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M.P. GULICH[1*], N.L. YEMCHENKO[1], V.G. KAPLINENKO[2], O.O. KHARCHENKO[1]

[1] State Institution «O.M. Marzieiev Institute for Public Health NAMSU»,
50 Popudrenko Str., Kyiv, 02094, Ukraine

[2] LLC «Nanomaterials and nanotechnologies»,
27 Vasylkivska Str., Kyiv, 03022, Ukraine

* Author for correspondence; e-mail: gumapa@ukr.net

TRACE ELEMENTS ZINC AND SELENIUM: THEIR SIGNIFICANCE IN THE CONDITIONS OF THE COVID-19 PANDEMIC

Within the conditions of the ongoing COVID-19 pandemic, when many questions regarding prevention and treatment strategies remain unsolved and the search for the best antiviral agents is underway, attention should be paid to the role of trace elements zinc and selenium in increasing the body's resistance to viral infections and their direct antiviral activity against SARS-CoV-2. Experimental data show that trace elements zinc and selenium not only actthrough regulating the immune response at all levels of humoral and cellular immunity, but also can play a significant role in adjuvant therapy for viral diseases. This is especially relevant in the case of COVID-19. Studies of the direct antiviral effect of these microelements testify to its 3 main ways to SARS-Cov-2: I — counteraction to virus replication and its transcription through: (i) their covalent binding to the SH-group of the cysteine of the main protease M(Pro) of the virus; (ii) inhibition of its RNA polymerase activity by zinc; II — preventing the penetration of the virus into cells due to blocking SH-groups of protein disulfide isomerase (RDI) of the protein of its spikes (peplomers); III — decreasing the adsorption capacity of the virus due to the blocking of the electrostatic interaction of SARS-CoV-2 peplomers and angiotensin-converting enzyme (ACE-2) in ultra-low, uncharacteristic oxidation states ($Zn^{+1}$and Se^{-2}). The intensity of the antiviral action of these trace elements may depend on their chemical form. It was found that zinc citrate (a five-membered complex of zinc with citric acid) and monoselenium citric acid obtained with the help of nanotechnology have a greater intensity of action and higher chemical purity. Taking into account the immunostimulating and direct antiviral effect of zinc and selenium, their use in the form of pharmaceuticals and dietary supplements should be considered as adjunctive therapy for SARS-CoV-2 in patients, or as a preventive strategy for uninfected people from risk groups during the spread of COVID-19.

Keywords: *trace elements, zinc, selenium, COVID-19, SARS-CoV-2, immunity, antiviral action, zinc citrate, monoselenium citric acid.*

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For more than three years, humanity has been in the conditions of the COVID-19 pandemic caused by the SARS-CoV-2 coronavirus. The world medical community believes that it is possible to overcome the COVID-19 pandemic by obtaining collective immunity against the SARS-CoV-2 coronavirus, provided that more than 70% of the population has specific immunity. It is clear that this is possible in case of vaccination, or transmission of the disease to COVID-19 of the main part of the population. But medical practice during the three-year period of the pandemic shows that the SARS-CoV-2 coronavirus mutates, which leads to the emergence of new strains. Currently, humanity is experiencing the sixth wave of the COVID-19 pandemic, caused by the O-micron strain, which is more contagious than previous strains and caused disease in both vaccinated people and those who have already contracted COVID-19. Today it is known that from the O-micron variant, new strains of coronavirus have been developed — BA.4, BA.5 and a new strain BA.2.75, the so-called «centaur». Compared to its original variant (BA.2), the new coronavirus strains have eight additional spike protein mutations.

It is possible that variants of the SARS-CoV-2 coronavirus will accompany our lives for many years, and humanity must adapt to that in everyday life, and this forces all countries to look at people's health differently.

Despite the fact that scientists all over the world are fruitfully working on the question of the origin and structure of the SARS-CoV-2 virus, channels of infection, diagnosis of the disease, use of pharmaceuticals, immune development, etc., many questions remain unsolved today [1]. Among them: why in one family some people get sick with COVID-19, and the others do not (or in a very mild form); why the mortality rate is different among those who have fallen *ill*; how effective the immune system is in the fight against viral infection and what is the role of the state of the general immunity of a person in preventing from COVID-19.

Recently, taking into account that the SARS-CoV-2 coronavirus mutates very quickly and this makes it difficult to carry out measures to prevent and fight against it, scientists suggest turning to the internal resources of the human body, namely to its ability to fight the disease on its own. To a large extent, it depends on the state of human immunity.

How can you maintain a high level of immunity so as not to get sick with COVID-19, or what affects the state of the immune system? As established, the strength of the immune system and the state of the body as a whole depend on the individual genetic characteristics, which determine the work of certain enzymes, in particular, angiotensin-converting enzyme (ACE—2), which determines strong innate immunity.

Recently, scientists have been investigated the possibility of non-specific strengthening of immunity against COVID-19 when using a vaccine against other diseases [2]. But the possibility of determining the strength of a person's immune system does not exist without the possibility of conducting tests on the immune system genes. It is a fallacy to assume the use of immunization against, for example, tuberculosis, whooping cough, or poliomyelitis on a large scale for non-specific stimulation of immunity in our time, as this issue requires further detailed study.

Today, the most realistic and affordable measure for the general population to maintain a high level of the general non-specific immunity of a person and increase the body's resistance to infectious diseases is to adequately provide it with vitamins and trace elements. A lot of experts believe that the best antiviral protection is created by a «cocktail» of three components, namely vitamin D and trace elements zinc and selenium.

Relating to vitamin D, there are numerous confirmations of its positive effect in the scientific literature for the prevention and treatment of COVID-19 [3]. In this article, we will dwell in more detail on the importance of zinc and selenium in the prevention and treatment of this disease.

It is known that the main physiological functions of zinc include immune protection of the body [4]. Thus, it regulates the proliferation, differentiation, maturation, and functioning of leukocytes and lymphocytes, which is the basis of cellular immunity, and hence the body's immune response, protecting it from viral and bacterial infections [5]. In the case of zinc deficiency, the body's protective cells, such as T-helpers and T-killers, are synthesized in insufficient quantities and, as a result, the immunity weakens [6]. Strengthening of antiviral immunity with zinc also occurs due to the increase in the production of α-interferon. These data indicate that zinc can significantly increase the antiviral resistance of the body in the case of COVID-19 [7]. In addition, it has been shown that Zn^{+2} cations suppress the activity of the RNA polymerase of the SARS-CoV-2 virus, reducing its replication [8]. As a result, zinc is considered as an antiviral agent in the therapy of the infection of COVID-19 due to not only its immunomodulation effect, but also its direct antiviral effect [9].

These important findings demonstrate that Zn^{+2} can be considered as a specific antiviral agent in the treatment of COVID-19. It should be noted that zinc has previously also been proposed as a potential agent for immune support and prevention of H1N1 (swine-origin influenza A viruses) [10].

Recent studies have shown the effectiveness of the antiviral activity against SARS-CoV-2 of the zinc ionophore-chloroquine [11], which increases the intake of zinc into body cells [12]. The authors believe that the increase in the intracellular concentration of zinc ions by chloroquine may mediate its antiviral effect. From this point of view, the intake of zinc without chloroquine can have the same positive effects without overlaying the negative ones caused by chloroquine [13].

Hypothetically, this effect can be achieved with the help of other zinc ionophores (complexing ligands), such as quercitin and epigallocatechingallate [14] with much lower toxicity, although clinical trials supported by *in vitro* experimental studies are needed to confirm this hypothesis.

Given the high prevalence of zinc deficiency worldwide, and according to current estimates, more than 1.5 billion people on earth are at risk of zinc deficiency [15—19], the impact of which on public health in the context of the COVID-19 pandemic is considered as an important medical problem.

Selenium is the second most important trace element in our time. As an essential trace element, it is involved in many life-important processes, implemented with the help of 25 selenium proteins which affect oxidative stress, hormonal metabolism, cognitive functions, and most importantly, the immune response [20].

Back in the early 2000s, it was thought that selenium has antiviral activity. It was found that such viral diseases as HIV, hepatitis C, Ebola, and various types of flu are more severe with its deficiency. Thus, mortality from HIV in selenium-deficient regions was 3—5 times higher than that in regions without selenium deficiency. There is a clear connection between selenium deficiency in various regions of the world with low levels of selenium in the soil and the spread of AIDS [21, 22].

Selenium, like zinc, is believed to play a key role in the maintenance of immunity and has long been known as a regulator of the immune response at all levels of nonspecific humoral and cellular immunity [23, 24]. Therefore, the level of selenium in the diet of the population can be of great importance during the COVID-19 pandemic, both at the beginning of the disease and for the severity of the disease and its complications, caused by the violation of the immune response and the development of oxidative stress [20].

In the latest epidemiological studies related to COVID-19, conducted in China by an international group of leading scientists, the existence of a correlative relationship between the content of selenium in the hair and the recovery was demonstrated: a fivefold increase in the survival of patients (Hubach Province, center of Wuhan), against the cases with reduced selenium status (Heilongjiang Province). There is an inverse correlation between the mortality rate from COVID-19 and the level of selenium intake. Selenium-deficient areas are known as the «Chinese disease belt» [25].

At the same time, selenium deficiency is increasing in many countries. Even in such countries as Great Britain, the intake of selenium with food products has decreased by 50% [26]. By now, monitoring studies have been conducted in European countries, including Ukraine, which revealed a deficiency of selenium in the population's diet [22, 27, 28].

What is the reason for the connection between selenium deficiency and the incidence of viral infections, including COVID-19? It turns out that all RNA viruses are selenium-dependent objects, that is, their genome contains the codes of the most important selenium proteins. Their synthesis under the conditions of the development of a viral infection at the expense of the host leads to a weakening of the synthesis of the body's own selenium proteins, which contributes to the development of oxidative stress and failure of the immune response [29].

All of the above determines the need to replenish zinc and selenium resources in the body, as well as the use of selenium-containing dietary supplements or pharmacopeial medications in the therapy of RNA virus infections.

It is known that in the implementation of the contact of glycoprotein spikes of the SARS-CoV-2 virus with the receptors of the membranes of the host cells, protein disulfide isomerase (PDI) actively participates, and its inhibition makes it difficult for the virus to penetrate into healthy cells. *In vitro* experiments have established that sodium selenite (selenase) actively reacts with SH groups of PDI and catalyzes their oxidation according to the scheme: PDI — $(SH)^{+2} + Se^{+4} \rightarrow$ PDI — S — S — PDI + Se^{+2} [30].

Since COVID-19 is associated with a complication related to increased blood coagulation, it is important that sodium selenite has an anti-aggregation effect, reducing the formation of thromboxane. However, the disadvantage of this inorganic compound is that after administration it is excreted from the body within 1—2 min [31].

After screening of 10,000 different chemical compositions, the low-toxic product «Ebselen», which is a synthetic molecule of organoselenium and has anti-inflammatory, antioxidant, and cytoprotective properties, was chosen as a specific agent for the treatment of COVID-19. It exhibits inhibitory activity against SARS-CoV-2, which can be explained by the irreversible inhibition of the main protease of the corona virus (M(pro)) due to the formation of covalent bonds by selenium with the SH group of cysteine (Cys-145), its active center [32].

In general, there are ***three main ways*** to combat the coronavirus with the help of zinc and selenium.

The first way is to slow down the virus replication in the host's body: (i) by irreversible binding of cysteine of the main protease of the virus (M(pro)), which encodes proteins, for example, through the covalent bond of selenium with the SH-group of cysteine (Cys-145) of its active center [32] (it can be expected that Zn^{+2} will act in a similar way, which,, having a filled 3d orbital, tends to form 4 strong covalent bonds with sulfur-containing ligands (for example, with cysteine in the metallothionein protein) [33]; (ii) by inhibiting the RNA polymerase enzyme with zinc [8].

The second way is to prevent the virus from entering the cells. It is known that the main impact of SARS-CoV-2 falls on the vascular system. The membrane of the vascular epithelium cells includes a number of integral proteins: ACE-2 — angiotensin-converting enzyme, transmembrane protease, metallopeptidases, which are able to interact with viral proteins [34, 35]. It is believed that blocking the virus contact of the with ACE-2 by changing the structure of its spike protein is a preventive measure for the development of the infectious process [36].

As previously noted [30], protein disulfide isomerase (PDI) plays the main role in the implementation of the contact of SARS-CoV-2 glycoprotein spikes (peplomers) with the receptors of the host cell membranes. Se^{+4}, by oxidizing it, prevents the virus from entering the cell. In our opinion, there is also a possibility of blocking SH-groups of PDI by zinc ions, which react with SH-groups of similar compounds to form stable complexes.

Modulation of ACE-2 itself was also considered as a potential therapeutic strategy for the treatment of COVID-19 [37]. It has been demonstrated that zinc in a physiological amount of 100 μmol reduces the recombinant activity of the virus and ACE-2 in the lungs of rats [38]. However, this appears to be only hypothetical [39]. Perhaps, this fact is due to not by the modulation of ACE-2, but by the same modulation of the coronavirus spikes through complexing their SH-groups with zinc. In our opinion, with an increase in zinc concentration, the effect could be more pronounced.

The third way is to use another factor that reduces the adsorption capacity of the virus — electricity. It was found that its adsorption on ACE-2 cell membrane receptors depends on the electric charge of the viral particle and the cell receptor [40]. The reality of such a process has been demonstrated in the works [41, 42].

In this context, the idea of using metals in extremely low, uncharacteristic degrees of oxidation to block the penetration of the virus into the host cells is definitely worthy of attention. Zn^{+1}, as well as Se^{-2}, can neutralize the charge (+) on the receptors of ACE-2 cells. After losing excess electrons, they turn into Zn^{+2} and Se^{+4} and compensate for the negative charge on SARS-CoV-2 peplomers. In this case, the electrostatic interaction between peplomers and cell receptors is blocked [43].

Hence, the role of zinc and selenium in the fight against COVID-19 is very important, but the effectiveness of the action largely depends on their chemical form. The most optimal form of biometal compounds for the body is chelates — cyclic complexes of metals with polydentate ligands.

Our body is a harmoniously functioning complex polymetallic-polyligand system, the driving force of which is the difference in the stability of complexes. Thus, the most active physiological role in the body is played by that complex, the stability of which is sufficient for the transport of the biometal in such a way that it could not be decomposed under the action of gastric juice, but is significantly less than the stability of its compounds in the body. The same mechanism will operate when the body is loaded with the SARS-CoV-2 coronavirus. It is believed that the best transport form of biometals is citrates — their five-membered complexes with citric acid. The stability of zinc citrate pK is 4.7, and the pK of its complexes with the body's amino acids is on average 6.8. The stability of zinc complexes with compounds containing SH-groups is much higher. Thus, for zinc complexes with unitiol and its analogues, in particular compounds that, like the PDI of peplomers of the COVID-19 virus, contain thiol (-SH) groups, pK is ~14 [44].

Accordingly, it can be concluded that zinc citrate is a more effective and reliable pharmaceutical chemist for blocking both the peplomer glycoproteins of the SARS-CoV-2 virus and its other sulfur-containing compounds. At the same time, unlike the proposed ionophores, it is absolutely non-toxic.

If we take into account the electrostatic interaction of the virus peplomers and the cell receptors of the host organism [45], it is possible that the negatively charged zinc citrate complex ($[Zn(C_6H_5O_7])$) in the body will be attracted to the positively charged ACE-2 receptors and neutralize them, which will make it difficult for them to interact with the negatively charged peplomers of the virus, and thus for virus particles to enter into the host cells. Zinc (Zn^{+2}), having lost its transport, will block the negatively charged peplomers of the virus.

So, it can be claimed that citrate is the most advanced chemical form of zinc to fight against COVID-19. However, the methods of chemical synthesis of metal citrates are complex, energy-consuming, environmentally dangerous, and, as a result, a small amount of the final product can be obtained, which is highly contaminated with chemical reagents. An alternative to obtaining citrates of biometals, in particular zinc, appeared thanks to the intensive development of nanotechnology [46—49].

Zinc citrate synthesized with the help of innovative nanotechnology contains a small excess of citric acid, which increases its stability, bioavailability, and effectiveness of biological action. At the same time, it is known that citric acid itself stimulates physiological and biochemical processes in the body and increases its immune and physiological response [50].

Among selenium compounds, its organic compounds have an advantage in terms of their low toxicity and prolonged action as a therapeutic and preventive agent in adjuvant therapy against viral diseases, including COVID-19 [51]. It is known that such compounds are similar to their sulfur analogues, but they are more reactive, especially in redox processes [52].

One of these representatives of organic selenium compounds is a selenium compound synthesized using nanotechnology, which belongs to the class of selenium carboxylic acids. According to X-ray structural analysis, this is monoselenium citric acid [53].

Monoselenium citric acid has low stability, slowly hydrolyzes to hydrogen selenide, where selenium is in the form of Se^{-2}, which is easily included in intracellular convergent reactions and is an antioxidant [50]. High antiviral activity of antioxidant compounds has been established in [54, 55], which may be due to their ability to prevent the interaction of viral proteins on the virus surface and virus-specific cell receptors. It is also possible that they modulate intracellular signaling pathways. This explains the effect of selenium on H1N1 (swine-origin influenza A viruses) *viruses* [56]. Selenium is separated from selenic acid in the form of Se^{-2}, which is needed for the synthesis of the body's own proteins. Se^{-2}, can be a donor of 8 electrons and neutralize the charge on ACE-2, making it difficult for the virus to enter the cell. It is important that, compared to selenium in selenomethionine and selenocysteine, it is released much easier for further action in the body. At the same time, as an organic compound, monoselenium citric acid is more stable and much less toxic than inorganic forms of selenium [51].

Therefore, it can be concluded that trace elements zinc and selenium play a significant role in the resistance to COVID-19, due to the stimulation of the host' immune response and their direct antiviral effect in SARS-CoV-2. Studies have shown that zinc regulates the proliferation, differentiation, maturation, and functioning of leukocytes and lymphocytes, which is the basis of cellular immunity, and therefore is responsible for the body's immune response, protecting it from viral and bacterial infections [4—6]. Strengthening of antiviral immunity by zinc can also occur due to increased production of α-interferon [7]. There is a practice of using zinc as a potential means of immune support and prevention of influenza H1N1 (swine-origin influenza A viruses) [10]. Selenium, like zinc, plays a key role in maintaining immunity and has long been known as a regulator of the immune response at all levels of nonspecific humoral and cellular immunity [20—24]. There is an inverse correlation between the mortality rate from COVID-19 and the level of selenium intake. Thus, in the case of COVID-19, trace elements zinc and selenium can significantly affect the antiviral resistance of the body. Accordingly, the deficiency of these trace elements in the diet of the population can be both a risk factor for the disease of COVID-19 and the progression of SARS-CoV-2 in patients.

In addition, it has been shown that Zn^{+2} cations suppress the activity of the RNA polymerase of the SARS-CoV-2 virus, reducing its replication [8] and therefore have a direct antiviral effect [9]. As a result, zinc is considered an antiviral agent. Recent studies have shown the antiviral activity against SARS-CoV-2 of the zinc ionophore — chloroquine [11—13], which increases the intake of zinc into body cells [12]. Such an effect can be achieved with the help of other less toxic ionophores (ligand complexformers) of zinc, such as quercetin and epigallocatechin gallate [14].

Selenium has antiviral activity as well. Viral diseases such as HIV, hepatitis C, Ebola, various types of flu are more severe with its deficiency. There is an inverse correlation between the mortality *rate* from COVID-19 and the level of selenium consumption [25, 36]. Mortality from these diseases is 3—5 times higher with its deficiency [21, 22, 25, 36]. (повтор). At the same time, the deficiency of selenium in the diet of the population has a global scale [15—20, 26—28].

The mechanisms of the antiviral action of these trace elements have been highlighted: (1) slowing down the replication of the virus in the host'body by binding the cysteine of the main virus protease (M(pro)) (due to their covalent linkage with the SH group of cysteine, its active center) [32], and inhibition by zinc of the enzyme RNA polymerases [8]); (2) preventing the penetration of the virus into the body cells by preventing the contact of the virus with the angiotensin-converting enzyme ACE-2 due to the blocking of SH groups of protein disulfide isomerase, glycoprotein spikes of SARS-CoV-2 [36, 30], and (3) the «electrical» way — blocking the electrostatic interaction of peplomers virus and ACE-2 cell receptors, in particular, the use of zinc and selenium in ultra-low oxidation states (Zn^{+1}, Se^{-2}) [12, 13]. It was concluded that zinc in the form of citrate and organic forms of selenium are most effective against the SARS-CoV-2 virus [44, 51, 52]. It has been established that zinc and selenium compounds obtained by innovative nanotechnology are promising for this purpose: zinc citrate (a five-membered complex of zinc with citric acid) and monoseleniumcitric acid [46—49].

Conclusions. It is arguable that trace elements zinc and selenium play a significant role in the prevention and adjuvant therapy of COVID-19 due to both their immunity-stimulating effect and direct antiviral action against SARS-CoV-2. The use of zinc and selenium in the form of pharmaceuticals and dietary supplements as an adjunctive therapy to limit the progression of SARS-CoV-2 in patients, as well as for uninfected people from risk groups during the spread of COVID-19 is promising.

REFERENCES

1. Komisarenko SV. [Scientist's pursuit for coronavirus SARS-CoV-2, which causes COVID-19: scientific strategies against pandemic]. Visn Nac Akad Nauk Ukr. 2020;8:29—71. Ukrainian.
2. Romaniuk SI, Komisarenko SV. [Immunity: what makes it work?] Visn Nac Akad Nauk Ukr. 2012;1:49—54.Ukrainian.
3. Kvashnina LV, Maidan IS. [The effect of vitamin D on the state of the immune system during the COVID-19 pandemic (latest data)]. Clin immunology allergology insectology. 2020;7(128):22—30. Ukrainian.
4. Prasad AS. Clinical immunological, anti-inflannatory and anti-oxidant role of zink. Exp Gerontol. 2008;43:370—377.
5. Wessels J, Maywald N, Rink Z. Zinc as a gatekeeper of immune function Nutrients. 2017;9(12):1286.

6. Skalny AV, Rudakov IA. [Bioelements in medicine]. M.: Onyx, 21st century; 2004. Russian.
7. Read SA, Obeid S, Ahlenstiel C, Ahlenstiel G. The Role of Zinc in Antiviral Immunity. Adv Nutr. 2019;1;10(4):696—710.
8. te Velthuis AJ, van den Worm SH, Sims AC, Baric RS, Snijder EJ, van Hemert MJ. Zn(2+) inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. PLoS Pathog. 2010;6(11):e1001176.
9. Zhang L, Liu Y. Potential interventions for novel coronavirus in China: A systematic review. J Med Virol. 2020;92(5):479—490.
10. Sandstead HH, Prasad AS. Zinc intake and resistance to H1N1 influenza. Am J Public Health. 2010;100:970—971.
11. Wang M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020;30:269—271.
12. Xue J, Moyer A, Peng B. Chloroquine is a zinc ionophore. PLoS One. 2014;9(10):e109180.
13. Guastalegname M, Vallone A. Could chloroquine/hydroxy-chloroquine be harmful in Coronavirus disease 2019 (COVID-19) treatment? Clin Infect Dis. 2020;71(15):888—889.
14. Dabbagh-Bazarbachi H, Clergeaud G, Quesada IM. Zinc ionophore activity of quercetin and epigallocatechin-gallate: From Hepa 1-6 cells to a liposome model. J Agric Food Chem. 2014;62(32):8085—93.
15. Lyubarska LS. [Hygienic assessment of the supply of zinc and copper in the diet of the population of Ukraine] [dissertation]. Kyiv: State Institution «Kundiiev Institute of Occupational Health of the National Academy of Medical Sciences of Ukraine»; 2016. Ukrainian.
16. Lyubarska LS. [Assessment of the supply of essential trace elements of the adult population of Kyiv]. Problems of aging and longevity. 2016;2 (25):348. Ukrainian.
17. Lyubarska LS. [Provision of the bioelement zinc to Kyiv residents]. In: Serdyuk AM, Polka NM, editors. Actual issues of hygiene and environmental safety of Ukraine; 2016 Oct 20—21; Kyiv, Ukraine. Next Advertising Group; 2016. p. 217—218. Ukrainian.
18. Bailey RL, West KP, Black RE. The epidemiology of global micronutrient deficiencies. Ann Nutr Metab. 2015;66(2):22—33.
19. Tronko MD, Polumbrik MO, Kovbasa VM, Kravchenko VI, Balloon YG. [The biological role of zinc and the need to ensure an adequate level of its consumption by humans]. Visn Nac Akad Nauk Ukr. 2013; 6:21—31. Ukrainian.
20. Huseynov TM, Gulieva RT, Yakhnyaeva FA. [The biological significance of selenium and its place in RNA — viral diseases]. Mycoelements in medicine. 2020;21(4): 21—31. Russian.
21. Levander OA, Beck MA. Selenium and virulence. Br Med Bull. 1999;55(3):528—533.
22. Huseynov TM, Safarov NS. [Selenium and some viral diseases]. Biomedicine. 2007(2): 3—7. Russian.
23. Hoffman PR, Berry MG. The influence of selenium on immune responses. Molecular Nutrition 2 Food Researel. 2008;52(11):1273—1230.
24. Jeng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID 19. J Pharm Anal. 2020;10(2):102—108.
25. Zhand G, Taylor EW, Bennett K, Saad R, Rayman MP. Association between regional selenium status and reported outcome of COVID-19 cases in China. The American Journal of Clinical Nutrition. 2020;111(6):1297—1299.
26. Rayman MP. The use of high-selenium yeast to raise selenium status: how does it measure up? Br J Nutr. 2004;92(4):557—73.
27. Thomson CD. Assessment of requirements for selenium and adequacy of selenium status: a review. Eur J Clin Nutr. 2004;8:91—402.
28. Goncharova OA. [Rationale for the need to correct selenium status in the treatment of thyropathology in the population of Ukraine]. Literature review and own observations. Journal of Endocrinology. 2018;4(23):362—368. Ukrainian.
29. Avery J, Hoffman P. Selenium, Selenoproteins and immunity. Nutrients. 2018;10(9):1203.
30. Guseynova SA. [Oxidative metabolism of sodium selenite in isolated human erythrocytes in vitro]. Biomedicine. 2019;3(17):18—23. Russian.
31. Perona G, Schiavon R, Guidi GC, Veneri D, Mimer P. Selenium dependent Glutation Peroxidase: A Phisiological Regulatory system for Platelet Function. Thromb Haemost. 1990;64(2):1312—318.
32. Jin Z, Du X, Xu Y, Deng Y, Liu M, Zhao Y, et al. Structure of M(pro) from SARS-Cov 2 and discovery of its inhibitors. Nature. 2020; 582:289—293.
33. Metzler D. [Biochemistry]. Moscow:Mir; T1; 1980. Russian.

34 Diwaker D, Mishra K, Janju Z. Potential role of protein disulfide isomerase in viral infections. Acta Viro. 2013;27:293—304.
35. Bourgonje AR, Abdulle AE, Timens W. Angiotensimconverting enzyme 2 (ACE -2), SARS-CoV-2 and the pathophysiologu of coronavirus dislase 2019 (Covid-19). J Pathol. 2020;251(3):228—248.
36. Kieliszeka M, Lipinski B. Selenium supplementation in the preventation of coronavirus infection (Covid-19). Medical wepotheses. 2020; 143: 109878.
37. Zhang H, Penninger J, Li Y. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: Molecular mechanisms and potential therapeutic target. 2020;46(4):586—590.
38. Speth R, Carrera E, Jean-Baptiste M, Joachim A, Linares A. The concentration-dependent effects of zinc on angiotensin-converting enzyme 2 activity. FASEB J. 2014;28 Suppl 1.
39. Chilvers M, McKean M, Rutman A. The effects of coronavirus on human nasal ciliated respiratory epithelium. European Respiratory Journal. 2001;18(6):965—70.
40. Stegny MY, Stegny BT, Goltsev AN. [Ultrastructure and biological properties of avian infectious bronchitis virus following cryopreservation]. Problems of cryobiology and cryomedicine. 2015; 4(25):340—349. Russian.
41. Zhdanov VM. [In the footsteps of the invisible: Biochemistry reveals the secrets of viruses]. Moscow; Knowledge, 1969. Russian.
42. Ponomarev AP. [Mechanisms of stabilization and inactivation of foot-and-mouth disease virus under the influence of physical and chemical factors] [dissertation]. Vladimir; 1996. Russian.
43. Spivak NY, Kaplunenko VG, Kosinov NV, Skalny AV. [Antiviral, antioxidant and catalytic activity of trace elements in a low oxidation state]. Trace elements in medicine. 2020;21 (3):3—23. Russian.
44. Emchenko NL. [Research and application in titrimetric analysis of complexes of unithiol and its analogues with metal ions] [dissertation]. Kyiv: Taras Shevchenko National University of Kyiv; 1980. Ukrainian.
45. Skalny A, Rink L, Ajsuvakova O. Zinc and respiratory tract infections: Perspectives for COVID 19 (Review). Int Journ Molecul Med. 2020;46(1):17—26.
46. Kosinov MV, Kaplunenko VG, inventors; Kosinov MV assignee. Patent of Ukraine for coris model No. 38391. IPC (2006): C07C 51/41, C07F 5/00, C07F 15/00, C07C 53/126 (2008.01), C07C 53/10 (2008.01), A23L 1/00, B83 3/00. Method for the extraction of metal carboxylates «Nanotechnology for the extraction of metal carboxylates»; 2009 Jan 12. Ukrainian.
47. Kosinov MV, Kaplunenko VG, inventors; Kosinov MV assignee. Ultrapure aqueous solution of metal nanocarboxylate. Patent of Ukraine for utility model No. 39397. IPC (2006): C07C 51/41, C07F 5/00, C07F 15/00; 2009 Feb 25. Ukrainian.
48. Serdyuk AM, Gulich MP, Kaplunenko VG, Kosinov MV. Nanotechnologies of micronutrients: problems, prospects and ways to eliminate the deficiency of macro- and microelements. Journ. of the Academy of Medical Sciences of Ukraine. 2010; 1(16):107—114. Ukrainian.
49. Serdyuk AM. [Nanotechnology of micronutrients: safety and biotic issues of nanomaterials in the production of food products]. Journal of the Academy of Medical Sciences of Ukraine. 2010; 3(16): 467—471. Ukrainian.
50. Gulich MP, Yemchenko NL. [Products of nanotechnology: citrates of bioelements (chemical characteristics, biological effect, scope of application)]. Kyiv: Medinform. 2018; Ukrainian.
51. Juillin OM, Vindry C, Ohlmann T. Selenium, selenoproteins and viral infection. Nutrients. 2019;11(9):2101.
52. Clive DI. The chemistry of sulfur, selenium, tellurium and polonium. J tetrahedron. 1978; 34(8):1049—1132.
53. Kharchenko OO, Yemchenko NL, Gulich MP. Study of the composition of monoselenic acid obtained by aqua nanotechnology. In: Serdyuk AM, Polka NM, editors. [Actual issues of hygiene and environmental safety of Ukraine]; 2016 Oct 20—21; Kyiv, Ukraine. Next Advertising Group; 2016. p. 238 — 240. Ukrainian.
54. Krylova NV, Fedoreev SA, Lavrov VF, Mischenko NP, Vasileva EA, Svitich OA, et al. [Antiviral and antioxidant activity of the composition of compounds based on echinochrome A]. Journal of microbiology, epidemiology and immunobiology. 2019;96(1):53—58. Russian
55. Zhang Y, Wang Z, Chen H, Chen Z, Tian Y. Antioxidants: potential antiviral agents for Japanese encephalitis virus infection. Int J Infect Dis. 2014;24:30—6.
56. Li Y, Lin Z, Guo M, Zhao M, Xia Y, Wang C, et al. Inhibition of H1N1 influenza virus-induced apoptosis by functionalized selenium nanoparticles with amantadine through ROS-mediated AKT signaling pathways. Int J Nanomedicine. 2018;13:2005—2016.

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М.П Гуліч[1], Н.Л. Ємченко [1], В.Г. Каплуненко[2], О.О. Харченко [1]

[1] ДУ «Інститут громадського здоров'я ім. О.М. Марзєєва НАМН України»
вул. Попудренка, 50, Київ, 02094, Україна
[2] ТОВ «Наноматеріали і нанотехнології»
вул. Васильківська, 27, Київ, 03022, Україна

МІКРОЕЛЕМЕНТИ ЦИНК ТА СЕЛЕН: ЗНАЧЕННЯ В УМОВАХ ПАНДЕМІЇ COVID-19

В умовах тривалої пандемії COVID-19, коли багато питань щодо стратегій профілактики та лікування залишаються невирішеними і йде пошук найкращих противірусних засобів, слід звернути увагу на роль мікроелементів цинку і селену в підвищенні опірності організму до вірусних інфекцій та їхньої прямої противірусної активності щодо SARS-CoV-2. Експериментальні дані показують, що мікроелементи цинк і селен не тільки проявляють себе як регулятори імунної відповіді на всіх рівнях гуморального і клітинного імунітету, але й можуть відігравати значну роль у анд'ювантній терапії при вірусних захворюваннях. Це особливо актуально при COVID-19. Дослідження прямої противірусної дії цих мікроелементів свідчать про три її основні шляхи до SARS-CoV-2: I — протидія реплікації вірусу та його транскрипції через: а) ковалентний зв'язок їх з SH-групою цистеїну основної протеази вірусу M(Pro), б) пригнічення цинком активності його РНК-полімерази; II — недопущення проникнення вірусу у клітини за рахунок блокування цими мікроелементами SH-груп протеїндисульфідізомерази (РДІ) білка його шипів (пепломерів); III — зниження адсорбційної здатності вірусу внаслідок блокування цими елементами у наднизьких ступенях окиснення (Zn^{+1}, Se^{-2}) електростатичної взаємодії пепломерів SARS-CoV-2 і ангіотензин-перетворюючого ферменту (ACE-2). Інтенсивність противірусної дії цих мікроелементів може залежати від їхньої хімічної форми. Встановлено, що більшу інтенсивність дії та високу хімічну чистоту мають цитрат цинку (п'ятичленний комплекс цинку з лимонною кислотою) і моноселенлимонна кислота, отримані за допомогою нанотехнології. Враховуючи імуностимулюючу та пряму противірусну дію цинку і селену, їх використання у вигляді фармпрепаратів та дієтичних добавок слід розглядати як допоміжну терапію при SARS-CoV-2 у хворих або як профілактичну стратегію для неінфікованих людей із груп ризику під час поширення COVID-19.

Ключові слова: *мікроелементи, цинк, селен, COVID-19, SARS-CoV-2, імунітет, противірусна дія, цитрат цинку, моноселенлимонна кислота.*