Proceedings of the Nutrition Society (2023), **82**, 1–12 doi:10.1017/S0029665122002646

First published online 19 August 2022

The Nutrition Society Scottish Section Conference 2022 was a hybrid event held at The Royal Society in Edinburgh on 4–5 April 2022

Conference on 'Nutrition, immune function and infectious disease' Plenary Lecture

The relevance of selenium to viral disease with special reference to SARS-CoV-2 and COVID-19

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In this review, the relevance of selenium (Se) to viral disease will be discussed paying particular attention to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease (COVID-19). Se, the active centre in selenoproteins has an ongoing history of reducing the incidence and severity of viral infections. Host Se deficiency increased the virulence of RNA viruses such as influenza A and coxsackievirus B3, the latter of which is implicated in the development of Keshan disease in north-east China. Significant clinical benefits of Se supplementation have been demonstrated in HIV-1, in liver cancer linked to hepatitis B, and in Chinese patients with hantavirus that was successfully treated with oral sodium selenite. China is of particular interest because it has populations that have both the lowest and the highest Se status in the world. We found a significant association between COVID-19 cure rate and background Se status in Chinese cities; the cure rate continued to rise beyond the Se intake required to optimise selenoproteins, suggesting an additional mechanism. Se status was significantly higher in serum samples from surviving than non-surviving COVID-19 patients. As regards mechanism, SARS-CoV-2 may interfere with the human selenoprotein system; selenoproteins are important in scavenging reactive oxygen species, controlling immunity, reducing inflammation, ferroptosis and endoplasmic reticulum (ER) stress. We found that SARS-CoV-2 significantly suppressed mRNA expression of *GPX4*, of the ER selenoproteins, *SELENOF*, *SELENOM*, *SELENOK* and *SELENOS* and down-regulated *TXNRD3*. Based on the available data, both selenoproteins and redox-active Se species (mimicking ebselen, an inhibitor of the main SARS-CoV-2 protease that enables viral maturation within the host) could employ their separate mechanisms to attenuate virus-triggered oxidative stress, excessive inflammatory responses and immune-system dysfunction, thus improving the outcome of SARS-CoV-2 infection.

Selenium: Viral disease: SARS-CoV-2: COVID-19

Abbreviations: COVID-19, coronavirus disease; ER, endoplasmic reticulum; GPX, glutathione peroxidase; Mpro, main protease; ROS, reactive oxygen species; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Se, selenium; TXNRD, thioredoxin reductase.

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From experiments in mice in the 1970s, we learned that not only was selenium (Se) supplementation able to affect the immune response[1] but data from the 1990s also showed that Se status influenced the ability of mice to deal with viral infection[2]. Part of the reason for those responses rests with the fact that Se, the only trace element to be specified in the genetic code, is an integral part of the large selenoprotein family; the mouse genome contains twenty-four genes that encode selenoproteins while the human genome contains twenty-five[3,4]. Selenoproteins carry out the major nutritional roles of Se and have a range of effects from antioxidant, redox-active, anti-inflammatory, anti-ferroptosis, transport of Se, reduction of endoplasmic reticulum (ER) stress, to the production of active thyroid hormone[3]. Many of these responses are relevant to the role of Se in dealing with viral infection as shown in Table 1[5].

In this review, we explore the ways in which selenoproteins and redox-active Se species interact with RNA viruses, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), to reduce adverse health effects such as coronavirus disease (COVID-19).

Se intake and status

Se is present in trace amounts in both organic and inorganic forms in marine and freshwater systems, soils, biomass and in the atmosphere[6]. In the terrestrial environment, rocks and minerals at the Earth's surface are a primary source of plant Se and depend on the physico-chemical properties that control the movement of Se in the food chain, e.g. soil pH, organic content and speciation[7]. However, the atmosphere is also an important and dynamic reservoir of Se supplying agricultural soils and terrestrial and marine ecosystems[6]. In the Se-poor belt in China which ranges from north-east to south-west, Se status is decisively affected by monsoonal precipitation[8].

There is an extremely wide range of intake of Se seen across the world[9]; it is high in Venezuela, Canada, the USA and Japan and much lower in Europe[3]. China has areas of both Se deficiency and excess where plasma concentrations of Se range from 22 to 550 μg/l[10,11]. Recommendations for Se intake, which are based on optimising plasma glutathione peroxidase (GPX3) activity, average 60 μg daily for men and 53 μg daily for women[12].

Organ meats (e.g. kidney and liver) are a rich source of Se. In addition, seafood and muscle meat are also good sources[13]. The Se content of cereals and grains, however, varies widely, ranging from very low in much of Europe (e.g. mean values of 0·025–0·033 mg/kg dry weight in the UK) to as much as 30 mg/kg in high-Se areas of the USA[13].

The effect of Se deficiency on RNA viruses

Se-deficient environments favour replication, virulence and mutation of RNA viruses[14]. Viral infections produce reactive oxygen species (ROS) and disturb the balance between the generation of ROS and their scavenging systems[14]. Selenoproteins such as the GPXs and thioredoxin reductases (TXNRD) are an important part of those scavenging systems[14]. In Se deficiency, GPX will fall and viral replication will increase. The more the virus replicates (e.g. in an immunosuppressed person, or in a Se-deficient population), the more viral copies will be generated per unit time, which, applying the multiplier from the basal mutation rate, leads to an increased pool of mutants because of the larger viral population size, thus providing further opportunity for selection of a more fit viral strain[15,16]. Perhaps the best known example of this effect is the often-stated hypothesis, supported by abundant evidence, that some of the newer highly mutated variants of SARS-CoV-2 may have developed in the body of a single immunocompromised individual; such observations were being made even before the emergence of the hypermutated Omicron variant[17].

Specific instances of an effect of host Se deficiency on RNA viruses or associated diseases

Coxsackie virus and Keshan disease

In the 1990s, Beck and colleagues showed that Se deficiency in mice, with its associated low or absent activity of protective GPX1, caused mutations in a non-virulent stain of coxsackie virus B3 that lead to the development of a virulent strain that caused myocarditis, even in a subsequent mouse that was Se-sufficient[18]. Those findings showed that host nutritional status could influence not only the host response to the pathogen, but also the genetic make-up of the viral genome[18]. They were also able to explain the appearance of an endemic cardiomyopathy known as Keshan disease in a Se-deficient area in north-east China detected in the early 1930s which mainly affected infants, children and women of childbearing age[19]. In the 1970s, Se supplementation of the diet was given to the people of those areas completely eradicating this disease in those provinces of China[14]. Coxsackie virus was subsequently isolated from the archived blood and tissues of patients with Keshan disease showing that Se deficiency in human subjects affects the viral genome in the same way as in mice resulting in viral mutation and the development of heart pathology[20].

Influenza virus

Significantly more harmful lung inflammation developed in Se-deficient mice infected with a mild strain of influenza, influenza A/Bangkok/1/79 (H3N2), than in those with adequate Se[21]. Lungs from infected mice were examined for histopathological changes at days 4, 5, 6, 10 and 21 post-inoculation. Mice fed the Se-deficient diet had significantly more lung inflammation than those on the Se-adequate diet. This increase in pathology was associated with significant alterations in mRNA levels for cytokines and chemokines involved

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Table 1. Multiple selenoprotein functions relevant to viral infection[5]

Selenoprotein function	Some relevant examples
Antiviral	GPX (GPX1), TXNRD (TXNRD1), ER selenoproteins (SELENOF, SELENOK, SELENOM, SELENOS)
Antioxidant	GPX1, GPX2, GPX3, GPX4, TXNRD1, TXNRD2, TXNRD3, MSRB1, SELENOP, SELENOW
Anti-ferroptosis	GPX4
Anti-inflammatory	GPX, TXNRD1, SELENOS
Immune regulation	GPX (GPX1, GPX4), TXNRD, SELENOS, SELENOK
Control of redox regulation	GPX1, GPX4, TXNRD1, TXNRD2, TXNRD3
Selenium transport	SELENOP

ER, endoplasmic reticulum; GPX, glutathione peroxidase; MSRB1, methionine sulfoxide reductase B1; selenoproteins F–W are represented by SELENOF – SELENOW; TXNRD, thioredoxin reductase.

in pro-inflammatory responses[21]. Following infection in the Se-deficient mice, there were twenty-nine mutations in one segment of the viral genome[21].

These results demonstrate that adequate Se nutrition is required for protection against viral infection and suggest that nutritional deprivation may be one of many factors that increase the susceptibility of individuals to influenza infection[21].

Polio virus

Sixty-six UK participants with plasma Se ≤95 μg/l were supplemented for 15 weeks in a double-blind study with 100 or 50 μg/d Se (as sodium selenite) or placebo[22]. All subjects received an oral, live, attenuated poliomyelitis vaccine after 6 weeks. Those given selenite, particularly at the higher dose, cleared the virus more quickly as measured at 7, 14 and 21 d and with fewer mutations in the viral genome[22]. The results suggested that plasma Se ≤95 μg/l represented a functional Se deficit with suboptimal immune status and a deficit in viral handling.

HIV and AIDS

Human subjects infected with HIV are under chronic oxidative stress[14]. A dramatic consequence of this oxidative stress is the fatal decrease in the number of CD4 T-cells by apoptosis and ultimately a failure of the immune system leading to death[14]. Low Se status is associated with a lower number of CD4 T-cells, faster progression of AIDS and 20 % increase in the risk of death[14]. Se deficiency in HIV disease has been associated with disease progression and mortality, whether antiretroviral therapy has been initiated or not[23].

A number of Se supplementation trials in HIV-infected individuals have been conducted: two in the US with Se-enriched yeast[24,25] and three with selenomethionine in Tanzania[26,27], in Botswana[28] and in Rwanda[29]. In Botswana, 878 antiretroviral therapy-naïve HIV-infected adults were supplemented daily for 24 months with multivitamins and 200 μg Se[28]. There was a significant reduction in the risk of immune decline and morbidity. Multivitamins alone and Se alone had no effect[28]. In Rwanda, 24-month Se supplementation with 200 μg Se significantly reduced the rate of CD4+ cell-count decline among antiretroviral therapy-naïve patients[29]. It therefore appears that Se supplementation can delay HIV progression through the maintenance of CD4 cell counts[23].

Hepatitis B and hepatocellular carcinoma

In Qidong county near Shanghai, hepatocellular carcinoma is highly prevalent[30,31]. Eleven to fifteen per cent of adults are infected with hepatitis B and are 200 times more likely to develop hepatocellular carcinoma[30,31]. Two thousand and sixty-five hepatitis B antigen-positive men from Qidong were randomised into two groups: 1112 received 0·5 mg Se/d (as sodium selenite) and 953 men received a placebo[31]. After 3 years treatment and follow-up, thirty-four cases of new hepatocellular carcinoma had developed in the Se group *v.* fifty-seven cases in the placebo group ($P < 0·01$) suggesting that the relatively large daily dose of Se had reduced the risk of hepatocellular carcinoma[31].

Hantavirus and 'epidemic haemorrhagic fever'

Hantaviruses are RNA viruses that are zoonotic pathogens[32]. Transmission among rodents and from rodents to human subjects generally occurs through inhalation of aerosolised excreta. There was a six-times higher incidence of hantavirus infection in severe Se-deficient regions of China than in non-deficient regions[33]. An epidemic of haemorrhagic fever caused by hantavirus in Henan province, China, was successfully treated with multiple oral doses of sodium selenite (≤2 mg/d for the first 9 d), giving an overall 80 % reduction in mortality[34].

Other viruses

Further information on the link between Se, selenoprotein and other viral infections prior to the appearance of SARS-CoV-2 can be found in Guillin *et al.*[14].

SARS-CoV-2 and COVID-19

Evidence for an effect of Se status on the SARS-CoV-2-related COVID-19 was first noticed in China in 2020 when the cure rate in cities with up to fifty COVID-19 patients appeared to be different and to relate to the Se status of those cities[35]. Cumulative data on the cure rate in Chinese cities were observed from the specific date of 18 February 2020[36]. With regard to Se status, we found that seventeen cities with more than forty cases (outside Hubei, the epicentre province in China) had documented data on hair Se[36]; hair Se was found to be highly correlated with Se intake[5,37]. We found a significant association between cure rate and background Se status, as represented by hair Se concentration, in cities outside Hubei (R^2 0·72) (see Fig. 1)[36]. No correlation analysis was done for cities inside Hubei because Se status was only available for two cities. Though our study has an important number of limitations[36], our results

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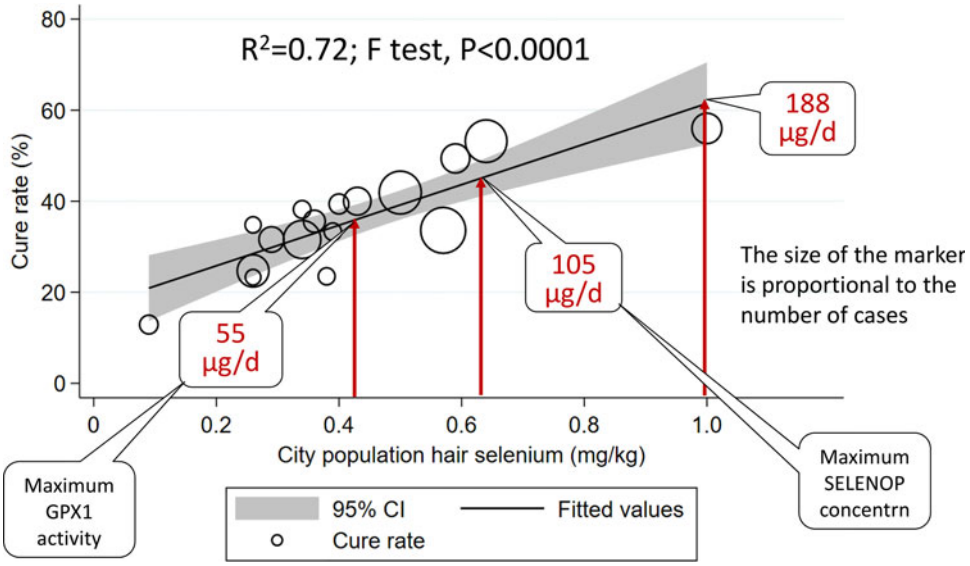

Fig. 1. Correlation between COVID-19 cure rate in seventeen cities outside Hubei on 18 February 2020, and city population Se status (hair Se concentration) analysed using weighted linear regression. Each data point represents the cure rate, calculated as percentage of patients hospitalised with SARS-CoV-2 deemed to be cured*. The size of the marker is proportional to the number of cases (adapted from *Am J Clin Nutr* with permission[36]). From the graph of Se intake *v.* hair Se concentration, $Se_{intake} = 232{\cdot}98Se_{hair} - 44{\cdot}521$, allowing the calculation of corresponding values of Se intake and hair concentration[5]. Thus value A represents the hair concentration corresponding to an intake of 55 µg/d where platelet GPX1 activity is maximised, value B represents the hair concentration corresponding to an intake of 105 µg/d where SELENOP concentration is maximised, and value C is the hair Se concentration (1·0 mg/kg) at the maximum cure rate in the investigated cities which corresponds to an intake of 188 µg/d[5]. **Cured patients are those in whom temperature has returned to normal for more than 3 d, respiratory symptoms are significantly improved, lung imaging shows significant reduction of inflammation, negative nucleic acid test of respiratory pathogen on two consecutive occasions with a sampling interval of at least 1 d.* COVID-19, coronavirus disease; GPX, glutathione peroxidase; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Se, selenium.

show an association between the reported cure rates for COVID-19 and Se status, consistent with the evidence of the antiviral effects of Se from the studies discussed earlier.

Interestingly, the final point on the correlation corresponded with a hair-Se status corresponding to an intake of 188 µg/d, significantly higher than that relating to the optimal Se intake for the hair concentration corresponding to an intake of 55 µg/d where platelet GPX1 activity is maximised[38] or for the production of SELENOP at which all selenoproteins are optimised[38]. This suggests that a factor other than a selenoprotein may be relevant to the mechanism by which Se affects SARS-CoV-2 and COVID-19.

A study corroborating these findings[36] was published the following year; it showed that the case fatality rate of COVID-19 was linked to Se deficiency in soils and crops at the city level in China[39]. Fourteen thousand and forty-five cases of COVID-19 were reported from 147 cities with >20 cases/city from December 2019 to December 2020. Cities were grouped by Se content in crops which was consistent with Se content in topsoil to show that 15 % of cities were severely-Se-deficient, 51 % that were moderately-Se-deficient and 34 % that were non-Se-deficient[39]. Co-variates included population density, gross domestic product per capita, proportion of population >60 years. Using zero-inflated negative binomial regression and correcting for the co-variates, the incidence rate ratio (95 % CIs) for case fatality was significantly different between non-Se-deficient, moderately-Se-deficient and severely-Se-deficient soils and crops, e.g. for soils 1, 2·38 (1·14–4·98), 3·06 (1·49–6·27)[39]. The highest COVID-19 case fatality rates fell within the Se-deficient belt in north-east and central China[39].

A number of studies have assessed the effect of Se status in patients with COVID-19. A German study looked at serum Se and SELENOP concentrations in COVID-19 patients[40]. The patients showed a pronounced deficit in total serum Se and SELENOP concentrations when compared to reference data from a cross-sectional analysis of the European EPIC study[40]. The Se status was significantly higher in samples from surviving COVID patients than in non-survivors (Se, 53·3(SD 16·2) *v.* 40·8(SD 8·1) µg/l; SELENOP, 3·3(SD 1·3) *v.* 2·1(SD 0·9) mg/l). Se status recovered with time in survivors while remaining low or even declining in non-survivors[41,42]. Apart from the studies conducted in Germany[40,41,42], some six other studies have assessed Se in serum/plasma (µg/l) in COVID-19 patients and found lower Se status in those with COVID than in healthy persons[43,44,45].

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These observations raise the question of whether serum/plasma Se was lower at baseline in these patients or was it simply lowered by SARS-CoV-2 or COVID-19? Indeed, it *may* have been lower at baseline but under inflammatory conditions (systemic inflammatory response) as in COVID, hepatic SELENOP biosynthesis is diminished and plasma or serum Se falls[41]. Infection by SARS-CoV-2 may reduce selenoprotein expression. However, when selenoprotein biosynthesis by hepatocytes recovers, SELENOP secretion and improved systemic Se transport occurs and SELENOP will rise in serum/plasma[41]. If selenoprotein biosynthesis does not recover, weak recovery and high mortality risk is indicated as seen in non-recovery from COVID-19[41]. The only way to be sure that Se status was low before disease occurs is to measure erythrocyte Se which, with a half-life of 120 d, will only vary after a longer period of inflammation[46].

Mechanisms by which Se affects SARS-CoV-2 and COVID-19

There is no doubt that selenoproteins are capable of antiviral effects as explained in Table 1 and in the studies previously cited and we will expand on those effects later. However, the data that show that the maximum intake of Se that had the greatest effect on COVID-19 cure rate in China[36] suggests that an intake above that required to optimise selenoproteins may be relevant to the mechanism by which Se affects SARS-CoV-2 and COVID-19. We believe that this includes redox-active Se species (Fig. 2)[5].

Selenoprotein mechanisms

Antioxidant effects. The balance between ROS and their scavenging systems is disturbed by viral infection which increases the number of ROS[14]. As previously explained, selenoproteins, particularly GPX and TXNRD, can reduce ROS thus helping to maintain the balance[14]. Loss of those selenoproteins in Se deficiency allows more viral copies to be generated per unit time giving more opportunities for the emergence of mutations that are the basis for evolutionary selection of more virulent strains[15,16,17]; hence Se adequacy is important.

Immune effects. The immune system needs adequate Se[47]. IL-2 is a necessary growth factor for most T-cells and acts via the IL-2 receptor[48]. Se supplementation was able to induce up-regulation of the IL-2-receptor enabling T and B lymphocytes to respond to IL-2[49,50]. An example of the need for adequate Se for immune function is shown by a UK study in which men were supplemented with 50 or 100 μg Se as sodium selenite or placebo daily for 15 weeks in a double-blind study[22]. All subjects received an oral, live, attenuated poliomyelitis vaccine after 6 weeks. Those given Se had improved immune response through an earlier peak T-cell proliferation and an increase in T-helper cells[22]. They showed more rapid clearance than those without extra Se. The data show that these subjects whose Se status was relatively low (plasma Se ≤95 μg/l) had a functional Se deficit with sub-optimal immune status and a deficit in viral handling[22].

Roles identified for selenoproteins in T-cells have been nicely shown by Ma and Hoffmann in 2021[48]. Selenoproteins involved are GPX1, GPX4, TXNRD1, TXNRD2, SELENOK and SELENOP in the manner specified in Fig. 3[48].

Reduction of inflammation: inflammatory cytokines and NF-κB. Evidence from clinical studies in human subjects and animals has linked the increased systemic levels of IL-6 with the exacerbation of clinical outcomes involving viral pathogens[51]. We also know that NF-κB is crucial for transcription of inflammatory cytokines associated with severe COVID-19[52]. Some data on Se/selenoproteins affect both those outcomes: (i) deficiency of Se is known to increase IL-6[53,54]; (ii) in acute respiratory distress syndrome patients, serum IL-1 and IL-6 correlated inversely with serum Se while intravenous selenite moderated the inflammatory response and meaningfully improved the respiratory system[55]; (iii) NF-κB has been shown to be specifically inhibited by selenite in cell culture studies[56]; (iv) optimal Se status (100 nM/l in cell culture) is critical for alternative macrophage activation, leading to attenuated expression of proinflammatory mediators[57].

In another anti-inflammatory function, Se/selenoproteins aid in the shunting of arachidonic acid towards endogenous anti-inflammatory mediators as an adaptive response to protect cells against pro-inflammatory gene expression induced by oxidative stress[58]. Thus, Se supplementation in macrophages increases the production of the PG, 15-deoxy-Δ-12,14-PG J2 (by the COX-1, cyclooxygenase pathway), an endogenous inhibitor of a key kinase of the NF-κB cascade, IκB-kinase β[59] (see Fig. 4). This effect results in decreased activation of NF-κB and down-regulates the expression of inflammatory genes such as COX-2, TNF-α, IL-6 and VCAM-1, vascular cell adhesion molecule 1[59,60]. In a second Se-dependent anti-inflammatory mechanism acting through 15-deoxy-Δ-12,14-PG J2, Se-supplemented macrophages activate the peroxisome PPAR-γ, repressing inflammatory gene expression (Fig. 4)[61,62].

Lastly, SELENOS is an ER membrane protein involved in the control of inflammation[63,64]. SELENOS has a role in the removal of stressor-induced misfolded proteins from the ER, preventing the accumulation of these proteins and the subsequent stress response that leads to activation of NF-κB, pro-inflammatory cytokine gene transcription and the inflammation cascade (Fig. 4). Genetic variation in *SELENOS* has been shown to influence the inflammatory response[65]. Impairment of SELENOS is directly associated with increased cellular cytokine production and release[65]. Other selenoproteins located in the ER that may also contribute to the reduction of ER stress are SELENOF, SELENOM and SELENOK[66].

The synthesis of host selenoproteins is targeted at the RNA level by SARS-CoV-2. Higher Se status is associated with a better clinical outcome of SARS-CoV-2[36,40], and some of that effect is likely to

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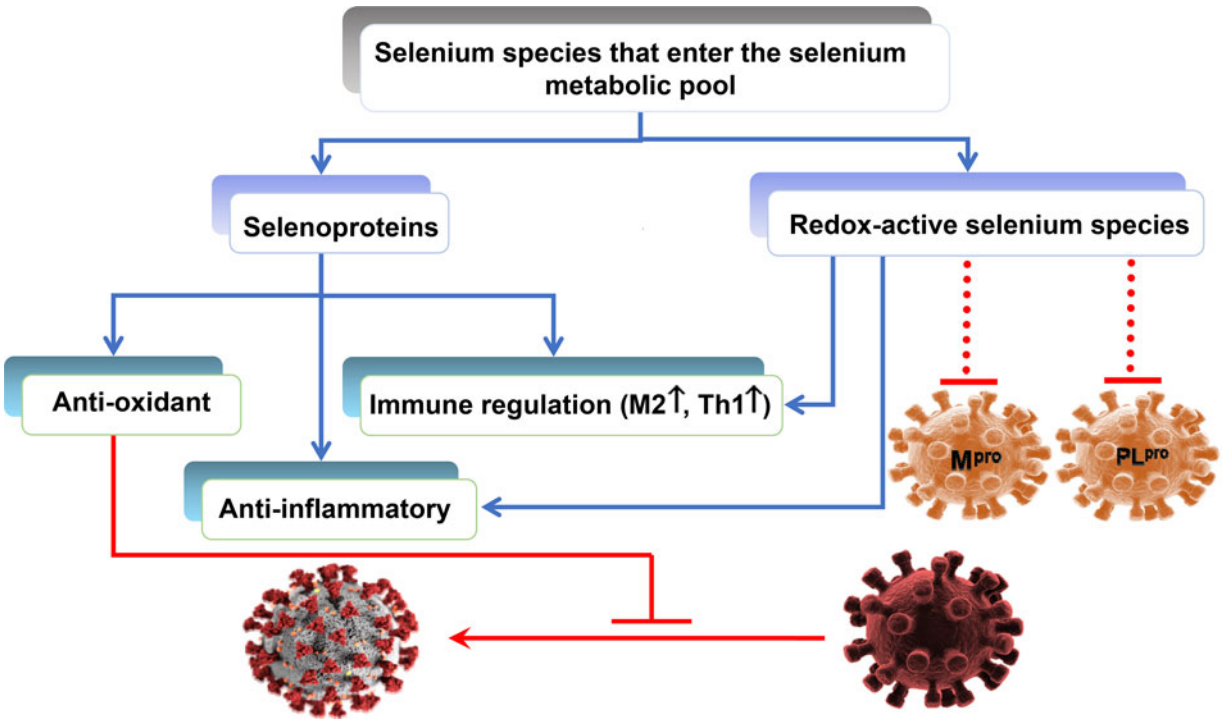

Fig. 2. Potential mechanisms by which selenoproteins or redox-active Se might suppress the life cycle and mutation to virulence of SARS-COV-2 while attenuating viral-induced oxidative stress[5] (published with permission of Redox Biology). M2, M2 macrophages; Mpro, main protease; PLpro, papain-like protease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Se, selenium; Th1, Th1-type cytokines.

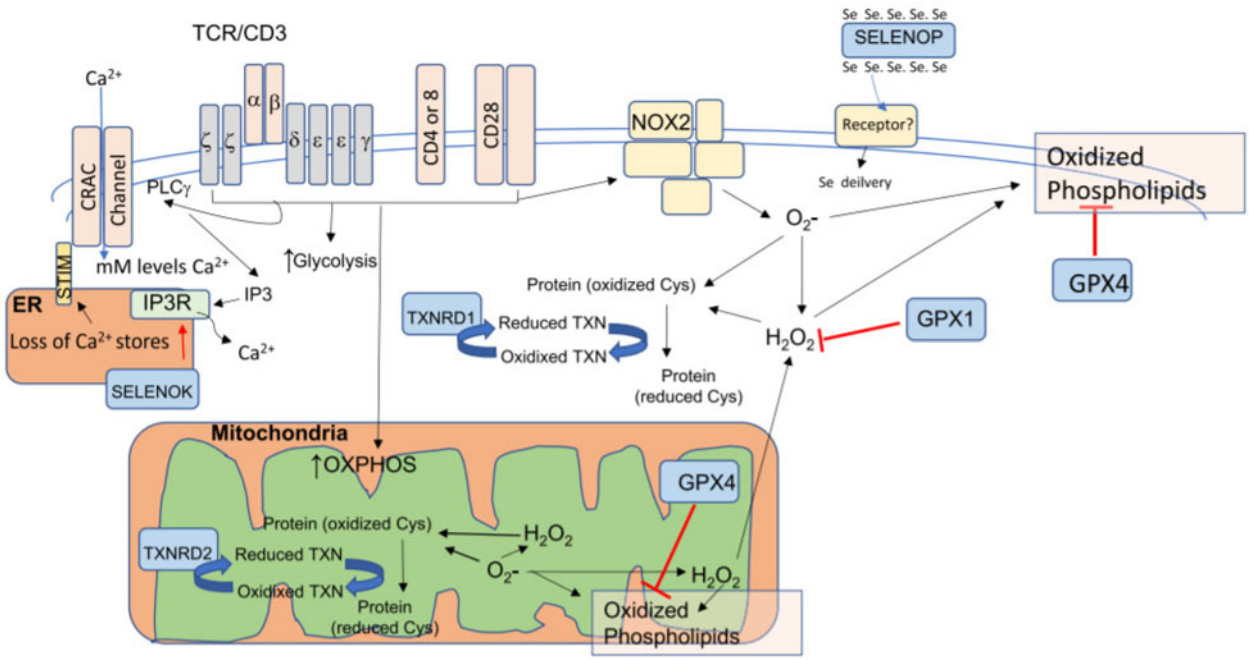

Fig. 3. Roles identified for selenoproteins in immune cells. Functions of the selenoproteins (blue background) are explained[48]: SELENOP delivers Se to the T-cell; SELENOK (with IP3R, STIM and the CRAC channel) raises the cytosolic Ca^{2+} content to μM levels, activating pathways for optimal T-cell activation; GPX1, GPX4, TXNRD1, TXNRD2 control redox regulation during T-cell receptor signalling; GPX4 prevents the accumulation of lipid-based ROS which drives the ferroptosis of T-cells (published with permission from *Seminars in Cell & Developmental Biology* 2021[48]). Cys, cysteine; ER, endoplasmic reticulum; GPX, glutathione peroxidase; NOX2, NADPH oxidase 2; OXPHOS, oxidative phosphorylation; ROS, reactive oxygen species; TCR/CD3, T cell receptor/CD3 complex plays a key role in antigen recognition; TXN, thioredoxin; TXNRD, thioredoxin reductases.

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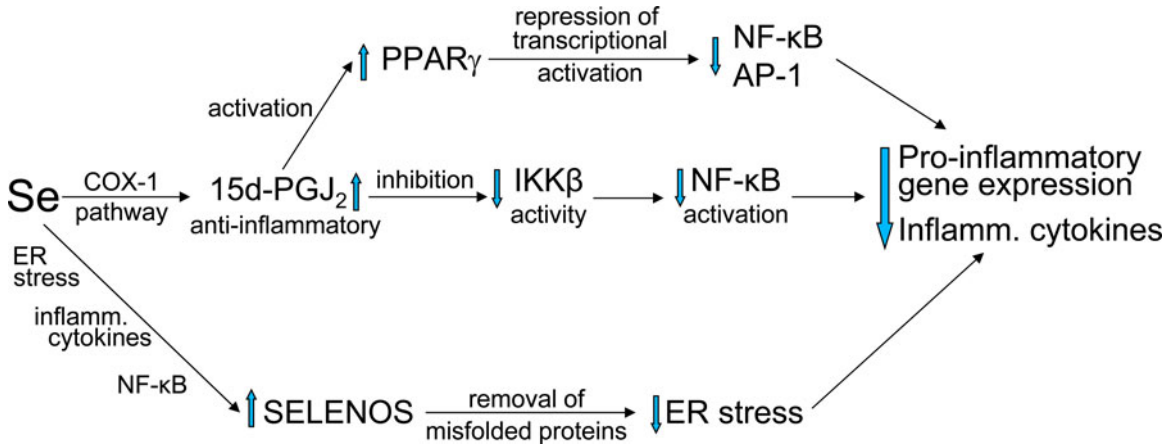

Fig. 4. Mechanisms by which inflammation is reduced by Se/selenoproteins[58]. AP-1, activator protein 1; COX-1, cyclooxygenase 1; 15d-PGJ2, 15-deoxy-Δ-12,14-PG J2; ER, endoplasmic reticulum; IKKβ, IκB-kinase β; Se, selenium; SELENOS, selenoprotein S.

be mediated through increased biosynthesis of host selenoproteins, as reviewed earlier. However, it is also possible that a partial basis of this effect is that SARS-CoV-2 infection can interfere with the synthesis of a subset of host selenoproteins so that increased dietary Se intake helps to counteract that effect. One mechanism by which the virus could impair host selenoprotein synthesis is by antisense targeting of host selenoprotein mRNA. This would require that regions of the viral genomic or mRNA have antisense complementary to regions of a host mRNA sequence. By pairing up with a complementary host mRNA sequence, the viral antisense strand could prevent translation of the host mRNA, thus suppressing host selenoprotein gene expression (Fig. 5)[67]. An example of this type of potential antisense interaction is shown as RNA secondary structures for SARS-CoV-2 *v.* human TNXRD3 in Taylor *et al.*[68]. The possibility of antisense interactions between viral RNAs and host selenoprotein mRNA was first proposed for HIV-1 and Ebola virus based on computational analysis[68] and has been supported experimentally for HIV-1 and Zika virus[69,70].

We looked at the effect of infection by SARS-CoV-2 on the expression of selenoprotein mRNA in Vero cells[66]. SARS-CoV-2 triggered an inflammatory response as evidenced by increased *IL-6* expression. Of the selenoproteins, SARS-CoV-2 significantly suppressed the mRNA expression of GPX4, TXNRD3 and ER-resident SELENOF, SELENOK, SELENOM and SELENOS[66]. Using a gel mobility shift assay and synthetic oligonucleotides, we assessed the potential antisense interaction previously mentioned between SARS-CoV-2 and a region of human TXNRD3 that was identified computationally, corresponding to the predicted antisense pair[66,71]. DNA oligos corresponding to those specific regions of SARS-CoV-2 and TXNRD3 mRNA hybridised quantitatively to form a single slower moving band corresponding to the expected duplex DNA. This interaction was sequence specific, because a negative control consisting of a randomly shuffled SARS-CoV-2 oligo of identical composition still moved as a single band in the presence of the TXNRD3 oligo[66]. These data present a plausible mechanism for a direct inhibitory effect of SARS-CoV-2 replication on the expression of a specific set of selenoprotein mRNA which may be relevant to the correlations between dietary Se status and the outcome of SARS-CoV-2 infection[66].

The possible consequences of SARS-CoV-2-induced down-regulation of selenoprotein genes that we demonstrated at the mRNA level are shown in Fig. 6. Very importantly, SARS-CoV-2 suppresses GPX4 gene expression; GPX4 is vital in the survival and expansion of recently activated T-cells by prevention of lipid peroxidation and ferroptotic cell death[72]. SARS-CoV-2 suppresses the expression of SELENOF, SELENOM, SELENOK and SELENOS, causing ER stress[73]. TXNRD3 is mainly expressed in the testis[74]. Down-regulating TXNRD3 may help explain COVID-19-associated orchitis[75] or gastrointestinal manifestations since suppression of TXNRD3 promotes colitis[76].

Host selenoproteins may be targeted at the protein level by the SARS-CoV-2 main protease (Mpro). Another mechanism by which SARS-CoV-2 could interfere with host selenoprotein function is by targeting it at a post-translational stage, *via* proteolytic degradation. Since RNA viruses typically encode one or more protease enzymes to process their own polyproteins, the targeting of specific host proteins by viral proteases is a well-known mechanism exploited by other RNA viruses including HIV-1, and which has been reported for SARS-CoV-2 by several independent research groups[77,78,79]. One of these studies identified amino acid sequences in several human selenoproteins matching known Mpro cleavage sites in the SARS-CoV-2 polyprotein[78]. The most obvious of these was an almost exact match between a region of SELENOF and the Mpro target site at the non-structural protein12/13 junction in SARS-CoV-2, the sequences of which are

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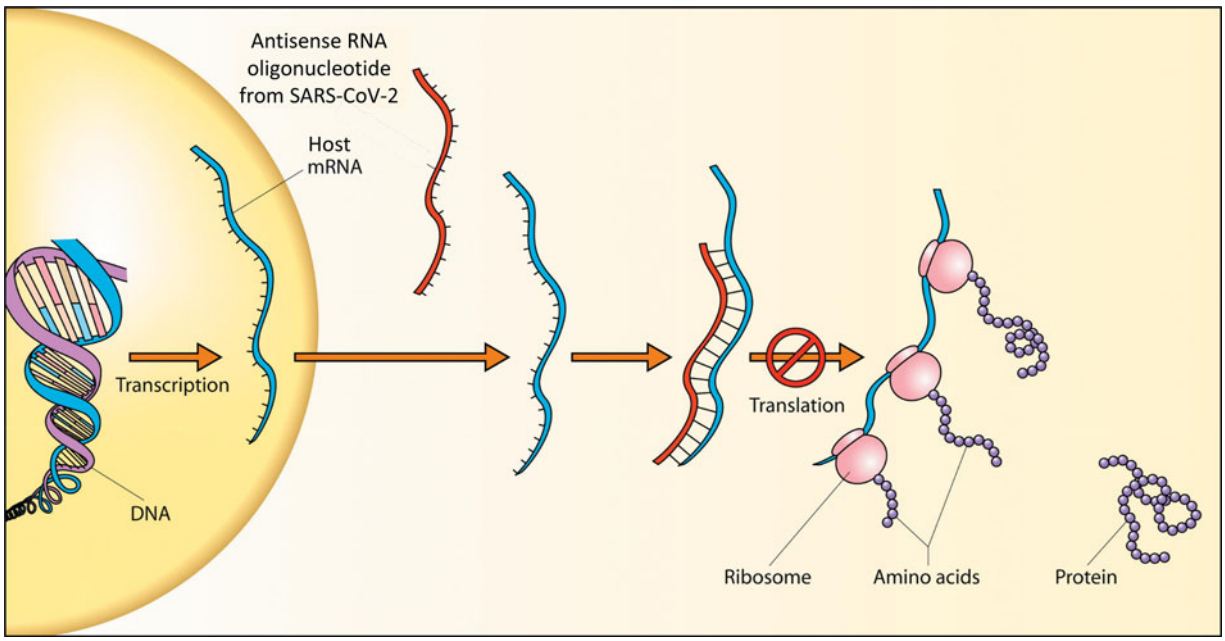

Fig. 5. How SARS-CoV-2 inhibits the synthesis of host selenoproteins. Antisense is a single strand of RNA complementary to a target mRNA sequence. By pairing up with it, the viral antisense strand prevents translation of the host mRNA (graphic modified from: Robinson[67]). SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

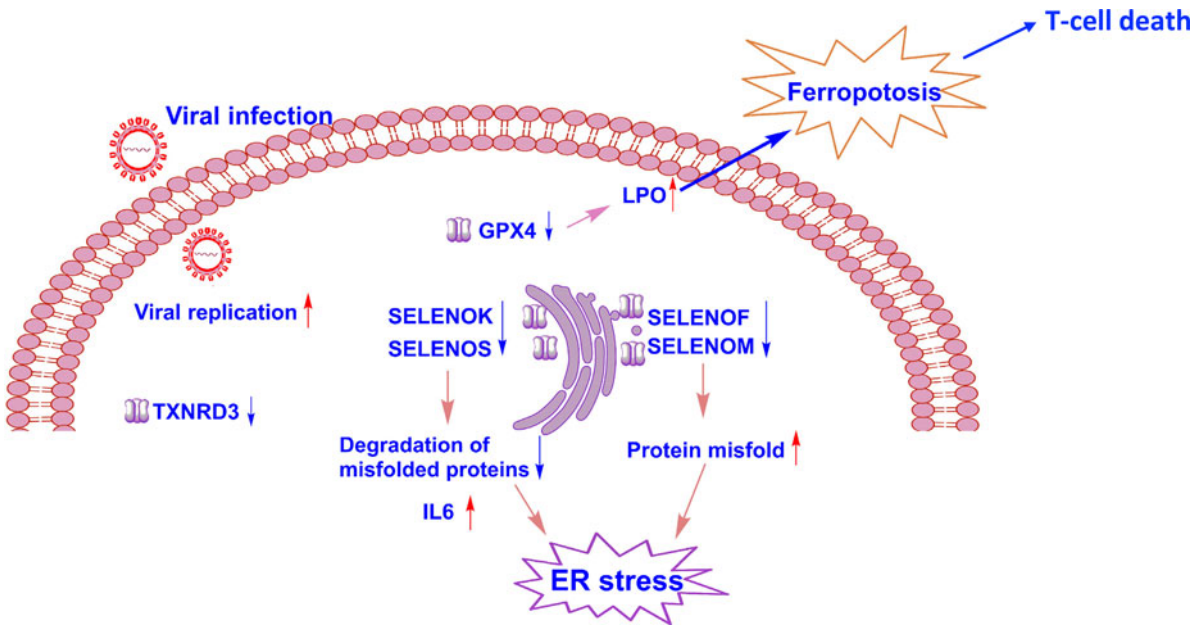

Fig. 6. SARS-CoV-2 suppresses GPX4 gene expression; GPX4 is vital in the survival and expansion of recently activated T-cells by prevention of lipid peroxidation and ferroptotic cell death[72]. SARS-CoV-2 causes ER stress and suppresses the expression of SELENOF, SELENOM, SELENOK and SELENOS. Down-regulating TXNRD3 may help explain COVID-associated gastrointestinal manifestations[76] and testicular function[75]. COVID-19, coronavirus disease; GPX, glutathione peroxidase; LPO, lipid peroxidation; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TXNRD, thioredoxin reductases.

TVLQ/AVSA and TVLQ/AVGA respectively, where / corresponds to the protease cleavage site. Other strong candidates for proteolysis by Mpro included sites in TXNRD1 and SELENOP. Synthetic peptides corresponding to all three of these putative cleavage sites in human selenoproteins have been found to be cleaved *in vitro* by recombinant Mpro using synthetic peptides and MS to identify the cleavage products[80].

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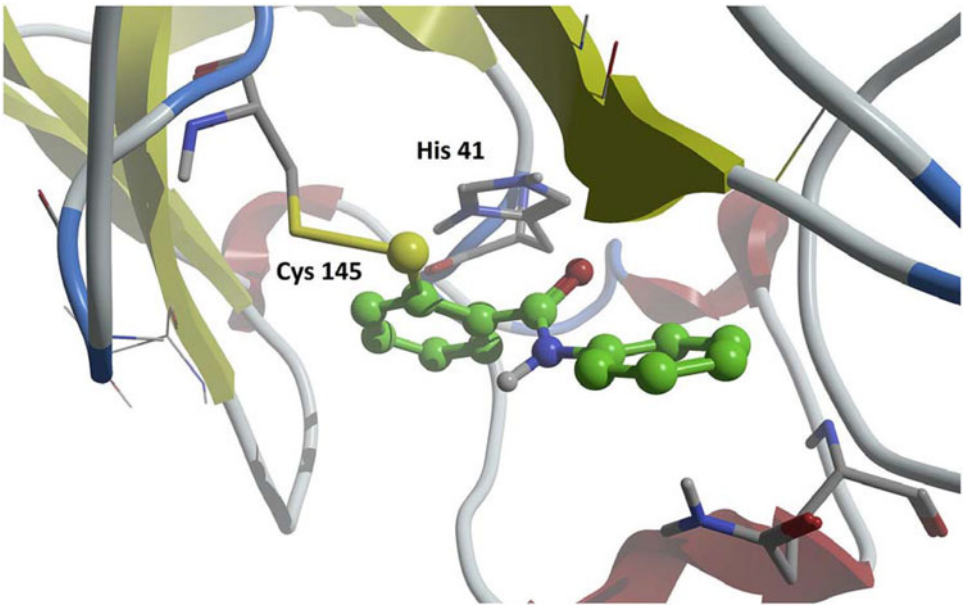

Fig. 7. *In silico* analysis of ebselen bound to the main protease M^{pro} of SARS-CoV-2[84] (*In silico* analysis was performed using MOE and ACEMD software. Kindly provided by Prof. G. Cozza, Padova; produced with permission of Free Radic Biol Med[84]). Cys-145, cysteine-145; His-41, histidine 41; Mpro, main protease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Significantly, viral knockdown of SELENOF via proteolysis is consistent with the observed knockdown of SELENOF mRNA, which was the most decreased of all the human selenoprotein mRNAs in SARS-CoV-2 infected cells[66]. This two-pronged assault on a host selenoprotein suggests that the virus must benefit significantly by the disruption of SELENOF activity. The results reviewed earlier further imply that TXNRD1 and SELENOP may also be actively degraded by the virus during SARS-CoV infection. This could help to explain the results of Moghaddam *et al.*[40], who found that a progressive decline in blood SELENOP levels was characteristic of COVID-19 patients who died, despite Se levels being low but unchanged, whereas SELENOP levels *increased* during the recovery of patients who survived[40]. The possible proteolytic deactivation of TXNRD1 by SARS-CoV-2 would be consistent with the hypothesis that RNA viruses may benefit by inhibiting DNA synthesis, in order to conserve the ribonucleotide pool for viral RNA synthesis[71].

Redox-active Se species inhibiting SARS-CoV-2 Mpro

The Mpro of SARS-CoV-2, critical for viral replication, is a key target for therapeutic development[81,82]. Redox-active Se species have the potential to react with Mpro. After entering into the host cell, SARS-CoV-2 releases its RNA. Two overlapping polyproteins, pp1a and pp1ab are encoded by the replicase gene that constitutes two-thirds of the RNA genome[81]. They are proteolytically digested into fifteen non-structural proteins by the two viral proteases, Mpro and papain-like protease that are critical for viral replication. The released non-structural proteins form the viral RNA polymerase complex allowing the replication and transcription of fresh virus in the host[81]. Therapeutic development has produced compounds which are Mpro inhibitors and can bind to the Mpro binding cleft resulting in inactivation with failure of virion assembly; the host cells cannot release the new virions and new infection is inhibited[82].

The GPX mimic, ebselen, one of 10 000 compounds examined for inhibiting the Mpro activity of SARS-CoV-2, powerfully inhibited it, suppressing its life cycle[83]. It showed a low concentration for maximal effect and a high concentration for cytotoxicity. From an *in silico* analysis of ebselen bound to the main protease Mpro of SARS-CoV-2, the Se atom of the open structure of ebselen establishes a covalent interaction with the Mpro catalytic cysteine-145 (see Fig. 7)[84]. His-41 of Mpro forms an interaction with the aromatic ring of ebselen and a polar interaction with its carbonyl group[84]. A chemical mechanism for the inhibition of SARS-CoV-2 Mpro cysteine-145 by ebselen and its derivatives has been published[81].

Redox-active Se compounds could similarly inactivate Mpro and papain-like protease by binding to the sulphur of cysteine and contributing to the anti-SARS-CoV-2 effect of Se[77,83,84,85,86]. The non-stoichiometric nature of redox-active Se compounds in oxidising thiols with the involvement of oxygen implies that these redox-active Se compounds may play an important role in inhibiting replication of SARS-CoV-2[87].

Another strongly redox-active Se species is known to be produced in the atmosphere from the metabolism of Se in plants, i.e. dimethyl-diselenide. Indeed, Se concentration in forage-crop alfalfa leaves has been used as a proxy for regional Se exposure[88]. Se in plant, soil, water and bacteria can be transformed into volatile

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dimethyl-diselenide and can be inhaled by, and excreted from, the lung[89]. We have hypothesised that atmospheric dimethyl-diselenide levels and lung Se exposure may be different in US states with different Se concentrations in alfalfa and have explored the interesting question of whether the strongly redox-active dimethyl-diselenide in the atmosphere may play a role in affecting COVID-19 mortality[90].

Conclusion

This review presents information supporting a role for Se/selenoproteins in reducing the effect of SARS-CoV-2 and COVID-19. There are some credible mechanisms relying on roles for selenoproteins and redox-active Se. However, as yet, there are no randomised controlled trials using Se, although one is planned in Texas entitled *Selenium as a potential treatment for moderately-ill, severely-ill, and critically-ill COVID-19 patients (SeCOVID)* (ClinicalTrials.gov identifier NCT04869579), though it is not yet recruiting. Until and unless randomised controlled trial information becomes available, proof of the importance of Se/selenoproteins in SARS-CoV-2/COVID-19 may never be confirmed.

Financial Support

None.

Conflict of Interest

None.

Authorship

The authors were solely responsible for all aspects of preparation of this paper.

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