OPINION

Role of trace element selenium in fighting COVID-19: are we ignoring this important element?

K. Indira Priyadarsini, V. K. Jain and Amit Kunwar

Selenium, a group 16 element in the periodic table was long considered as the highly toxic element causing several disorders, including cancers in humans and animals. Extensive research in the last few decades has confirmed the biochemical role of this element as the constituent of the active site of an important antioxidant enzyme glutathione peroxidase (GPx) that catalyses the reduction of hydrogen peroxide by using glutathione as a co-factor[1,2]. Till date, 25 selenoproteins have been identified in humans including GPx, thioredoxin reductases, iodothyronine deiodinases and selenophosphate synthetase[1,2]. These redox active selenoproteins have selenocysteine, a selenium analogue of cysteine as the active centre[1,2]. Additionally, selenomethionine, a selenium analogue of methionine, also gets non-specifically incorporated into proteins. Selenoproteins are involved in maintaining normal physiological functions of body like redox-homeostasis, proliferation and differentiation of immune cells, thyroid hormone metabolism, etc.[1,2]. Considering the importance of selenium in human physiology, the World Health Organization (WHO) has classified selenium as a micronutrient. The nutritional supply of selenium for human is met through food chain and depends on the selenium content of the soil. Recommended daily allowance of selenium is about 55–70 μg/day for different populations and a lower intake or deficiency may cause health concerns[1–3]. In China, 72% of its population is selenium deficient exhibiting serious health consequences and endemic diseases like Keshan (cardiomyopathy) and Kaschin-Beck (osteoarthropathy). Selenium deficiency is also prevalent in other countries like in Europe and North America. On contrary, excessive selenium is toxic and causes selenosis among other diseases.

Of late selenium deficiency has been associated with the susceptibility and progression of viral pathogens including coxsackie virus, human immune deficiency virus (HIV), hepatitis C virus, influenza A virus (IAV), Ebola, etc.[2–4]. Laboratory studies using cellular and animal models have confirmed that selenium deficiency causes impairment of immune function by mechanisms like inducing cytotoxicity in lymphocytes, reducing production of antibodies (IgG and IgM) and suppressing the proliferation and differentiation of T cells (CD^{8+} and CD^{2+}), and phagocytic functions of macrophases[2–4]. On the other hand, selenium supplementation improves immune functions through increased GPx level and antioxidant defence. Indeed, there are also clinical evidences showing the benefits of selenium supplementation in management of some of these viral diseases[5,6].

Having postulated the role of selenium in previous viral outbreaks, it is pertinent to think whether selenium deficiency is also linked to the recent outbreak of coronavirus disease-2019 (COVID-19). This disease is caused due to infection of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) and was initially reported from Wuhan city in Hubei province, a selenium-deficient area in China[7–9]. Currently, this disease has spread to nearly 200 countries with more than 0.7 million deaths and twenty million infections world-wide. Considering the very high transmission rate of this viral disease, the WHO declared it as pandemic on 11 March 2020. As of now, there is no treatment available for COVID-19. In order to examine the involvement of selenium with this disease, a group of researchers from UK and China has meticulously correlated the mortality and/or cure rates of COVID-19 patients in the different cities of Hubei and Heilongjiang provinces of China with the selenium content[9]. This analysis has revealed an inversive correlation between the soil selenium content and mortality as well as cure rate due to COVID-19. For example, Enshi city of Hubei province with high soil selenium content showed higher cure rate than rest of the cities in and outside Hubei. Similarly, Heilongjiang province with very low selenium status (16 μg/day) had a much lower cure rate than other provinces. Further, Hiffler and Rakotoambinina[10] have postulated that selenium supplementation at different stages of COVID-19 infection may provide significant clinical benefits. Like other viruses, SARS-CoV-2 during its replication within host may induce selenium deficiency, thereby reducing the capability of host to make their own selenoproteins, necessary for their immunity. Exogenous supplementation of selenium can restore the host 'stock' needed for the biosynthesis of cellular selenoproteins. Additionally, anti-thrombotic properties of selenium can help in protecting endothelial cells and prevent blood platelet aggregation, which is one of the serious effects of COVID-19. Indeed a recent study in actual Covid-19 patients from European countries has justified the above postulations[11]. At least ~2.5 times deficit in total serum selenium status was observed in COVID-19 patients compared to reference healthy population. Further, serum selenium concentration was significantly higher in surviving (53.3 ± 16.2 μg/l) COVID-19 patients compared with non-survivors (40.8 ± 8.1 μg/l). This level increased with time in survivors and decreased in non-survivors. A point worth mentioning here is that elderly people and patients with co-morbid conditions, like heart problems, thyroid problems, cancer, etc. show decrease in selenium status which may explain for their higher susceptibility to COVID-19 (ref. 12).

Although the role of selenium as a micronutrient in the viral diseases is well established, it is also the right time to think about its possible role in design of active pharmacophores against viral diseases. This is not an exaggerated statement considering the significant advancements in synthesis methods, variety of organoselenium compounds developed and evaluated for therapeutic potential in last two decades[1]. Ebselen is one such synthetic organoselenium compound, reported for various pharmacological activities ranging from GPx mimic, antioxidant, anti-inflammatory, anticancer and radioprotective activities and is also an FDA approved drug for bipolar disorder[1]. In general, antiviral drugs are designed with an aim to use them as inhibitors of target viral proteins involved in entry,

replication and transcription within the host cells. Accordingly, it has been demonstrated that diselenodibenzamide class of compounds exhibit potent antiviral activity against HIV[13]. On similar lines, a recent publication has indicated that ebselen exhibits potent anti-viral activity against SARS-CoV-2 by inhibiting one of its target proteins such as chymotrypsin-like protease ($3CL^{pro}$) or main protease (M^{pro}) in the nanomolar concentration range[8]. Taking clue from this study, Ewelina *et al.*[14] evaluated twelve ebselen derivatives for inhibition of the papain-like protease (PL^{pro}) from SARS-CoV-2, which is also a key target protein essential for viral infection cycle. Based on this study, the authors proposed that hydroxyl and methoxy substituted ebselen derivatives could be prospective antiviral drugs against SARS-CoV-2. Alternately, the organoselenium compounds that can reduce the inflammatory response or acute pneumonitis in the lung may also be effective in reducing the pathogenesis of COVID-19 (ref. 15). In this context, our group has previously identified one water soluble selenium compound, diselenodipropionic acid (DSePA) for its efficacy in elevating GPx level and preventing the radiation-induced pneumonia in mice model[1,16]. Encouraged from this study, we also perfomed *in silico* analysis to understand the probable interaction of DSePA and other related organoselenium compounds with the target proteins of SARS-CoV-2 including $3CL^{pro}$ or M^{pro} and spike (S) protein[17]. In this analysis, ebselendiselenide and nicotinamidediselenide exhibited the highest binding affinity (in range of $\sim 10^5$ M^{-1}) and DSePA exhibited a moderate interaction with these viral proteins. With this background, as selenium researchers working for more than a decade, some of our suggestions are as follows:

- Unlike many developed countries or severely affected countries like China, we have no database for selenium status in our population nor in Indian soils. There is only one study indicating that selenium levels are normal in Punjab and Himachal Pradesh[18], however in view of its critical role in viral diseases, it is important to take up a task of evaluating selenium status among different populations and clusters, and provide necessary supplementation if required.
- More and more information regarding the structure and function of SARS-CoV-2 proteins involved in its infection cycle is being reported and this is a good opportunity for synthetic chemists and biochemists to design structure aided ligands for antiviral activity. Some of important protein targets for organoselenium compound could be M^{pro}, PL^{pro} and S protein of SARS-CoV-2 and host proteins such as angiotensin-converting enzyme 2 (ACE2) and/or transmembrane protease, serine 2 (TMPRSS2) as these are vital for viral entry into host cells.
- Till date, this important trace element is overlooked in SARS-CoV-2 infections. The growing scientific evidence clearly suggests that this trace element could be a game changer in our fight against viral pandemics including COVID-19.

1. Jain, V. K. and Priyadarsini, K. I. (eds), In *Organoselenium Compounds in Biology and Medicine*, RSC, London, 2018.
2. Papp, L. V. *et al.*, *Antioxid. Redox. Signal*, 2007, **9**, 775–806.
3. Guillin, O. M. *et al.*, *Nutrients*, 2019, **11**, 2101–2133.
4. A-ElMoemen, N. *et al.*, *Int. J. Pept. Res. Ther.*, 2016, **22**, 135–141.
5. Hurwitz, B. E. *et al.*, *Arch. Intern. Med.*, 2007, **167**, 148–154.
6. Hou, J. C. *et al.*, *Zhonghua Yi Xue Za Zhi*, 1993, **73**, 645–646.
7. DiMaio, D. *et al.*, *Annu. Rev. Virol.*, 2020; doi:10.1146/annurev-vi-07-0420-20-100001.
8. Jin, Z. *et al.*, *Nature*, 2020; doi: 10.1038/s41586-020-2223-y.
9. Zhang, J. *et al.*, *Am. J. Clin. Nutr.*, 2020, **111**, 1297–1299.
10. Hiffler, L. and Rakotoambinina, B., *SSRN*; http://dx.doi.org/10.2139/ssrn.3594240.
11. Moghaddam, A. *et al.*, *Nutrients*, 2020, **12**, 2098.
12. Robberecht, H. *et al.*, *Curr. Pharm. Des.*, 2019, **25**, 1694–1706.
13. Sancineto, L. *et al.*, *J. Med. Chem.*, 1995, **58**, 9601–9614.
14. Ewelina, W. T. *et al.*, *BioRxiv*; https://doi.org/10.1101/2020.05.20.107052.
15. Zhang, W. *et al.*, *Clin. Immunol.*, 2020, **214**, 108393.
16. Gandhi, K. A. *et al.*, *Free Radic. Biol. Med.*, 2019, **145**, 8–19.
17. Singh, B. G. and Kunwar, A., *ChemRxiv*; https://doi.org/10.26434/chemrxiv.1259-4134.v1.
18. Yadav, S. K. *et al.*, *J. Environ. Manage.*, 2005, **75**, 129–132.

K. Indira Priyadarsini and V. K. Jain are in the UM-DAE Centre for Excellence in Basic Sciences, University of Mumbai, Vidyanagari Campus, Santacruz (E), Mumbai 400 098, India; Amit Kunwar is in the Radiation and Photochemistry Division, Bhabha Atomic Research Centre, Trombay, Mumbai 400 085, India.*
**e-mail: k.indira@cbs.ac.in*