Sodium Selenite As Potential Adjuvant Therapy for COVID-19

T. M. Huseynov, R. T. Guliyeva, S. H. Jafarova, and N. H. Jafar

Institute of Biophysics, National Academy of Sciences of Azerbaijan, Baku, AZ1143 Azerbaijan
Clinic "MediClub", Baku, AZ1010 Azerbaijan

*e-mail: tokus@mail.ru

Received May 23, 2022; revised July 19, 2022; accepted July 20, 2022

Abstract—The review considers the role that selenium plays in RNA virus infections and, in particular, COVID-19. Many RNA viruses are selenium dependent because antisense interactions arise between viral RNAs and host mRNA regions containing the selenium cysteine insertion sequence to cause selenium deficiency, oxidative stress, immune response impairment, etc. Sodium selenite is a licensed selenium-containing product and is widely used in medicine, veterinary, and agriculture. Its advantages include the following. Sodium selenite rapidly penetrates through cell membranes in all tissues of the body; is intensely involved in metabolic processes accompanied by oxidation of sulfur-containing cell proteins; exerts an antiaggregation effect by reducing thromboxane activity; interrupts the contact of a virion (SARS-CoV-1 and SARS-CoV-2) with the membrane of a healthy cell; and suppresses NF-κB activity, which significantly increases in coronavirus infections. Arguments supporting the use of sodium selenite as adjuvant therapy in COVID-19 are discussed.

Keywords: RNA viruses, COVID-19, oxidative stress, sodium selenite, glutathione peroxidase, thioredoxin reductase

DOI: 10.1134/S0006350922050074

INTRODUCTION

Selenium is an absolutely indispensable, essential element in many organisms from viruses to mammals, including humans (what is of importance). Although its total content is only 14–15 mg in a 70-kg human body, selenium is involved in many vital regulatory processes [1–3]. Selenium occurs in a minor amount in the Earth’s crust, its so-called Clarke is only 10^−5%, and its distribution is extremely irregular. By convention, soils with a selenium content lower than 10^−5% are considered poor and those with a content higher than 10^−5%, rich in selenium [4]. The content of selenium in foods consequently depends on its regional occurrence, and the selenium status (content) in the human body may greatly vary even within the same country. Selenium assimilation was found to differ between different organisms. Certain plants, such as cereals and locoweeds, provide indicators of the selenium abundance in soil. Although the selenium content in seawater is extremely low, certain marine organisms and, in particular, various algae (e.g., spirulina) are capable of accumulating selenium in their tissues [4]. Organ specificity is known as well as species-specific features. Higher selenium contents are observed in the liver, kidney, retina, thyroid, adrenal, testis, and blood (lymphocytes, platelets, and erythrocytes) and nervous cells, suggesting an important role in their functions for selenium [2, 5]. Studies of the selenium status have intensely been performed in the populations of many countries from the 1970s [4, 6]. An appreciable decrease observed in selenium status is associated with deteriorated ecological conditions due to anthropogenic factors. For example, gaseous anhydrides are released in substantial amounts and soils are consequently acidified because of the intense development of energy production (ach from hydrocarbon burning), other industries, and means of communication and transportation. Pollution with heavy elements, which form insoluble complexes with selenium, eventually reduces the mobile selenium pool, that is, the selenium forms that are assimilated by plants and thus find their way into the human body [2, 4].

Governmental programs aimed at normalizing the selenium status have been adopted or considered at the legislative level in many regions of the world, including developed countries; major parts of Asia, Australia, and Africa; many CIS countries; and the Baltic states, where selenium deficiency is known. In Azerbaijan, the selenium status is close to deficiency, and this circumstance poses a certain health risk [6].

Selenium is a component of more than 25 important proteins [9], which perform significant regulatory functions, including the regulation of iodine metabolism [2], protection of hemoglobin from oxidation [4], maintenance of the normal reproductive function [2], functions of the cardiovascular system [2], carbohydrate metabolism [2, 10], disorders of the nervous system (including cognitive functions) [2], regulation of
immunity [2, 11], a role in tumor growth suppression in a number of cancers [2, 12], intoxication from heavy metal poisoning [2], and regulation of blood clotting (thromboxane inhibition) [9].

It is of special importance that unique antioxidant properties are characteristic of the majority of selenium-containing proteins. Higher cancer-related mortality was observed in selenium-deficient regions in the 1970s [2, 12], and mortality from cardiomyopathy (Keshan disease) was found to be several fold higher than in the normal population in the 1980s [3]. In the past 20 years, studies of HIV infection [13, 14], Ebola fever [13], Coxackie virus [3, 9], hantavirus [15], Zika virus [15], various influenza types (avian flu, etc.) [16, 17] showed that lethality of these diseases in selenium-deficient regions is substantially higher than in regions with a sufficient selenium status. The genomes of the viruses were assumed to code for selenoproteins, such as glutathione peroxidase, which is a main antioxidant enzyme [14, 18–20]; the SeP selenium–transporting protein [14], which includes ten or more selenium atoms [15]; and thioredoxin reductase [14]. It is important to note that thioredoxin reductase performs redox functions to protect the cell from DNA damage during a virus attack, which leads to oxidative modification [13, 14]. However, more recent studies of HIV-1 and Ebola virus as examples showed that antisense tethering interactions arise between viral RNAs and host mRNAs in respective infections [21, 22]. The interactions lead to a selective capture of the selenocysteine insertion sequence (SECIS) element in the spike protein–coding sequence to produce a complementary double-stranded helical structure, which ensures expression of viral selenoproteins. The selenium pool of the host cell is utilized in their expression, leading to selenium deficiency. Immunity is affected by selenium deficiency, being already impaired as a result of oxidative stress in virus infections [15, 23].

ANTIVIRUS PROPERTIES OF SELENIUM AND PREREQUISITES TO USING SODIUM SELENITE AS ADJUVANT THERAPY IN COVID-19

The mechanism of the antivirus effect of selenium is multifaceted and targets several steps in the development of virus infection from virion penetration into healthy cells to fighting the infection sequels. Below we briefly consider the beneficial properties of selenium with the example of sodium selenite, which is the main inorganic selenium compound that is used in biology and medicine, in particular, to treat HIV infection and Ebola fever [13, 18].

 Interruption of contacts between viral spikes and healthy cell membranes. Sodium selenite may act to interrupt the contact of a virion (SARS-CoV-1 and SARS-CoV-2) with the membrane of a healthy host cell. The SARS-CoV-2 virion has a hydrophobic envelope. Protein protrusions known as the spikes are on the outer surface of the envelope, and the RNA genome of the virus is within the envelope. Spike proteins interact with the membrane of the host cell attacked by the virus. The interaction is mostly mediated by angiotensin-converting enzyme 2 (ACE2), which is an integral membrane protein. The membrane integrity is impaired as a result to facilitate penetration of viral genetic material into the healthy cell. Then the viral RNA is integrated into the host cell genome, thus causing its modification, and the virus is replicated by utilizing resources of the host cell [24, 25]. Interruption of the contact between viral spikes and healthy cell membranes may therefore prevent infection [26]. The hypothesis was considered in detail [27].

Passive transport and a role in active selenium metabolism within the cell. Sodium selenite is a small nonpolar molecule and, as such, easily penetrates through the cell membrane via passive transport. Sodium selenite is involved in intense intracellular selenium metabolism, which is accompanied by oxidation of sulfur-containing cell proteins and simultaneous reduction of selenite (+4) to selenide (–2). Given that selenium and sulfur are similar in chemical properties, it is possible to assume that selenium, which has a higher chemical reactivity, displaces sulfur in sulfur-containing cysteine (2-amino-3-mercaptopropionic acid) or interacts with SH groups of proteins to abstract a hydrogen atom from the thiol group, thus oxidizing the group and producing the R–S–S–R and R–S–Se–r bonds [28, 29]. In the case of virus infection, sodium selenite may additionally interact with viral selenoproteins, including protein disulfide isomerase (PDI), which is a component of spikes in the COVID-19 agent. The enzyme is consequently deactivated; the reaction is as follows:

\[
PDI-(SH)_2 + Se^{4+} \rightarrow PDI-S-S-PDI + Se^{2+}.
\]

This means that contact penetration of the virus into healthy cells may be prevented by sodium selenite [26, 27].

As mentioned above, antisense genomic interactions lead to selenium deficiency, which reduces the pool of selenium-containing enzymes and, primarily, thioredoxin reductase, which supplies protons for DNA synthesis in normal cells [30]. Greater amounts of selenium are therefore spent to produce both host and viral selenoproteins. Selenium deficiency arises as a result, leading to generation of reactive oxygen species [14, 31], impairing immunity in oxidative stress, and decreasing antioxidant protection of the body [10]. Sodium selenite is an adequate selenium form in these conditions, allowing selenium to rapidly penetrate into cell structures and pass through the blood–brain barrier [10, 28]. The body takes advantage of this property and utilizes selenium derived from sodium selenite to maintain the vital level of selenoproteins and to prevent oxidative stress [2].
Tumor growth suppression. Model experiments with cancer cells showed that sodium selenite specifically inhibits the RNA and DNA polymerase reactions because stable copolymeric products of polymerases form with selenium through the selenotrisulfide covalent bond. Thus, tumor growth may be suppressed by selenium. The circumstance indicates that virus replication may similarly be inhibited in the host cell (given that there is a concept of virus-driven carcinogenesis) [32]. Such inhibition was demonstrated in the case of influenza virus A [17].

Inhibited activation of nuclear factor κB (NF-κB). Based on the similarity between SARS-CoV-1 and SARS-CoV-2, certain assumptions can be made as to how selenium possibly affects the replication and transcription processes in COVID-19 infection. For example, substantial activation in SARS-CoV-1 infection was observed for NF-κB, which plays a key role in regulating the immune response [33–35]. NF-κB is involved in transcription of viral genome material, which is accompanied by toxic inflammatory processes [36]. There is ample data that selenium inhibits NF-κB activation, while selenium deficiency stimulates it [9]. Another argument that NF-κB inhibition is of importance is provided by the fact that NF-κB plays a crucial role in transcription processes in HIV infection [9]. As already noted, the HIV genome is similar in many properties to the genome of the COVID-19 agent.

Regulation of the immune response. Anti-inflammatory processes are known to accompany NF-κB activation [37], meaning increased secretion of many cytokines. Uncontrolled production of cytokines, including certain interleukins (IL-6, IL-8, IL-10, and IL-1β) and tumor necrosis factor α, acts together with reactive oxygen species and reactive nitrogen species to trigger the acute respiratory distress syndrome (ARDS) [38–41]. All these factors lead to the most dangerous sequels of COVID-19 in an infected patient, including mass interleukin attack involving IL-2 and IL-6 (cytokine storm) and distortion of the immune response as a whole. In this context, selenium is long known to regulate the immune response at various levels (nonspecific, humoral, and cell dependent) and, at the same time, to limit T-helper activity [1, 43, 44].

Antiaggregation effect. As already noted, dangerous sequels of COVID-19 include not only respiratory pathology, but also vascular disorders due to excessive blood clotting [36, 37, 42] and thrombocytopenia [45]. Thromboxane A2 production underlies these disorders. Thromboxane A2 increases platelet aggregation, which causes blood clotting within various vessels, from alveolar vessels to large pulmonary arteries (ground-glass opacities), in the lung and other highly vascularized organs, including the heart, kidney, retina, adrenal, etc. [30, 46]. Sodium selenite inhibits thromboxane production and thus exerts an antiaggregation effect [9].

CONCLUSIONS

As COVID-19 spread through the world from 2020 to 2022, many reviews and original articles were published to understand how the contents of essential minerals and various vitamins in humans and animals are associated with the pathogenesis and successful treatment of COVID-19 [5, 21, 34, 38, 47–51]. Selenium occupies an important place among these nutrients, and the selenium status considerably affects the course of this virus infection [22, 49–52]. Hypothetic mechanisms were advanced to explain the regulation of the immune response by selenium and selenium compounds [22, 38, 44, 53–55]. An important role was assumed for the effect of selenium on NF-κB activity and, consequently, expression of anti-inflammatory cytokines (a cytokine storm) [33, 35]. Sodium selenite was used in many model experiments and showed high metabolic activity in various regulatory processes, and the findings supported its broad application. It should be noted that the roles of selenium and several other microelements (zinc, iron, copper, etc.) were considered in comprehensive recent reviews (e.g., see [8, 26, 56]).

Several conclusions are possible to make to summarize our brief review on the role of selenium in virus infections and, in particular, SARS-CoV-2 infection.

1. The selenium status affects the susceptibility to SARS-CoV-2 infection and the severity of COVID-19.

2. Sodium selenite is involved in oxidative metabolism and thus contributes to the regulation of virus replication and damage repair in infected cells.

3. Sodium selenite has been approved for medical application and is used as a component of selenium-containing drugs and selenium-containing food additives. Sodium selenite has several undeniable advantages over other selenium forms (L-selenomethionine, L-selenocysteine, etc.). Synthesis of selenoproteins employs the specific SECIS-dependent mechanism without utilizing preformed selenium-containing amino acids. Such amino acids undergo a multistep degradation pathway (selenium elimination from amino acid molecules) to yield selenide, and their de novo synthesis occurs. Sodium selenite ensures fast delivery of selenium into damaged cells, and a rapid reparative effect is its advantage.

Given that SARS-CoV-2 is highly contagious and that risk of infection is high in healthcare professionals who have contacts with COVID-19 patients, especially in ambulance service, it is advisable to reach body saturation with selenium, zinc, and other immunity-enhancing agents in their case as a preventive measure to improve immunity.

The above data indicate that sodium selenite is expedient to use as an adjuvant to treat coronavirus infection, especially at its early stages.
COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest. The authors declare that they have no conflicts of interest. This article does not contain any studies involving animals or human subjects performed by any of the authors.

REFERENCES

1. J. R. Arthur, R. C. McKenzie, and G. J. Beckett, J., Nutrition 133 (5), 14575 (2003).
2. M. P. Rayman, Lancet 379 (9822), 1256 (2012).
3. J. K. Wrobel, R. Power, and M. Toborek, IUBMB Life 68 (2), 97 (2015).
4. V. V. Ermakov, V. V. Koval’skii, Biologicheskoe Znanie (Nauka, Moscow, 1974).
5. F. Zhou, T. Yu, R. Du, et al., Lancet 395, 1054 (2020).
6. E. M. Zainally, R. T. Gulieva, and F. R. Yakh”yaeva, in Materials of Scientific and Practical Conference Dedicated to the 80th Anniversary of Professor E. I. Ibragimov (Tsentr Onkol. Minist. Zdravookhr. Azerbaidzhana, ed to the 80th Anniversary of Professor E. I. Ibragimov (Tsentr Onkol. Minist. Zdravookhr. Azerbaidzhana, Baku, 2010), pp. 65–66.
7. N. A. Golubkina, A. V. Sindireva, V. F. Zaitsev, Yug Nutrition (2015).
8. L. N. Iovanovich and V. V. Ermakov, in Proceedings of the International Biogeochemical Symposium (Tiraspol’, 2020), pp. 71–83.
9. S. Tomo, G. Saikiran, M. Banerjee, and S. Paul, EXC-MOL Biochemistry. Curr. Top Med. Chem. 16 (3), 1530 (2016).
10. O. M. Guillin, C. Vindry, T. Ohlmann, and L. Chavatte, Nutrients 11 (9), 2101 (2019).
11. G. Gong, Y. Li, K. He, et al., RSC Adv. 10 (13), 8002 (2020).
12. Z. A. Lazimova, I. I. Abdullaev, F. I. Abdullaev, and T. B. Asadullaev, Voprosi Virusol. 31 (2), 236 (1986).
13. T. M. Guseinov and N. S. Safarov, Biomeditsina, No. 2, 3 (2007).
14. E. W. Taylor, J. A. Ruzicka, L. Premadasa, and L. Zhao, Biochemistry. Curr. Top Med. Chem. 16 (3), 1530 (2016).
15. O. M. Guillin, C. Vindry, T. Ohlmann, and L. Chavatte, Nutrients 11 (9), 2101 (2019).
16. G. Gong, Y. Li, K. He, et al., RSC Adv. 10 (13), 8002 (2020).
17. Z. A. Lazimova, I. I. Abdullaev, F. I. Abdullaev, and T. B. Asadullaev, Voprosi Virusol. 31 (2), 236 (1986).
18. T. M. Guseinov and N. S. Safarov, Biomeditsina, No. 2, 3 (2007).
19. E. W. Taylor, J. A. Ruzicka, L. Premadasa, ResearchGate (2015).
20. E. W. Taylor, Natural Health, News, June 18 (2020).
21. R. A. Heller, Q. Sun, J. Hackler, et al., Redox Biol. 38, 101764 (2021).
22. M. Majeed, K. Nagabhushanam, S. Gowda, and L. Mundkur, Nutrition 82, 111053 (2021).
23. L. Delgado-Roche and F. Mesta, Arch. Med. Res. 51 (5), 384 (2020).
24. R. Lu, X. Zhao, J. Li, et al., Lancet 395 (10224), 565 (2020).
25. A. Mittal, K. Manjunath, R. K. Ranjan, et al., PLoS Pathog. 16 (8), 1008762 (2020).
26. V. V. Ermakov and L. N. Jovanović, Geochem. Int. 60, 137 (2022).
27. M. Kieliszek and B. Lipinski, Med. Hypotheses 143, 1 (2020).
28. S. Ya. Guseinova, Biomeditsina 17 (3), (2019).
29. M. Hongoh, M. Haratake, N. Fachigame, et al., Roy. Soc. Chem. 41 (24), 7340 (2012).
30. S. Miller, S. W. Walker, J. R. Arthur, et al., Clin. Sci. 100 (5), 543 (2001).
31. L. Hiffler and B. Rakotoambinina, Front. Nutr. 7, 164 (2020).
32. J. L. Larabee, J. R. Hocker, R. J. Hansa, et al., Biochem. Pharmacol. 64 (12), 1757 (2002).
33. C. A. Lutomski, T. J. El-Baba, J. R. Bolla, and C. V. Robinson, bioRxiv, 2020.
34. E. W. Taylor, J. A. Ruzicka, L. Premadasa, and L. Zhao, Nutrition 82, 111049 (2021).
35. W. Zeng, et al., Biochem. Biophys. Res. Commun. 527, 618 (2020).
36. M. L. De Diego, J. L. Nieto-Torres, J. A. Regla-Nava, et al., J. Virol. 88 (2), 913 (2014).
37. Z. Varga, A. J. Flammer, P. Steiger, et al., Lancet 395 (10234), 1417 (2020).
38. X. Jing, G. Liangqin, L. Huiqing, and Ch. Shao-dong, Nutrition 82, 111049 (2021).
39. S. S. Martinez, Y. Huang, L. Acuna, et al., Int. J. Mol. Sci. 23 (1), 280 (2021).
40. S. H. Tian, W. Hu, L. Niu, et al., Preprint (2020).
41. D. Wang, B. Hu, C. Hu, et al., China, JAMA (2020).
42. R. Jayawardena, P. Sooriyaarachchi, M. Chourdakis, et al., Clin. Res. Rev. 14 (4), 367 (2020).
43. M. Fakhrolmobasheri, Z. Nasr-Esfahany, H. Khanahmad, and M. Zeinalian, Int. J. Vitam. Nutr. Res. 91 (3–4), 197 (2020).
44. S. Harirhan and S. Dharmaraj, Inflammopharmacology 28, 667 (2020).
45. G. Ackermann, et al., N. Engl. J. Med. 383 (2), 120 (2020).
46. S. J. Bernet, M. Plebani, and B. M. Henry, Clin. Chim. Acta 506, 145 (2020).
47. J. Katz and S. Yue, Nutrition 84, 111106 (2021).
48. R. Kumar, H. Rathi, A. Haq, et al., Virus Res. 159, 292 (2021).
49. A. Moghaddam, R. A. Heller, Q. Sun, et al., Nutrients 12 (7), 2098 (2020).
50. J. Zhang, R. Saad, E. W. Taylor, and M. P. Rayman, Redox Biol. 37, 1017 (2020).
51. J. Zhang, E. W. Taylor, K. Bennett, et al., Am. J. Clin. Nutr. 111, (6), 1297 (2020).
52. G. Bermano, C. Meplan, D. K. Mercer, and J. E. Hesketh, Br. J. Nutr. 125 (6), 618 (2021).
53. Y. Fu, Y. Cheng, and Y. Wu, Virol. Sin. 35, 266 (2020).
54. K. R. Sachitra, R. Nirmal, R. Ismail, and B. Faizal, Nutrition 83, 111089 (2021).
55. H. Shakoor, J. Feehan, A. S. Al Dhaheri, et al., Matu-ritas 143, 1 (2021).
56. S. Khatiwada and A. Subedi, Curr. Nutr. Rep. 10 (2), 125 (2021).

Translated by T. Tkacheva