack of certain elements in animals is due to the intensification of productivity compared to natural conditions, and in humans - due to the deep processing of food (Shah, N. C. et al., 2014; Yamamoto, M., & Yamaguchi, T., 2007). A common problem for humans and animals is the absence or imbalance of some elements in geochemical zones (Shenkin, A., 2006).

A chelate is an organic coordination compound consisting of a central metal atom and a polydentate ligand connected in a cyclic or ring structure. Chelates of mineral substances are most often obtained by the interaction of metal ions from a solution of their salt with free amino acids or peptides. The chelation process is characterized by the formation of two or more coordination bonds between one metal cation and two or more separate binding sites of one ligand. Usually, chelates are used, in which the ligands are amino acids or proteins, as they demonstrate the highest bioavailability (Cao, J. et al., 2000).

Chelates of chemical elements are increasingly used in therapeutic practice, as they have higher bioavailability compared to organic and inorganic salts of the same elements and, as a result, show more pronounced therapeutic effects (Grande, A. et al., 2020; Jahanian, R., & Rasouli, E., 2015). The use of compounds with higher bioavailability makes it possible to introduce a smaller amount of the drug in terms of metal, which will avoid the irritating effect and improve the organoleptic indicators, preserving or even enhancing the therapeutic effect. Chelates have a lower irritating effect at the same concentrations as saline agents (Fouad, G. T et al.., 2013).

The use of peptides, rather than individual amino acids for the synthesis of chelates, makes it possible to create complex multi-element complexes with a single ligand. The high bioavailability of chelates with proteins as ligands can be explained by the fact that they can be absorbed as oligopeptides after hydrolysis to di- and tripeptides. It was established that di- and tripeptides are absorbed by enterocytes of the small intestine with the help of the PepT1 cotransport system. The PepT1 system does not participate in the absorption of free amino acids from the alimentary canal. The rate of absorption of amino acids in the form of di- and tripeptides using PepT1 is 70-80% higher than the rate of absorption of free amino acids (Miner-Williams, W. M. et al., 2014). This gives reason to assert that the main number of amino acids assimilated by the body is absorbed in the form of di- and tripeptides and that oligopeptides are effective conductors increasing the bioavailability of substances combined with them.

The absorption efficiency of chelates is determined by several criteria of their bioavailability, namely: low molecular weight, the ability of ligands to be metabolized in the body, stability, etc. (Ashmead, S. D., 2001). An equally important factor that determines the high bioavailability of elements in the composition of chelates is that the ligand protects the metal ion from the formation of insoluble complexes (Thongon, N., & Krishnamra, N., 2011; Thongon, N., & Krishnamra, N.; 2012).

The degree of assimilation of ions of many metals is directly correlated with the degree of their chelation (Robberecht, H. et al., 2020). After assimilation by the body, chelates are hydrolyzed with the release of a metal ion and amino acid residues. Amino acid residues are used for the synthesis of peptides, and the metal ion is transported through the circulatory system to the place of performance of its functions (Hertrampf, E., & Olivares, M., 2004; Jeppsen, R. B., 2001; Pineda, O., & Ashmead, H. D., 2001).

Since chelates have several unique chemical properties, their therapeutic use is not limited to the correction of the lack of macro- and microelements (Ibrahim, O., & O'Sullivan, J., 2020; Kwiatkowski, J. L., 2008; Kontoghiorghe, C. N. et al.,2015). Studies demonstrate numerous advantages of chelates of microelements and macroelements in comparison with inorganic and organic salts of these elements (Name, J. J. et al., 2018; Ma, W. Q. et al., 2012; Case, D. R. et al., 2021).

Assimilation of magnesium ions in the body occurs in the digestive system. The divalent magnesium ion can combine with two amino acids through ionic bonds through carboxyl groups and donor-acceptor bonds with the amino groups of these amino acids (Figure 1).

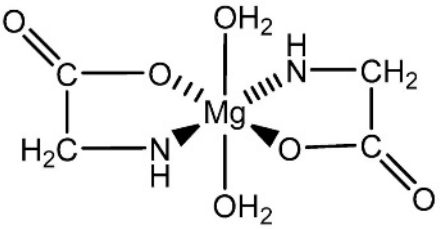


**Fig. 1. Chemical structure of magnesium chelate on the example of Magnesium bis-glycinate (Case, D. R. et al., 2020).**

Crystallographic studies show that the Mg2+ cation mainly has a coordination number of 6. Its radius is relatively small and is 0.86 Å, and according to the Pearson classification, it is a rigid ion, due to which the ligand-Mg2+ complexes are stable. The most stable complexes are formed with O-donors and less stable with N-donors. Many biological molecules can be effective ligands for magnesium ions, among them peptides and free amino acids due to free carboxyl and amino groups, nucleic acids, and free nucleotides due to phosphate groups, water molecules, etc. (Rutkowska-Zbik, D. et al., 2013).

The use of magnesium preparations in the form of chelates has several advantages, since magnesium mineral compounds, for example, magnesium sulfate, has a pronounced irritating effect on the intestines in high concentrations (Durlach, J. et al., 2005).

## *Biophosphomag is a combined magnesium and phosphorus preparation based on casein.*

The combined magnesium and phosphorus preparation based on casein (Biophosphomag) is chemically

composed of artificially phosphorylated cow's milk casein as a ligand that chelates magnesium ions. The appearance of the finished drug is a homogeneous powder from white to pale yellow (Калачнюк Л. Г. та ін., 2020a). In aqueous solutions with neutral and acidic pH, it is almost insoluble and easily soluble at pH > 8. It is recommended to combine the drug with vitamin B6 to enhance and supplement the therapeutic and preventive effect (Калачнюк Л. Г. та ін., 2020b). The drug obtained during the original synthesis protocol is easily subject to further modification and can be used as a raw material for the further development of more complex drugs (Калачнюк Л. Г. та ін., 2020a). Cow's milk casein, which is a mixture of several phosphoproteins (Rehan, F.et al.,2019; Madende, M. et al., 2015), serves as the raw material for the synthesis of the drug. The choice of casein as a chelating agent and carrier of functional groups is determined by its physicochemical and biological characteristics. First, casein is a complete protein, so it has in its amino acid sequence all essential amino acids in the optimal ratio for the body. Some serine residues in the structure of casein are naturally phosphorylated, which explains its ability to coagulate at low pH values. Coagulation of casein under the influence of low pH values is used by mammals for more effective hydrolysis and assimilation, and this property is also used to isolate casein from whole milk (Rafiq, S. et al., 2016). Another advantage of choosing casein for the synthesis of the drug is its prevalence and commercial availability. The above advantages of casein should contribute to the effectiveness of the drug synthesized on its basis and its introduction.

To obtain the drug, casein is chemically modified in two stages. The first stage of modification was protein phosphorylation. The reaction of direct esterification of orthophosphoric acid with O-nucleophiles (free hydroxy groups) is covered in sources (Li, C. et al., 2016; Xiong, B. et al., 2018; Matheis, G. et al., 1983). The main reaction mechanism is SN2 since the reaction by the asynchronous SN1 mechanism involves a slow first stage of nucleophile dissociation. The attacking groups in this reaction are the hydroxyl groups of threonine, serine, and tyrosine. The electrophilic center is the Phosphorus atom of orthophosphoric acid, from which the hydroxyl group is split off. The reaction can be catalyzed by transition metal ions (Cu2+, Fe2+). The scheme of this reaction based on the example of esterification of threonine with orthophosphoric acid is shown in Figure 2.

The second stage of the synthesis was magnesium chelation with additionally phosphorylated casein. The mechanism of chelation of magnesium ions by peptides is explained by their structure. Peptides are organized into primary,

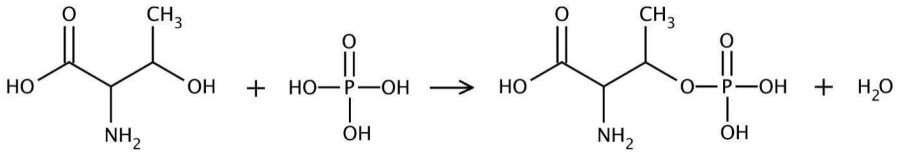


**Fig. 2. Scheme of the esterification reaction of orthophosphoric acid with an O-nucleophile using threonine as an example**

secondary, tertiary, and some quaternary structures. The primary structure is a sequence of amino acid residues interconnected by peptide bonds formed by the carboxyl group of one amino acid and the amino group of the next (-CONH-) (Li, Q. et al., 2014). Peptide bonds are characterized by reverse isomerism – tautomerism (Smith, M. B., 2001). The tautomerism of the peptide bond is explained by the migration of Hydrogen from Nitrogen to Oxygen, due to this, the peptide bond tautomerizes from the keto form to the enol (-C(OH)N-) isoform and vice versa. The enol form, due to the labile proton, is more reactive. The transition of one isoform to another and a stable balance between them can be achieved artificially (Kamiya, K. et al., 2006).

The formation of complex compounds by peptides occurs after the tautomerization of their keto-enol form. The formed enol form of the peptide bond contains a hydroxyl group, in which the proton becomes labile due to a strong shift of the electron cloud from Hydrogen to Oxygen and partial attraction of this electron cloud by Nitrogen. Showing lower electronegativity, metal cations can displace hydrogen from the enol form of a peptide bond (Sproul, G. D., 2020). Metal ions, which have free unfilled electronic orbitals, are also able to interact with nitrogen by the donor-acceptor mechanism. With the simultaneous formation of ionic and coordination bonds, the peptide seems to wrap around the metal ion, which is called chelation (from the Greek Chelè - claw) (Flora, S. J., & Pachauri, V., 2010).

The formation of complex compounds by peptides occurs after the A review of literary sources shows the prevalence of the problem of the development of oxidative stress as a side effect of many pathological processes in animals and humans (Hybertson, B. M. et al., 2011; Melov, S., 2002). Considering this, it is important to develop methods and means of its prevention and correction, since its correction can be a non-specific therapy in developing many pathological processes (Tarallo, A. et al., 2021) .

It was mentioned above that Magnesium is involved in maintaining the functional state of the oxidative stress (Morais, J. B. et al, 2017). Studies indicate a direct relationship between the content of magnesium in the body and glutathione, as well as the activities of enzymes (Kaliaperumal, R. et al., 2021; Chen, Y. et al., 2019). Since glutathione is involved in the detoxification of toxic metabolites, magnesium, which is necessary for its synthesis, exhibits pronounced antioxidant properties. Preparations that contain phosphorus combined with organic radicals are used as a source of organic phosphorus to enhance the course of metabolic processes (Weiller, M., 2020; Pereira, R. A. et al., 2013).

As a complete protein, casein contains all proteinogenic amino acids in the optimal ratio for the mammalian body. Due to its availability, distribution, and several physicochemical features, casein is used in the pharmaceutical industry as a carrier of active components (Głąb, T. K., & Boratyński, J., 2017).

The use of chelates of mineral elements has many advantages, which is the reason for the spread of their use. The main ones are higher bioavailability and lower irritating effect in comparison with salt means of the same elements (Udechukwu, M. C. et al., 2016; Allen, L. H., 2002).

Neutralizing the effects of oxidative stress requires drugs that can stimulate the body's natural antioxidant defense system (ADS) and neutralize the toxic effects of xenobiotics (Barnes, P. J., 2020). Since Magnesium can stimulate many metabolic processes, as well as maintaining the functional state of the ADS, its combination with Phosphorus as part of a chelate complex is potentially promising for combating oxidative stress.

Based on the theoretical generalization and analysis of the results of our experimental studies, it is possible to propose a hypothetical biochemical mechanism of the adaptogenic action of the combined magnesium and phosphorus preparation based on casein under conditions of oxidative stress (Figure 3).

The mechanism of adaptogenic action of the drug is explained by its chemical structure and biological properties. After entering the digestive tract, the biological preparation hydrolyzes to oligopeptides. According to literature data, oligopeptides consisting exclusively of L-amino acid residues are most intensively absorbed, those containing individual D-amino acid residues are assimilated less intensively, and di- and tripeptides, which consist exclusively of D-amino acid residues, are not absorbed in all. Since casein is the starting material for the synthesis after the hydrolytic splitting of the drug only oligopeptides consisting of L-amino acid residues are formed (Rubio-Aliaga, I., & Daniel, H., 2008).

After entering enterocytes, oligopeptides can be subjected to cytosolic hydrolysis or transported unchanged through the basolateral membrane to the portal system of the liver [209]. At the same time, the magnesium ions combined with them are strongly absorbed,

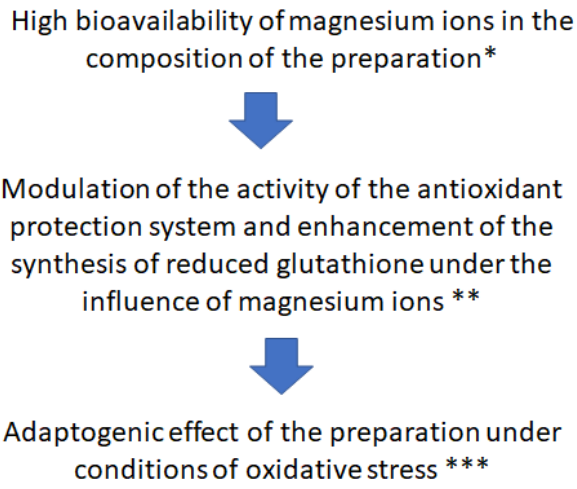


**Figure 3. Hypothetical biochemical mechanism of the adaptogenic action of the combined magnesium and phosphorus preparation based on casein under conditions of oxidative stress. Note: * – bioavailability of the drug and magnesium content; ** – antioxidant properties of the drug; *** – research under conditions of induced oxidative stress.**

which are then used by the body to ensure the functioning of magnesium-dependent enzymatic systems, etc.

## *Conclusion and Perspectives.*

Therefore, the investigation of the biochemical mechanisms of the biopreparation's action (in particular, when correcting oxidative stress) is an urgent problem, which prompts its study to develop a drug with high bioavailability and confirm its effectiveness.

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### References

1. Hybertson, B. M., Gao, B., Bose, S. K., & McCord, J. M. (2011). Oxidative stress in health and disease: The therapeutic potential of Nrf2 activation. Molecular Aspects of Medicine, 32(4-6), 234–246. https://doi.org/10.1016/j.mam.2011.10.006
2. Tarallo, A., Damiano, C., Strollo, S., Minopoli, N., Indrieri, A., Polishchuk, E., Zappa, F., Nusco, E., Fecarotta, S., Porto, C., Coletta, M., Iacono, R., Moracci, M., Polishchuk, R., Medina, D. L., Imbimbo, P., Monti, D. M., De Matteis, M. A., & Parenti, G. (2021). Correction of oxidative stress enhances enzyme replacement therapy in Pompe disease. EMBO Molecular Medicine, 13(11), e14434. https://doi.org/10.15252/emmm.202114434
3. Melov, S. (2002). Animal models of oxidative stress, aging, and therapeutic antioxidant interventions. The International Journal of Biochemistry & Cell Biology, 34(11), 1395–1400. https://doi.org/10.1016/s1357-2725(02)00086-9
4. Barnes, P. J. (2020). Oxidative stress-based therapeutics in COPD. Redox Biology, 33, 101544. https://doi.org/10.1016/j.redox.2020.101544
5. Morais, J. B., Severo, J. S., Santos, L. R., de Sousa Melo, S. R., de Oliveira Santos, R., de Oliveira, A. R., Cruz, K. J., & do Nascimento Marreiro, D. (2017). Role of magnesium in oxidative stress in individuals with obesity. Biological Trace Element Research, 176(1), 20–26. https://doi.org/10.1007/s12011-016-0793-1
6. Kaliaperumal, R., Venkatachalam, R., Nagarajan, P., & Sabapathy, S. K. (2021). Association of serum agnesium with oxoidative stress in the pathogenesis of diabetic cataract. Biological Trace Element Research, 199(8), 2869–2873. https://doi.org/10.1007/s12011-020-02429-9
7. Chen, Y., Xiong, S., Zhao, F., Lu, X., Wu, B., & Yang, B. (2019). Effect of magnesium on reducing the UV-induced oxidative damage in marrow mesenchymal stem cells. Journal of Biomedical Materials Research Part A, 107(6), 1253–1263. https://doi.org/10.1002/jbm.a.36634
8. Hax, L. T., Rincón, J., Schneider, A., Pegoraro, L., Franco Collares, L., Alves Pereira, R., Pradieé, J., Del Pino, F., & Nunes Corrêa, M. (2019). Effect of butafosfan supplementation during oocyte maturation on bovine embryo development. Zygote, 27(5), 321–328. https://doi.org/10.1017/S0967199419000327
9. Nuber, U., van Dorland, H. A., & Bruckmaier, R. M. (2016). Effects of butafosfan with or without cyanocobalamin on the metabolism of early lactating cows with subclinical ketosis. Journal of Animal Physiology and Animal Nutrition, 100(1), 146–155. https://doi.org/10.1111/jpn.12332
10. Kreipe, L., Deniz, A., Bruckmaier, R. M., & van Dorland, H. A. (2011). First report about the mode of action of combined butafosfan and cyanocobalamin on hepatic metabolism in nonketotic early lactating cows. Journal of Dairy Science, 94(10), 4904–4914. https://doi.org/10.3168/jds.2010-4080
11. Rollin, E., Berghaus, R. D., Rapnicki, P., Godden, S. M., & Overton, M. W. (2010). The

effect of injectable butaphosphan and cyanocobalamin on postpartum serum beta-hydroxybutyrate, calcium, and phosphorus concentrations in dairy cattle. Journal of Dairy Science, 93(3), 978–987. https://doi.org/10.3168/jds.2009-2508

12. Патент України на корисну модель №139707. Препарат ветеринарний «Біофосфомаг». МПК, A61K 31/66 (2006.01). Калачнюк Л. Г., Арнаута О. В., Вірьовка В. М., Пальонко Р. І., Смірнов О. О., Мартиненко О. А., Прис-Каденко В. О., Аль-Баду Л-Є. Н. Номер заявки: u 201907874. Дата подання заявки: 11.07.2019 р. Опубліковано 10.01.2020, Бюл. № 1/2020 (a)
13. Патент України на корисну модель №139707. Препарат ветеринарний «Біофосфомаг-Плюс». МПК, A61K 31/66 (2006.01). Калачнюк Л. Г., Арнаута О. В., Вірьовка В. М., Пальонко Р. І., Смірнов О. О., Мартиненко О. А., Прис-Каденко В. О., Аль-Баду Л-Є. Н. Номер заявки: u 201907874. Дата подання заявки: 11.07.2019 р. Опубліковано 10.01.2020, Бюл. № 1/2020 (b)
14. Grande, A., Leleu, S., Delezie, E., Rapp, C., De Smet, S., Goossens, E., Haesebrouck, F., Van Immerseel, F., & Ducatelle, R. (2020). Dietary zinc source impacts intestinal morphology and oxidative stress in young broilers. Poultry Science, 99(1), 441–453. https://doi.org/10.3382/ps/pez525
15. Jahanian, R., & Rasouli, E. (2015). Effects of dietary substitution of zinc-methionine for inorganic zinc sources on growth performance, tissue zinc accumulation and some blood parameters in broiler chicks. Journal of Animal Physiology and Animal Nutrition, 99(1), 50–58. https://doi.org/10.1111/jpn.12213
16. Breymann, C., Honegger, C., Hösli, I., & Surbek, D. (2017). Diagnosis and treatment of iron-deficiency anaemia in pregnancy and postpartum. Archives of Gynecology and Obstetrics, 296(6), 1229–1234. https://doi.org/10.1007/s00404-017-4526-2
17. Fong, J., & Khan, A. (2012). Hypocalcemia: Updates in diagnosis and management for primary care. Canadian Family Physician, 58(2), 158–162. https://pubmed.ncbi.nlm.nih.gov/22439169/
18. Shah, N. C., Shah, G. J., Li, Z., Jiang, X. C., Altura, B. T., & Altura, B. M. (2014). Short-term magnesium deficiency downregulates telomerase, upregulates neutral sphingomyelinase and induces oxidative DNA damage in cardiovascular tissues: Relevance to atherogenesis, cardiovascular diseases and aging. International Journal of Clinical and Experimental Medicine, 7(3), 497–514. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3992387/
19. Yamamoto, M., & Yamaguchi, T. (2007). Causes and treatment of hypomagnesemia. Clinical Calcium, 17(8), 1241–1248. https://europepmc.org/article/MED/17660622
20. Shenkin, A. (2006). Micronutrients in health and disease. Postgraduate Medical Journal, 82(971), 559–567. https://doi.org/10.1136/pgmj.2006.047670
21. Cao, J., Henry, P. R., Guo, R., Holwerda, R. A., Toth, J. P., Littell, R. C., Miles, R. D., & Ammerman, C. B. (2000). Chemical characteristics and relative bioavailability of supplemental organic zinc sources for poultry and ruminants. Journal of Animal Science, 78(8), 2039–2054. https://doi.org/10.2527/2000.7882039x
22. Fouad, G. T., Evans, M., Sharma, P., Baisley, J., Crowley, D., & Guthrie, N. (2013). A randomized, double-blind clinical study on the safety and tolerability of an iron multi-amino acid chelate preparation in premenopausal women. Journal of Dietary Supplements, 10(1), 17–28. https://doi.org/10.3109/19390211.2012.758217
23. Miner-Williams, W. M., Stevens, B. R., & Moughan, P. J. (2014). Are intact peptides absorbed from the healthy gut in the adult human? Nutrition Research Reviews, 27(2), 308–329. https://doi.org/10.1017/S0954422414000225

24. Ashmead, S. D. (2001). The chemistry of ferrous bis-glycinate chelate. Archivos Latinoamericanos de Nutricion, 51(1), 7–12. https://pubmed.ncbi.nlm.nih.gov/11688084/
25. Thongon, N., & Krishnamra, N. (2011). Omeprazole decreases magnesium transport across Caco-2 monolayers. World Journal of Gastroenterology, 17(12), 1574–1583. https://doi.org/10.3748/wjg.v17.i12.1574
26. Thongon, N., & Krishnamra, N. (2012). Apical acidity decreases inhibitory effect of omeprazole on Mg(2+) absorption and claudin-7 and -12 expression in Caco-2 monolayers. Experimental & Molecular Medicine, 44(11), 684–693. https://doi.org/10.3858/emm.2012.44.11.077
27. Robberecht, H., Verlaet, A., Breynaert, A., De Bruyne, T., & Hermans, N. (2020). Magnesium, iron, zinc, copper and selenium status in attention-deficit/hyperactivity disorder (ADHD). Molecules, 25(19), 4440. https://doi.org/10.3390/molecules25194440
28. Hertrampf, E., & Olivares, M. (2004). Iron amino acid chelates. International Journal for Vitamin and Nutrition Research, 74(6), 435–443. https://doi.org/10.1024/0300-9831.74.6.435
29. Jeppsen, R. B. (2001). Toxicology and safety of Ferrochel and other iron amino acid chelates. Archivos Latinoamericanos de Nutricion, 51(1), 26–34. https://pubmed.ncbi.nlm.nih.gov/11688078/
30. Pineda, O., & Ashmead, H. D. (2001). Effectiveness of treatment of iron-deficiency anemia in infants and young children with ferrous bis-glycinate chelate. Nutrition, 17(5), 381–384. https://doi.org/10.1016/s0899-9007(01)00519-6
31. Ibrahim, O., & O'Sullivan, J. (2020). Iron chelators in cancer therapy. Biometals, 33(4-5), 201–215. https://doi.org/10.1007/s10534-020-00243-3
32. Kwiatkowski, J. L. (2008). Oral iron chelators. Pediatric Clinics of North America, 55(2), 461–482. https://doi.org/10.1016/j.pcl.2008.01.005
33. Kontoghiorghe, C. N., Kolnagou, A., & Kontoghiorghes, G. J. (2015). Phytochelators intended for clinical use in iron overload, other diseases of iron imbalance and free radical pathology. Molecules, 20(11), 20841–20872. https://doi.org/10.3390/molecules201119725
34. Name, J. J., Vasconcelos, A. R., & Valzachi Rocha Maluf, M. C. (2018). Iron bisglycinate chelate and polymaltose iron for the treatment of iron deficiency anemia: A pilot randomized trial. Current Pediatric Reviews, 14(4), 261–268. https://doi.org/10.2174/1573396314666181002170040
35. Ma, W. Q., Sun, H., Zhou, Y., Wu, J., & Feng, J. (2012). Effects of iron glycine chelate on growth, tissue mineral concentrations, fecal mineral excretion, and liver antioxidant enzyme activities in broilers. Biological Trace Element Research, 149(2), 204–211. https://doi.org/10.1007/s12011-012-9418-5
36. Case, D. R., Zubieta, J., Gonzalez, R., & Doyle, R. P. (2021). Synthesis and chemical and biological evaluation of a glycine tripeptide chelate of magnesium. Molecules, 26(9), 2419. https://doi.org/10.3390/molecules26092419
37. Rutkowska-Zbik, D., Witko, M., & Fiedor, L. (2013). Ligation of water to magnesium chelates of biological importance. Journal of Molecular Modeling, 19(11), 4661–4667. https://doi.org/10.1007/s00894-012-1459-3
38. Case, D. R., Zubieta, J., & P Doyle, R. (2020). The coordination chemistry of bio-relevant ligands and their magnesium complexes. Molecules, 25(14), 3172. https://doi.org/10.3390/molecules25143172
39. Durlach, J., Guiet-Bara, A., Pagès, N., Bac, P., & Bara, M. (2005). Magnesium chloride or magnesium sulfate: A genuine question. Magnesium Research, 18(3),

187–192. https://pubmed.ncbi.nlm.nih.gov/16259379/

40. Rehan, F., Ahemad, N., & Gupta, M. (2019). Casein nanomicelle as an emerging biomaterial-A comprehensive review. Colloids and Surfaces B: Biointerfaces, 179, 280–292. https://doi.org/10.1016/j.colsurfb.2019.03.051
41. Madende, M., Osthoff, G., Patterton, H. G., Patterton, H. E., Martin, P., & Opperman, D. J. (2015). Characterization of casein and alpha lactalbumin of African elephant (Loxodonta africana) milk. Journal of Dairy Science, 98(12), 8308–8318. https://doi.org/10.3168/jds.2014-9195
42. Rafiq, S., Huma, N., Pasha, I., Sameen, A., Mukhtar, O., & Khan, M. I. (2016). Chemical composition, nitrogen fractions and mino aacids profile of milk from different animal species. Asian-Australasian Journal of Animal Sciences, 29(7), 1022–1028. https://doi.org/10.5713/ajas.15.0452
43. Li, C., Chen, T., & Han, L. B. (2016). Iron-catalyzed clean dehydrogenative coupling of alcohols with P(O)-H compounds: A new protocol for ROH phosphorylation. Dalton Transactions, 45(38), 14893–14897. https://doi.org/10.1039/c6dt02236g
44. Xiong, B., Wang, G., Zhou, C., Liu, Y., Li, J., Zhang, P., & Tang, K. (2018). DCC-assisted direct esterification of phosphinic and phosphoric acids with O-nucleophiles. Phosphorus, Sulfur, and Silicon and the Related Elements, 193(4), 239-244. https://doi.org/10.1080/10426507.2017.1395438
45. Matheis, G., Penner, M. H., Feeney, R. E., & Whitaker, J. R. (1983). Phosphorylation of casein and lysozyme by phosphorus oxychloride. Journal of Agricultural and Food Chemistry, 31(2), 379–387. https://doi.org/10.1021/jf00116a049
46. Li, Q., Dahl, D. B., Vannucci, M., Joo H., & Tsai, J. W. (2014). Bayesian model of protein primary sequence for secondary structure prediction. PloS one, 9(10), e109832. https://doi.org/10.1371/journal.pone.0109832
47. Smith, M. B. (2001). Acyl substitution reactions. In M. B. Smith & J. March (Eds.), Advanced organic chemistry (5th ed., pp. 1218-1223). New York: Wiley Interscience.
48. Kamiya, K., Boero, M., Shiraishi, K., & Oshiyama, A. (2006). Enol-to-keto tautomerism of peptide groups. The Journal of Physical Chemistry B, 110(9), 4443–4450. https://doi.org/10.1021/jp056250p
49. Sproul, G. D. (2020). Evaluation of electronegativity scales. ACS Omega, 5(20), 11585–11594. https://doi.org/10.1021/acsomega.0c00831
50. Flora, S. J., & Pachauri, V. (2010). Chelation in metal intoxication. International Journal of Environmental Research and Public Health, 7(7), 2745–2788. https://doi.org/10.3390/ijerph7072745
51. Hybertson, B. M., Gao, B., Bose, S. K., & McCord, J. M. (2011). Oxidative stress in health and disease: The therapeutic potential of Nrf2 activation. Molecular Aspects of Medicine, 32(4-6), 234–246. https://doi.org/10.1016/j.mam.2011.10.006
52. Melov, S. (2002). Animal models of oxidative stress, aging, and therapeutic antioxidant interventions. The International Journal of Biochemistry & Cell Biology, 34(11), 1395–1400. https://doi.org/10.1016/s1357-2725(02)00086-9
53. Tarallo, A., Damiano, C., Strollo, S., Minopoli, N., Indrieri, A., Polishchuk, E., Zappa, F., Nusco, E., Fecarotta, S., Porto, C., Coletta, M., Iacono, R., Moracci, M., Polishchuk, R., Medina, D. L., Imbimbo, P., Monti, D. M., De Matteis, M. A., & Parenti, G. (2021). Correction of oxidative stress enhances enzyme replacement therapy in Pompe disease. EMBO Molecular Medicine, 13(11), e14434. https://doi.org/10.15252/emmm.202114434
54. Morais, J. B., Severo, J. S., Santos, L. R., de Sousa Melo, S. R., de Oliveira Santos, R., de Oliveira, A. R., Cruz, K. J., & do Nascimento Marreiro, D. (2017). Role of magnesium in

oxidative stress in individuals with obesity. Biological Trace Element Research, 176(1), 20–26. https://doi.org/10.1007/s12011-016-0793-1

55. Kaliaperumal, R., Venkatachalam, R., Nagarajan, P., & Sabapathy, S. K. (2021). Association of serum agnesium with oxoidative stress in the pathogenesis of diabetic cataract. Biological Trace Element Research, 199(8), 2869–2873. https://doi.org/10.1007/s12011-020-02429-9
56. Chen, Y., Xiong, S., Zhao, F., Lu, X., Wu, B., & Yang, B. (2019). Effect of magnesium on reducing the UV-induced oxidative damage in marrow mesenchymal stem cells. Journal of Biomedical Materials Research Part A, 107(6), 1253–1263. https://doi.org/10.1002/jbm.a.36634
57. Weiller, M., Alvarado-Rincón, J. A., Jacometo, C. B., Barros, C. C., de Souza, I., Hax, L. T., da Silva, T. C., Mattei, P., Barbosa, A. A., Feijó, J. O., Pereira, R. A., Brauner, C. C., Rabassa, V. R., Del Pino, F., & Corrêa, M. N. (2020). Butaphosphan effects on glucose metabolism involve insulin signaling and depends on nutritional plan. Nutrients, 12(6), 1856. https://doi.org/10.3390/nu12061856
58. Pereira, R. A., Silveira, P. A., Montagner, P., Schneider, A., Schmitt, E., Rabassa, V. R., Pfeifer, L. F., Del Pino, F. A., Pulga, M. E., & Corrêa, M. N. (2013). Effect of butaphosphan and cyanocobalamin on postpartum metabolism and milk production in dairy cows. Animal: An International Journal of Animal Bioscience, 7(7), 1143–1147. https://doi.org/10.1017/S1751731113000013
59. Głąb, T. K., & Boratyński, J. (2017). Potential of casein as a carrier for biologically active agents. Topics in Current Chemistry, 375(4), 71. https://doi.org/10.1007/s41061-017-0158-z
60. Udechukwu, M. C., Collins, S. A., & Udenigwe, C. C. (2016). Prospects of enhancing dietary zinc bioavailability with food-derived zinc-chelating peptides. Food & Function, 7(10), 4137–4144. https://doi.org/10.1039/c6fo00706f
61. Allen, L. H. (2002). Advantages and limitations of iron amino acid chelates as iron fortificants. Nutrition Reviews, 60(7), S18–S45. https://doi.org/10.1301/002966402320285047
62. Barnes, P. J. (2020). Oxidative stress-based therapeutics in COPD. Redox Biology, 33, 101544. https://doi.org/10.1016/j.redox.2020.101544
63. Rubio-Aliaga, I., & Daniel, H. (2008). Peptide transporters and their roles in physiological processes and drug disposition. Xenobiotica, 38(7-8), 1022–1042. https://doi.org/10.1080/00498250701875254

***Р. Пальонко, Л. Калачнюк (2022). ВПЛИВ ХЕЛАТІВ МІНЕРАЛЬНИХ ЕЛЕМЕНТІВ НА АДАПТАЦІЙНІ ПРОЦЕСИ В ОРГАНІЗМІ ЗА ОКСИДАТИВНОГО СТРЕСУ .***
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***Анотація.*** *Огляд літературних джерел свідчить про розповсюдженість проблеми розвитку оксидативного стресу як побічного явища багатьох патологічних процесів у тварин і людей. Зважаючи на це, важливе значення мають розробка способів і засобів його профілактики та корекції, оскільки його корекція може бути неспецифічною терапією при розвитку багатьох патологічних процесів.*

*В умовах розвитку оксидативного стресу спостерігають порушення окисно-відновних процесів, проникності клітинних мембран та їх цілісності. Подолання наслідків оксидативного стресу потребує препаратів з високою біодоступністю, які здатні сти-*

*мулювати природну систему антиоксидантного захисту організму та нейтралізувати токсичні ефекти ксенобіотиків. Зниження прояву оксидативного стресу часто полягає в адаптації природної системи антиоксидантного захисту організму до збільшення надходження чи утворення активних форм кисню та продуктів вільнорадикального окиснення.*

*Макро- і мікроелементи засвоюються організмом тварин і людини переважно через систему травлення. Для корекції дефіцитів окремих елементів використовують мінеральні та вітамінно-мінеральні добавки до раціону, а у випадку гострого дефіциту – препарати для парентерального введення.*

*Хелати хімічних елементів все частіше використовуються в терапевтичній практиці, оскільки їм властива вища біодоступність порівняно з органічними та неорганічними солями цих же елементів*

*Застосування сполук з вищою біодоступністю дозволяє вводити меншу кількість препарату в перерахунку на метал, що дозволить уникнути подразнюючої дії та покращити органолептичні показники зберігши або навіть посиливши терапевтичний ефект. Хелатам властива нижча подразнювальна дія за тих же концентрацій, що і в сольових засобах.*

*Отже, дослідження біохімічних механізмів дії препарату (зокрема при корекції оксидативного стресу) є актуальним питанням, що спонукає нас до його вивчення з метою розробки препарату з високою біодоступністю та підтвердження його ефективності.*

***Ключові слова:*** *біопрепарати, оксидативний стрес, магній, фосфор, хелат.*