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LETTER TO THE EDITOR

ORIGINAL ARTICLES

Letter to the Editor

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Computational Nanomedicine: Helping Us Get Through COVID-19

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At a time when Universities closed their doors to research during the COVID-19 pandemic out of safety concerns, researchers endured and even thrived. While some faculty and graduate students used this closure time to write review papers, grants, or develop research plans for their specific fields of interest, many academic researchers turned towards computational modeling to solve COVID problems. Although we all knew that computational modelling can be done at home, not requiring access to University research labs, we did not realize how helpful computational modelling would be to find solutions for COVID-19.

3 years after the onset of the COVID-19 pandemic, it is clear that computational modeling significantly helped us get through COVID-19 [1-7]. From using molecular dynamics to understand binding of the SARS-CoV-2 spike protein to the ACE2 receptor of mammalian cells during the virus replication process to optimizing the design of small molecules to bind to the envelop protein of SARS-CoV-2 to stop it from replicating, the field of computational modeling was critical at a time when academic research labs were unavailable [4]. Further, adsorption, distribution, metabolism and excretion (ADME) and quantitative structure-activity relationship (QSAR) computational modeling was also instrumental towards understanding the pharmacological properties of COVID therapies and vaccines [8]. Without such advances in computational modeling made throughout the decades, it is clear that we would not have the COVID-19 solutions that we have today, including COVID prevention, diagnosis, and treatment.

Our personal story includes one of frustration then exultation where upon the onset of COVID-19 in the Fall of 2019 and Spring of 2020, we believed as scientists it was our duty to help the world get through the COVID-19 pandemic. Many researchers did the same, making masks for healthcare workers when there were shortages, developing new more sensitive and easy to use diagnostic kits, and trying to develop vaccines and therapies for COVID-19 [10]. While we had over 20 years of experience in biomaterials and tissue engineering, we had little to no experience in viruses or virology. So, how could we contribute to finding COVID solutions? And, even if we did have ideas, it got worse. Like many Universities, our University research labs were shut down due to COVID safety protocols, despite the fact that many industries kept their labs open enabling their researchers to conduct life saving research.

So, in the early days of COVID-19, we were stuck. We did not know how to help and we had no where to conduct studies anyway. Thankfully, during this critical time in our global health, the scientific community initiated virtual webinars, conferences, and other activities to keep our minds active. We distinctly remember giving several webinars concerning how nanotechnology was trying to provide solutions to COVID-19 through embedding nanoparticles in masks which could release reactive oxygen species to passivate SARS-CoV-2 when trapped in masks to using iron oxide nanoparticles functionalized to attach to SARS-CoV-2 increasing detection sensitivity under an applied magnetic field [6]. Even Moderna and Pfizer were researching nanodimensional liposomes for brand new mRNA based vaccines [9]. After one of these webinars, we had an idea: transition the self-assembled nano materials that we were previously developing for tissue engineering applications into those which can attach, self-assemble

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around, and "blanket" SARS-CoV-2 inhibiting it from entering mammalian cells to replicate [4-8, 10]. Our nanomaterials were similar in size to SARS-CoV-2, so the idea theoretically could work. But what could we functionalize onto our self-assembled materials to attract them to SARS-CoV-2? And where could we experimentally prove this concept?

Computational modeling came to our rescue. We quickly contacted several virologist friends to obtain the amino acid sequence of the envelop protein of SARS-CoV-2 and developed peptide sequences that compliment those regions for attachment [11]. While everyone else was targeting the spike protein in SARS-CoV-2, we targeted the envelop protein since we knew the spike protein would eventually possess more mutations than the envelop protein. Then, as we were still unable to complete research in our academic research labs (going well into 2020), we used molecular dynamics extensively to identify a self-assembled nano material that would strongly attach to SARS-CoV-2, "blanket it", and keep it from replicating. After extensive molecular dynamics simulation, we then completed pharmacological computational modeling (ADME and QSAR) to further validate our self-assembled nanomaterial [8]. We then spun out this molecule commercially and we were able to conduct in vitro and in vivo studies validating the efficacy of this self-assembled nanomaterial towards passivating SARS-CoV-2 (and other viruses) [12].

Looking back at our experience, we are incredibly grateful to the computational modeling community. At a time when we and others needed them most due to experimental lab closures, we were able to quickly and effectively learn computational models that have been developed and optimized over the decades. We would not have developed a therapy or so many other technologies to help fight COVID had it not been for computational nanomedicine.

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References

[1] S. Ghosh and S. Bhattacharya. SN Comput Sci (2021), 2(3), 230.
[2] W. E. Schiesser. Computational Modeling of the COVID-19 Disease, World Scientific Publishers, Singapore, 2020.
[3] P. Gerlee, A. Jöud, A. Spreco, T. Timpka. Scientific Reports (2022), 12,13256.
[4] A.F. Nahhas, T.J. Webster. OpenNano (2022), 7, 100054.
[5] A.F. Nahhas, T.J. Webster. Journal of Biomedical Nanotechnology (2022), 18, 1158–63.
[6] A.F. Nahhas, T.J. Webster. Journal of Nanobiotechnology (2021), 19, 1-14.
[7] A.F. Nahhas, T.J. Webster. Nanomedicine (2021), 16(14), 1237–54.
[8] A.F. Nahhas, A. A. Alshaikh, and T.J. Webster. Journal of Biomedical Nanotechnology (2022), 18, 1-10.
[9] L. R. Baden, et al. New England Journal of Medicine (2021), 384, 403-416.
[10] L. Zhang, S. Ramsaywack, H. Fenniri, and T.J. Webster. Tissue Engineering Part A (2008), 14 (8), 1353-1364.
[11] V.S. Mandala et al. Nat Struct Mol Biol (2020), 27, 1202–1208 (2020).
[12] Website: https://researchoutreach.org/articles/nanomedicine-prevention-treatment-covid-19-other-viruses/, accessed September 23, 2022.

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Essential elements as critical players against SARS-CoV-2 activity

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ABSTRACT

Background: SARS-CoV-2 virus is currently one of the main causes of death worldwide. Several studies have suggested that various trace elements play a vital role in the immune activity during viral infection, being an important tool to understand the SARS-CoV-2 infection and its systemic behavior, which affects different organs.

Purpose: To summarize recent studies that report the effect of trace elements on the immune system and their role in fighting SARS-CoV-2 infection, presenting potential biochemical routes.

Method: The main databases (ScienceDirect®, Scopus®, PubMed®) were consulted to search for works published up to October 2022, focusing on the role of trace elements in the immune activity against viral infection, including SARS-CoV-2.

Conclusion: Many elements can act both in the activation of the host's immune activity and in the survival of the virus since these processes occur with the participation of essential metals to guarantee the integrity of their functions. However, the relationship between trace elements and viral infection is complex, and requires further studies, mainly, focusing on the systemic behavior of SARS-CoV-2 infection.

Keywords: *Viral infection; immune system; trace elements homeostasis; biochemical mechanisms.*

1. Introduction

Viruses are small particles composed of genetic material (RNA or DNA) surrounded by a layer of proteins or lipids that replicate rapidly after infection in the host [1, 2]. SARS-CoV-2 (Severe Acute Respiratory Syndrome-Coronavirus-2), responsible for Coronavirus disease-19 (COVID-19) has become the deadliest virus in the last two years, causing more than six million deaths (data up to October 2022) worldwide [3]. Unlike other viral infections, SARS-CoV-2, originating in Wuhan (China), presents a systemic infection, affecting different parts of the body, including the respiratory tract, hematological, gastrointestinal, and neurological [2, 4].

Several essential metals play central roles in viral infections since some trace elements are present in the structure of essential metalloproteins responsible for the immune activity against the infection and for virus attachment to the host [1, 5]. For example, copper (Cu), iron (Fe), and zinc (Zn) are some of the most important cofactors present in metalloproteins associated with some infections [5-8]. Thus, various trace elements participate in different functions, including reverse transcription, catalytic mechanisms, genome maturation (RNA or DNA), initial integration, and the protection of newly synthesized DNA [9, 10].

This review summarizes recent studies on the impact of dysregulation (excessive and deficient) of the main trace elements in the body and their effects on the immune system against SARS-CoV-2 infection.

2. The function of essential elements in the immune activity against viral infection

The search was conducted in the databases ScienceDirect, Scopus, and PubMed using the keywords "viral infection", "immune system" and "trace elements homeostasis". These main databases were consulted to search for works published in the last ten years (up to October 2022). The

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articles selected were recent studies that reported the role of trace elements in the immune activity against viral infection, including SARS-CoV-2.

3. The function of essential elements in the immune activity against viral infection

The immune system is modulated by several antigen-presenting cells that maintain the physiological integrity of the organism. After being infected by a virus through the angiotensin-converting enzyme 2 (ACE2), the human body undergoes some changes to fight the infection [11]. The first change is vasodilation, which allows immune cells to reach to the infected tissue [2, 11]. Then, the virus is attacked by the first line of defense (innate response) which is constituted by neutrophils and macrophages [1, 2, 11] (Figure 1). Thus, when any virus infects the organism, it is initially phagocyted by T- and B-lymphocytes (macrophages) [12, 13]. Then, the second line of defense of the immune system (adaptative response) is activated. The adaptative response consists of antibodies (IgA, IgM, and IgG) [4, 12, 14]. Another important component during the fight against viral infection is the cytokines, which act in the establishment of intercellular communication [1, 15-17].

Essential elements such as Fe, Se, Zn, Cu, among others have immunomodulatory activity influencing various components of the immune system [18]. In this regard, several studies have reported changes in the levels of trace elements in the body during viral infections, including SARS -CoV-2 [8, 19, 20]. Below, we discuss the importance of the main essential elements for the immune system, highlighting how their imbalance can lead to severe infections.

3.1 The importance of zinc in antiviral immunity

Zinc is a trace element that is associated with the regulatory function and maintenance of the immune system (Figure 2) [21-23].

Zn can be found in different organs, representing an integral component of the human body, and is found in free form (zinc ions) or bound to biomolecules [24]. As several enzymes have Zn as a cofactor, the integrity of immune barriers is preserved by Zn, improving the activity of natural killer cells (NKCs), and maintaining strong antiviral activity [25-27]. Thus, in a viral infection, including SARS-CoV-2, Zn can effectively act to inhibit the activity of the virus, inhibiting the elongation phase of RNA synthesis [2]. This action is justified due to its effect on the mold binding of Zn, thus, affecting SARS-CoV-2 replication [1]. In addition, evidence has shown that Zn deficiency is associated with decreased activity of NKCs and reduced antibody production, impairing immune activity [26-29]. Macrophage production is also affected by Zn deficiency, dysregulating cytokine production, and phagocytosis. Zn deficiency also potentiates apoptosis.

Although there is not clearly a biochemical mechanism described, studies report that Zn can assist in the inhibition of viral protease and virus fixation, preventing infection [1, 29]. Thus, it is possible that Zn supplementation may be of great importance against SARS-CoV-2 infection, regulating some cell functions, such as cell activation and division, playing a vital role in the immune system (adaptative and innate immunity) [30, 31]. In addition, zinc also can act as an antioxidant and can stabilize membranes.

In a case study, Gordon & Hardigan [32] examined the

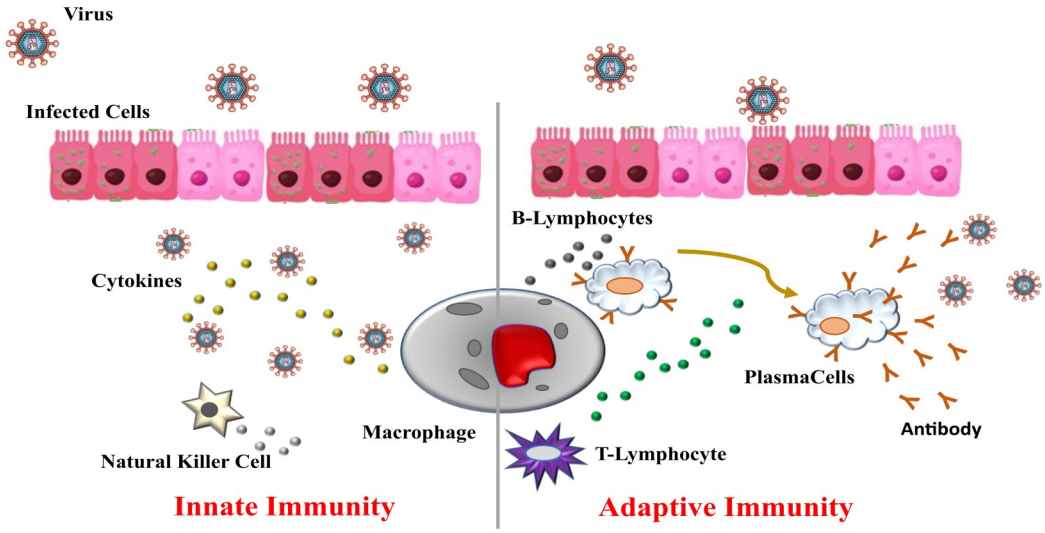

Figure 1 | General mechanism illustrating the action of the immune system against viral infection. In summary, the immune system triggers innate and adaptive responses. The innate response represents the first line of defense and consists of the release of chemical mediators and phagocytosis of the aggressive agent. While the adaptive consists of the second defense's line of the immune system and is responsible for antibody production to neutralize the offending agent. Adapted from [1].

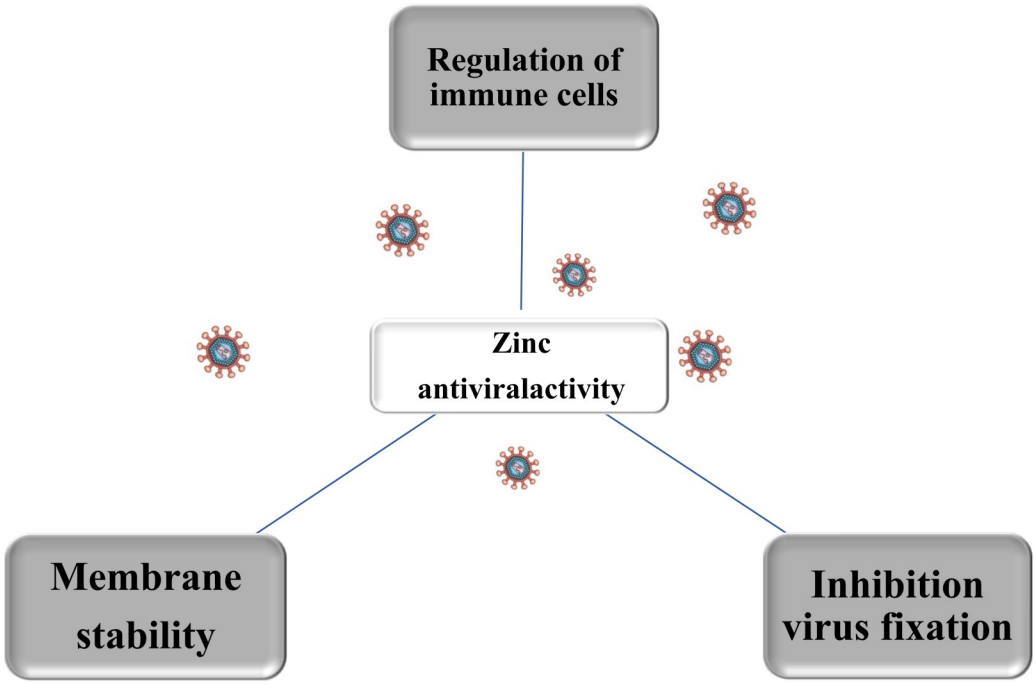

Figure 2 | General scheme summarizing the role of Zn in the immune system against viral infection

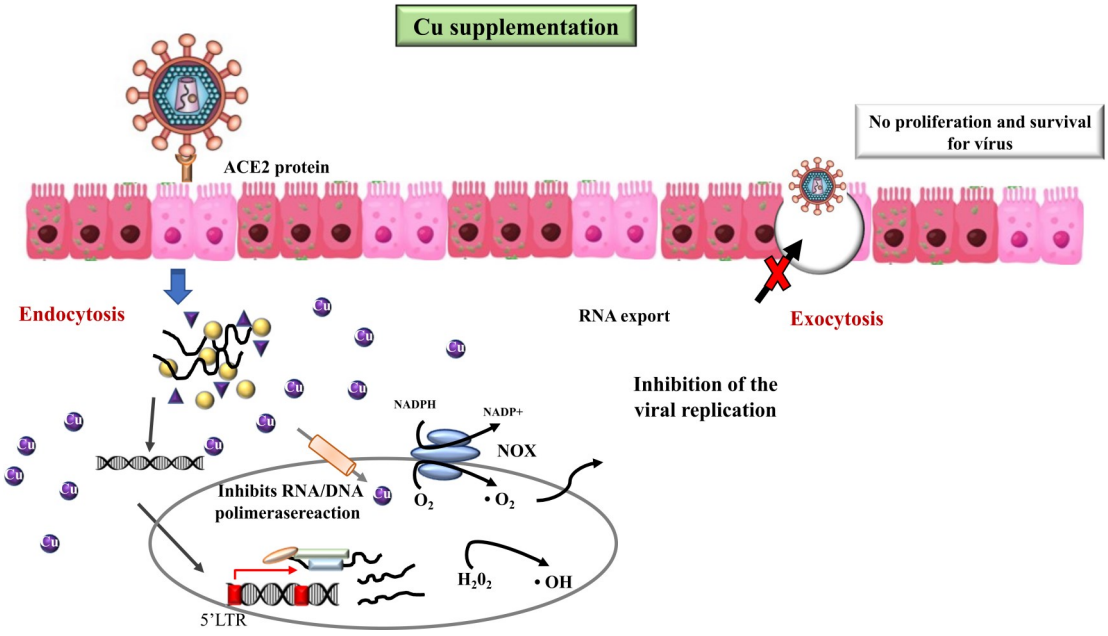

Figure 3 | General Scheme of antiviral activity of Cu. Copper can generate ROS that inhibit viral replication. Adapted from [8, 35].

effectiveness of Zn supplementation against COVID-19. They randomized some participants (n= 104), in a clinic, to receive different doses (ranging from 10 to 50 mg) of Zn daily. A control group (n=96) was used to examine the effect of Zn supplementation on COVID-19 symptoms. All participants were compared based on demographic data, renal functions, vitamin D levels, clinical comorbidities, blood counts, and symptoms after SARS-CoV-2 infection. As a result, COVID-19 symptoms were significantly lower among the treatment participants (1.9%) than control group participants (10.4%), suggesting that Zn supplementation may be vital against COVID-19, mitigating the severe symptoms of SARS-CoV-2 infection. However, it is important to highlight that the number of participants who showed some symptoms of COVID-19 was small and that more studies are needed to confirm this finding. In addition, there is evidence that warns of the risk of side effects involving high-dose Zn supplementation [33].

3.2 The role of copper in antiviral activity

Copper is another essential metal with important immunoregulatory properties [34, 35]. In the human immune system, Cu acts by assisting in the function of neutrophils and macrophages, as well as improving the activity of NKCs and stimulating T cells' hematopoiesis [8]. In this sense, Cu also plays an important role against viral infections, including SARS-CoV-2 [36]. An imbalance of Cu homeostasis can result in abnormal cell function, affecting adaptive and innate immunity, and increasing the susceptibility to SARS-CoV-2 infection [35]. The adverse effects of Cu insufficiency on immune function appear to be pronounced in older people and infants. Although it is still unclear how Cu deficiency alters the biological system, it is known that Cu normalizes impaired immune functions by modulating the blastogenic response of neutrophil activity to T cell mitogens. In fact, Cu induces viral death via reactive oxygen species (ROS), and in this sense, hydrogen peroxide and Cu play vital roles [1, 8, 35]. Normally, ROS, including superoxide anion, hydrogen peroxide, nitric oxide, and hydroperoxide radical are present in the human body. The enzyme SOD (superoxide dismutase) is responsible for converting superoxide to hydrogen peroxide. Physiologically, nitric oxide is an important vasodilator produced by NOS (nitric oxide synthase). In a healthy human, the imbalance of the ROS levels is associated with the pathogenesis of many infections.

In this sense, evidence suggests that Cu supplementation can help fight SARS-COV-2, especially in older people, where Cu deficiency is a strong possibility. Cu can restore the secretion and activity of IL-2. High levels of IL2 are crucial for T cell proliferation and NK cell cytotoxicity [1]. In addition, other evidence suggests that Cu has properties that can destroy the virus membranes (envelopes). Figure 3 shows a possible biochemical mechanism involving the Cu element in case of viral infections, including SARS-CoV-2.

Recently, Clark & Taylor-Robinson [37] suggested sodium copper chlorophyllin as a potential agent antiviral and immunomodulator in SARS-CoV-2 infection. In another study, after Cu supplementation, approximately 88% of COVID-19 patients recovered [38]. In an in vitro study, Rodriguez et al. [39] showed that Cu mitigated COVID-19 infection in Vero cells. However, further studies are needed to confirm these findings.

3.3 Iron homeostasis during viral infection

Once Fe is responsible for the synthesis/replication of genetic material, and cell proliferation, Fe is another element with vital functions for both the virus and the host [40]. In

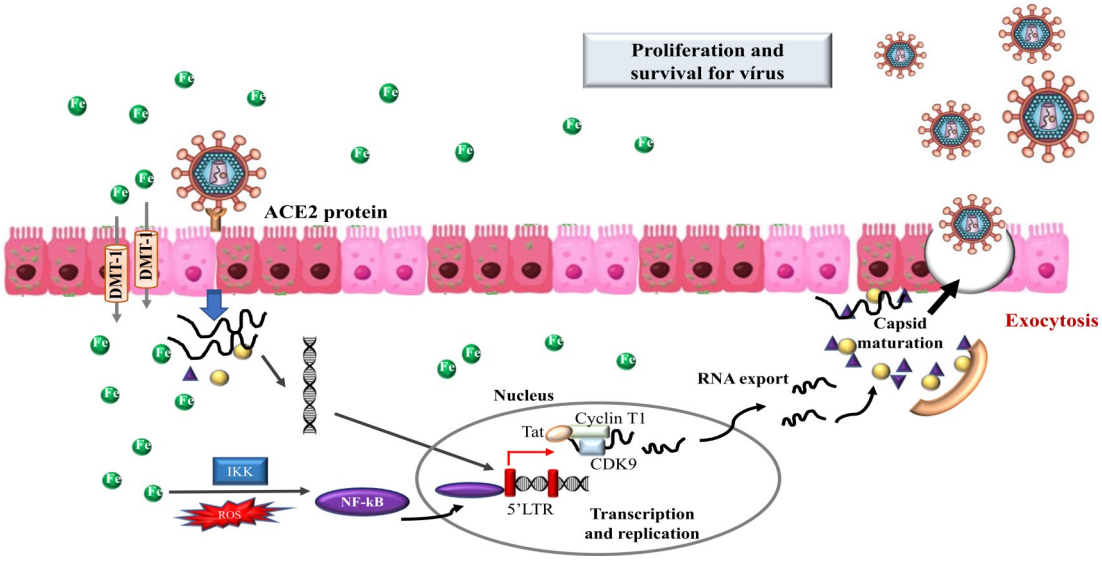

Figure 4 | General scheme illustrating the effect of Fe on viral infection The iron ion 519 is absorbed by the cell through the DMT1. Sufficient levels of intracellular iron 520 support the proliferation and survival of the virus. For further explanation, see the text. Adapted from [41, 43].

Table 1 | Suggested supplementation of trace elements to promote vital function, as suggested from [9].

Trace elements	Quantity/day for male (g)	Quantity/day for female (g)
Zn	11×10^{-3}	8×10^{-3}
Fe	8×10^{-3}	18×10^{-3}
Cu	900×10^{-6}	900×10^{-6}
Se	55×10^{-6}	55×10^{-6}
Mg	400×10^{-3}	310×10^{-3}

the immune system, Fe participates in the reaction of oxygen binding and electron transport, as well as in the production and mechanism of action of the cytokine [41]. In this scenario, the susceptibility to infection can be increased by the imbalance of Fe homeostasis [42]. When there is a deficiency of Fe in the body, the proliferation of lymphocytes strongly decreases, as well as there is a reduction of antigens [42]. On the other hand, excess Fe can improve virus activity, increasing its mutation rates [40]. Fe-containing enzymes are important for the virus to complete their replication process. Figure 4 shows a biochemical mechanism involving Fe in proliferation and survival of virus [1, 40].

Through DMT1 (divalent metallic iron transport protein 1), Fe is absorbed by the cell [43]. ATP and Fe-containing enzymes are required during this process. Nuclear factor (NF-κB) can be activated by Fe, activating IκB kinase (IKK) and generating ROS, which leads to the location of NF-κB in the nucleus [1, 41, 43]. The long terminal 5 repetition (LTR) which mediates the transcription of viral genes is linked by (NF)-κB. Efficient replication of the virus involves the transactivating protein Tat and its interaction partners CDK9 and cyclin T1 that are regulated for Fe [1]. Therefore, an adequate amount of Fe is required for the replication of SARS-CoV-2. Under conditions of low cellular Fe, Tat-mediated transcription is inhibited and CDK9 and cyclin T1 are dissociated [1].

In a recent study, Dahan et al. suggested ferritin, a cellular protein that stores Fe, as a marker to evaluate the severity in COVID-19 patients. For them, ferritin is a key molecule in the immune system, which orchestrates the cellular defense against inflammation during viral infection [44]. Lv et al. also suggested that Fe metabolism parameters may be risk factors and clinical biomarkers for COVID-19 prognosis [45]. They reported that patients with low serum Fe status likely suffered from severe conditions and multiple-organ injuries during COVID-19. However, more studies are required to confirm this evidence [45].

4. Role of others trace elements in antiviral activity

In addition to the trace elements above mentioned, other elements can present several functions against infection of SRAS-CoV-2 [9]. For instance, nickel (Ni) also is an essential element with immunoregulatory function. There is evidence that in the suggested quantity, Ni increases spleen T and B cell activities and decreases NKCs activities [2]. In addition, several studies have shown that selenium (Se) deficiency is associated with altered mitochondrial electron transport and, particularly, is associated with deficiency of vitamin E, decreasing the antibodies response [46–48]. Thus, Se supplementation also can increase the number of antibodies [46]. Regarding Mg (magnesium), a low level of this element results in decreased levels of antibodies (IgG and IgM) in the blood, as well as decreased levels of T cells and NK. Furthermore, Mg deficiency can activate latent viruses; therefore, Mg supplementation should be considered [49–51]. However, more data are needed to confirm the Mg-mediated immunity. Another element that has been shown to play an important role against viral infection is lithium (Li) [52]. Evidence suggests that Li inhibited both the fixation of the coronavirus and its replication in the Vero cell. However, it was observed that its efficiency depends on the dose [2]. For manganese (Mn), so far there is not much information about its role in immune activity against viral infection. Thus, further studies focusing on this element are strongly recommended [53]. In addition, there is evidence that exposure to toxic elements, such as, arsenic (As), cadmium (Cd), mercury (Hg), lead (Pb), among others may be a risk factor, increasing susceptibility to SARS-CoV-2 infection [2].

5 Nutritional importance of trace elements in available treatment for SARS-CoV-2 infection

Treatments for SARS-CoV-2 infection are now widely available [15, 17, 54]. For example, a variety of vaccines produced by different technologies have been developed and are being applied to prevent severe cases of COVID-19 [17, 54]. In the case of new variants, which may decrease the protective efficacy of the vaccines and lead to severe symptoms of the disease, some antiviral drugs, such as molnupiravir (Merck ®) and paxlovid (Pfizer®), have been approved by FDA (Food and Drug Administration) to be used in the treatment of SARS-CoV-2 infection [55,56]. Both drugs are to be effective and safe against the severity of COVID-19 [57]. Furthermore, monoclonal antibody therapies (mAb) are available for patients ages 12 years or older who are at high risk of becoming seriously ill [57, 58]. These Monoclonal antibodies are laboratory-made molecules that act as substitutive antibodies, responding more effectively to the virus. However, it is important to emphasize that for the success of these treatments against COVID-19 infection, micronutrients supplementation can

be fundamental, as these elements can help in the normalization of immune functions [2, 58]. In this sense, a balanced diet, including essential elements, gives a clear framework for a healthy life free from severe infections. Table 1 shows a recommended diet of essential trace elements to promote immune functions, as suggested by Dharmalingam et al. [9].

The levels of trace elements can be estimated from serum/whole blood samples, using powerful techniques capable of quantifying trace elements in levels ranging from ng L-1 to mg L-1. Atomic absorption spectrometry (AAS); inductively coupled plasma-optical emission spectrometry (ICP-OES) and inductively coupled plasma–mass spectrometry (ICP-MS) are some examples of these powerful techniques. For further information about the metallomics approach, see the review [1, 59].

6. Concluding remarks

There is no doubt that trace elements play a fundamental role in the immune system since they help to normalize important components of the innate and adaptative immunity against SARS-CoV-2 infection. Although some biochemical mechanisms have been suggested to understand metal homeostasis during viral infections, the relationship between many trace elements, including Zn, Cu, Fe, Se, Ni among others, is still complex. Thus, there is still a lot to be explored to better understand the systemic effect of SARS-CoV-2 infections in different organs.

Abbreviations

AAS: atomic absorption spectrometry
ACE2: angiotensin-converting enzyme 2
CDK9: cyclin-dependent kinase
COVID-19: coronavirus disease-19
DCs: dentritic cells
DMT1: divalent metallic iron transport protein 1
FDA: Food and Drug Administration
ICP-MS: inductively coupled plasma–mass spectrometry
ICP-OES: inductively coupled plasma-optical emission spectrometry
IFNγ: interferon-gamma
Ig: immunoglobulin
IKK: IκB kinase
LTR: long terminal 5 ´repetition
mAb: monoclonal antibody therapies
MHCII: major histocompatibility complex II
NF-κB: nuclear factor
NKCs: natural killer cells
ROS: reactive oxygen species
SARS-CoV-2: severe acute respiratory syndrome-coronavirus-2
SOD: superoxide dismutase

Author contribution

JRJ contributed conception and design of the study; JRJ and TAA organized the database. All authors contributed to manuscript revision, read, and approved the submitted version.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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References

[1] J.R. de Jesus, T. de Araújo Andrade, Metallomics. 12 (2020) 1912–1930.
[2] J.R. de Jesus, R.M. Galazzi, C.A. Lopes Júnior, M.A.Z. Arruda, Journal of Trace Elements in Medicine and Biology. 71 (2022).
[3] World Health Organization, WHO Coronavirus (COVID-19) Dashboard (URL: https://covid19.who.int/), 2022.
[4] N.L. Bert, A.T. Tan, K. Kunasegaran, C.Y.L. Tham, M. Hafezi, A. Chia, M.H.Y. Chng, M. Lin, N. Tan, M. Linster, W.N. Chia, M.I. Chen, L.F. Wang, E.E. Ooi, S. Kalimuddin, P.A. Tambyah, J.G. Low, Y.J. Tan, A. Bertoletti, Nature. 584 (2020) 457–462.
[5] S. Sivasubramanian, J. Shenoy, S.P. Kamath, V. Kulkarni, M. Srinivasan, S.B. Baliga, HIV and AIDS Review. 19 (2020) 56-60.
[6] Gasmi, T. Tippairote, P.K. Mujawdiya, M. Peana, A. Menzel, M. Dadar, A. Gasmi Benahmed, G. Bjørklund, Clinical Immunology. 220 (2020).
[7] A.L. Pasulka, K. Thamatrakoln, S.H. Kopf, Y. Guan, B. Poulos, A. Moradian, M.J. Sweredoski, S. Hess, M.B. Sullivan, K.D. Bidle, V.J. Orphan, Environmental Microbiol. 20 (2018) 671–692.
[8] T. Ishida, World Scientific News. 99 (2018)148-168.
[9] K. Dharmalingam, A. Birdi, S. Tomo, K. Sreenivasulu, J. Charan, D. Yadav, P. Purohit, P. Sharma, Indian Journal of Clinical Biochemistry. 36 (2021) 416-426.
[10] C.T. Chasapis, A.K. Georgiopoulou, S.P. Perlepes, G. Bjorklund, M. Peana, Journal of Inorganic Biochemistry. 219 (2021).
[11] J.R. de Jesus, M.A.Z. Arruda, Journal of Integrated OMICS 11 (2021) 16–28.
[12] X. Ou, Y. Liu, X. Lei, P. Li, D. Mi, L. Ren, L. Guo, R. Guo, T. Chen, J. Hu, Z. Xiang, Z. Um, X. Chen, J. Chen, K. Hu, Q. Jin, J. Wang, Z. Qian, Nature Communications. 11 (2020).
[13] E. Andreano, R. Rappuoli, Nature Medicine. 27 (2021) 759–761.
[14] M. Ezhilan, I. Suresh, N. Nesakumar, Measurement.

168 (2021).
[15] Y. Slabakova, D. Gerenska, N. Ivanov, T. Velikova, Exploration of Immunology. 2 (2022) 9–24.
[16] Y. Peng *et al.*, Nature Immunology. 21 (2020) 1336-1345.
[17] S. Hintistan, H. Demirağ, Exploration of Immunology. 1 (2021) 341-355. DOI: 10.37349/ei.2021.00023.
[18] J.A. de Souza Monnerat, P.R. de Souza, L.M. da Fonseca Cardoso, J.D Mattos, G. de Souza Rocha, R.F. Medeiros, European Journal of Nutrition. 60 (2021) 559 –579.
[19] A. Pormohammad, N.K. Monych, R.J. Turner, International Journal of Molecular Medicine. 47 (2021) 326–334.
[20] M. Wessling-Resnick, Annual Review of Nutrition. 38 (2018) 431–458.
[21] J.R. de Jesus, A.Z.B. Aragão, M.A.Z. Arruda, C.H.I. Ramos, Frontiers in Chemistry. 7 (2019) 1–10.
[22] J.R. de Jesus, in: Springer Theses. Springer, Cham (Ed.), Proteomic and Ionomic Study for Identification of Biomarkers in Biological Fluid Samples of Patients with Psychiatric Disorders and Healthy Individuals, 2019, pp. 39-58.
[23] J.R. de Jesus, M.A.Z. Arruda, Metallomics. 12 (2020) 1878–1896.
[24] G.D.S. Pessôa, J.R. de Jesus, T.S. Balbuena, M.A.S. Arruda, Rapid Communications in Mass Spectrometry. 34 (2020).
[25] P. Sharma, P.K. Reddy, B. Kumar, Biological Trace Element Research. 199 (2021) 3213-21.
[26] H. Gao, W. Dai, L. Zhao, J. Min, F. Wang,. Journal of Immunology Research. (2018).
[27] M. Maywald, I. Wessels, L. Rink, International Journal of Molecular Sciences. 18 (2017).
[28] C. Andreini, L. Banci, I. Bertini, A. Rosato, Journal of Proteome Research. 5 (2006) 3173–3178.
[29] S.A. Read, S. Obeid, C. Ahlenstiel, G. Ahlenstiel, Advances in Nutrition. 10 (2019) 696–710.
[30] S.A. Read, K.S. O'Connor, V. Suppiah, C.L.E. Ahlenstiel, S. Obeid, K.M. Cook, A. Cunningham, M.W. Douglas, P.J. Hogg, D. Booth, J. George, G. Ahlenstiel, Nature Communications. 8 (2017).
[31] A. Kumar, Y. Kubota, M. Chernov, H. Kasuya, Medical Hypotheses. 144 (2020).
[32] A.M. Gordon, P.C. Hardigan, Frontiers in Medicine. 8 (2021).
[33] S. Thomas, D. Patel, B. Bittel, K. Wolski, Q. Wang, A. Kumar, Z.J. Il'Giovine, R. Mehra, C. McWilliams, S.E. Nissen, M.Y. Desai, JAMA Network Open. 4 (2021).
[34] V. Hodgkinson, M.J. Petris MJ, J Biol Chem. 287 (2012) 13549-13555.
[35] S. Raha, R. Mallick, S. Basak, A.K. Duttaroy, Med Hypotheses. 142 (2020) 109814.
[36] C. Hewawaduge, A. Senevirathne, V. Jawalagatti, J.W. Kim, J.H. Lee, Environmental Research. 196 (2021).
[37] N.F. Clark, A.W. Taylor-Robinson, Frontiers in Medicine. 8 (2021).
[38] S. Patil, V.R. Us, G. Arakeri, S. Patil, P.A. Brennan, Medical Hypotheses. 146 (2021).
[39] K. Rodriguez, F. Saunier, J. Rigaill, E. Audoux, E. Botelho-Nevers, A. Prier, Y. Dickerscheit, S. Pillet, B. Pozzetto, T. Bourlet, P.O. Verhoeven, Journal of Trace Elements in Medicine and Biology. 68 (2021).
[40] R. Lawaczeck, ACS Chemical Neuroscience. 11 (2020) 3996–4000.
[41] J.E. Cassat, E.P. Skaar, Cell Host and Microbe. 13 (2013) 509–519.
[42] T. Ganz, E. Nemeth, Nature Reviews Immunology. 15 (2015) 500–510.
[43] W. Liu, S. Zhang, S. Nekhai, S. Liu, Current Clinical Microbiology Reports. 7 (2020) 13–19.
[44] S. Dahan, G. Segal, I. Katz, T. Hellou, M. Tietel, G. Bryk, H. Amital, Y. Shoenfeld, A. Dagan, The Israel Medical Association Journal. 22 (2020) 494-500.
[45] Y. Lv, L. Chen, X. Liang, X. Liu, M. Gao, Q. Wang, Q. Wei, L. Liu, Clinical Nutrition. 40 (2021) 3462–3469.
[46] M. Kieliszek, B. Lipinski, Medical Hypotheses. 143 (2020).
[47] S. Khatiwada, A. Subedi, Current Nutrition Reports. 10 (2021) 125–136.
[48] H.Y. Zhang, A.R. Zhang, Q.B. Lu, X.A. Zhang, BMC Infectious Diseases. 21 (2021) 452.
[49] T.C. Wallace, Journal of The American College of Nutrition. 39 (2020) 685-693.
[50] C.F. Tang, H. Ding, R.Q. Jiao, X.X. Wu, L.D. Kong, European Journal of Pharmacology. 886 (2020).
[51] K. Minton, Nature Reviews Immunology. 13 (2013) 548-549.
[52] G. Gómez-Bernal, Medical Hypotheses. 142 (2020).
[53] N.C.N. Perera, G.I. Godahewa, S. Lee, M.J. Kim, J.Y. Hwang, M.G. Kwon, S.D. Hwang, J. Lee, Fish and Shellfish Immunology. 68 (2017) 435–442.
[54] G. Bauer, Exploration of Immunology. 2 (2022) 133–156.
[55] M.C. Andrade, L.G. Gomes, V.K. Mendes, H.O. Rosa, Exploration of Immunology. 1 (2021) 432–439.
[56] Food and Drug Administration (FDA), U.S. Food & Drug Administration, (URL: https://www.fda.gov/), 2021.
[57] World Health Organization (WHO), Coronavirus (COVID-19) vaccines, (URL: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines), 2019.
[58] M. Marovich, J.R. Mascola, M.S. Cohen, JAMA - Journal of the American Medical Association. 324 (2020) 131–132. DOI: 10.1001/jama.2020.10245.
[59] M.A.Z. Arruda, J.R. de Jesus, C.A. Blindauer, A.J. Stewart, Journal of Proteomics. 263 (2022) 104615.