CM & NH Cellular Medicine & Natural Health JOURNAL

Journal of Cellular Medicine and Natural Health
15. January 2021 **A. Niedzwiecki**

Scientific basis of micronutrient applications as an effective, safe and affordable global public health strategy to help to control the coronavirus pandemic

Aleksandra Niedzwiecki, Ph.D. and Matthias Rath, M.D.
Dr. Rath Research Institute, San Jose, CA

Global impact of COVID-19 pandemic

More than 70 million cases of COVID-19 had been confirmed worldwide by mid-December 2020, and the disease had claimed more than 1.6 million lives. According to a joint statement issued on 13 October 2020 by the World Health Organization (WHO), the Food and Agricultural Organization (FAO), and other UN-Organizations, "the COVID-19 pandemic has led to a dramatic loss of human life worldwide and presents an unprecedented challenge to public health, food systems and the world of work. The economic and social disruption caused by the pandemic is devastating: tens of millions of people are at risk of falling into extreme poverty, while the number of undernourished people, currently estimated at nearly 690 million, could increase to over 800 million by end of the year."[1] In addition, the wide socio-economic impact of this pandemic has threatened the sustainability of all sectors of society all over the globe, impacting mental health, the food supply, medical services, education, and energy, among many other aspects.[2]

This statement highlights the important, but often overlooked, fact that healthy nutrition, including an optimum supply of a full spectrum of micronutrients, is the foundation of the effective functioning of our immune system, and provides powerful protection against infections, including COVID-19.

Correspondence to
Dr. Aleksandra Niedzwiecki,
Dr. Rath Research Institute,
5941 Optical Court,
San Jose, Ca 95138,
USA.

Email: author@jcmnh.org

Cellular mechanisms of SARS-CoV-2 infection

The virus identified as the cause of the COVID-19 pandemic is a type of coronavirus designated as SARS-CoV-2 (see Figure 1). In the worst-affected people, the virus can cause a serious respiratory illness known as severe acute respiratory syndrome (SARS), which often has fatal consequences.

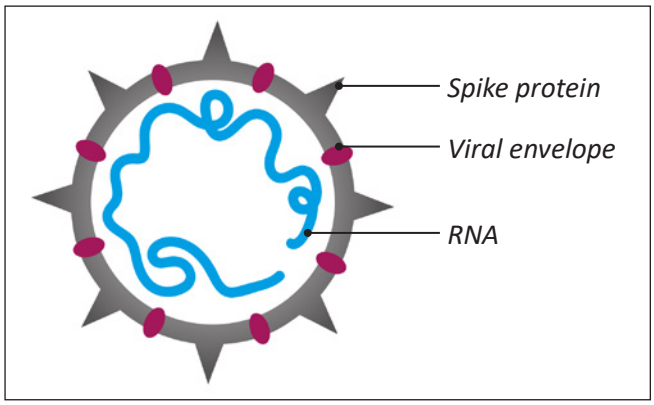

Figure 1: *Coronavirus structure*

The entry of the SARS-CoV-2 virus into the cell involves the binding of a viral spike (S) glycoprotein to its cellular receptor, ACE2 (angiotensin-converting enzyme 2) (see Figure 2).[3] ACE2 is present on many cell types throughout the human body, with strong expression in alveolar cells of the lung, and in the nasal epithelial cells, as well as cells of the heart, blood vessels and other organs.[4,5] Recently, another cellular receptor for the SARS-CoV-2 virus, known as Neuropilin-1 (NRP-1), has been identified.[6] This receptor is abundantly expressed in endothelial and epithelial cells in the respiratory tract, and is involved in the SARS-CoV-2 infectivity process.[7]

The viral binding to cellular receptors occurs through a specific sequence on the SARS-CoV-2 spike protein known as the receptor-binding domain (RBD), which determines viral infectivity and forms the potential target for therapeutic intervention and vaccination (see Figure 3). The RBD, located on a subunit of the viral spike termed "S1", recognizes the ACE2 receptor based on a specific complementary structure (the lock-and-key principle).[8] The RBD stands up and keeps the S1 protein domain in an "open" state to enable attachment of the virus to the human ACE2 receptor on the cell surface. This conformational change of the viral RBD results in fusion with the host cell membrane through another subunit of the spike protein, termed "S2". The S2 subunit also helps to keep the virus in a

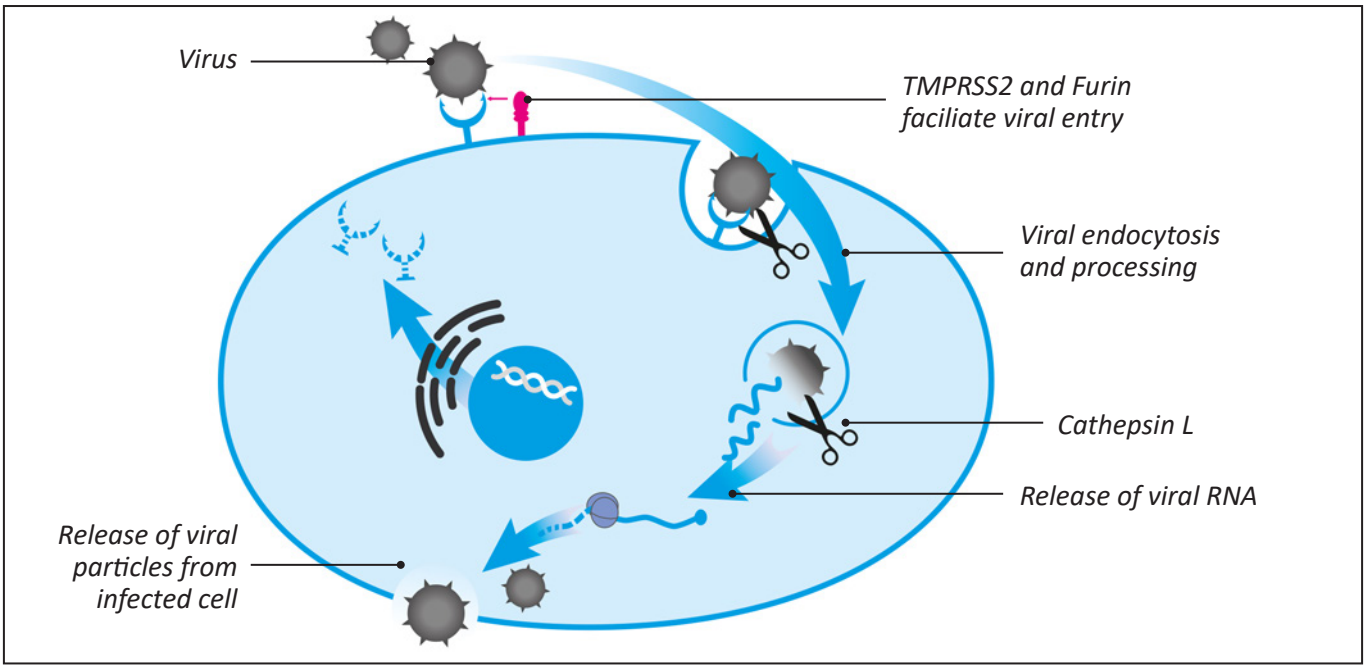

Figure 2: *Key stages of SARS-CoV-2 infection of human cells*

certain conformation that is essential for the fusion of the virus with structures inside the cell, a precondition for its intracellular replication.[9,10]

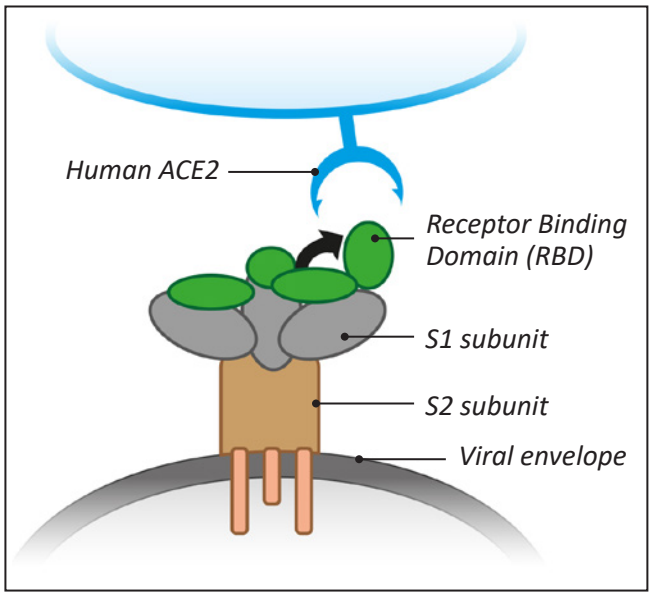

Figure 3: *Features of SARS-CoV-2 binding to ACE2 cellular receptors*

As presented in Figure 2, both the binding and viral processing inside the cells involve several protein-digesting enzymes (proteases), such as the type II transmembrane serine protease (TMPRSS2), furin, cathepsin L, and others.[11,12]

Once inside the cell, SARS-CoV-2 uses its RNA-dependent RNA polymerase (RdRp) to "hijack" the cellular machinery and translate its genetic material (RNA), a precondition for the multiplication (replication) of the viral genetic material (genome) within the cells.[13]

Current approaches to COVID-19 pandemic

Despite so much advancement in medicine, science, and technology, we still rely on basic social distancing and isolation methods to limit viral spread. Medical intervention and treatments have brought mixed results, with only some improvements in some countries.

The most recent strategy to end the COVID-19 pandemic relies on vaccines developed using experimental RNA- and DNA-based technology. These vaccines are different from traditional vaccines, which contain weakened or killed viruses. Instead, they contain only a genetic blueprint (RNA or DNA) of the spike protein of SARSCoV-2. The DNA-based vaccines use viral DNA packed into another type of virus – generally adenoviruses – with the goal of introducing the viral gene fragment into the human body to initiate the production of viral protein and to trigger an immune response. In RNA-based vaccines the messenger RNA (mRNA) encoding the viral spike protein is packaged in lipid nanoparticles, in order to enter the cell, where it is translated by host ribosomes into the viral protein. This protein is further processed inside the cell to ultimately trigger T-cell immunity and the production of antibodies directed against the virus.

Since the introduction of mRNA vaccines there have been reports of mostly mild, transient adverse side effects, including fever, headache, etc. However, some patients experienced a severe allergic reaction immediately after the injection. Facial nerve paralysis and inflammation of the spine have also been reported.[14] At the same time, the long-term immune efficacy and side effects of such vaccination are not known. All these facts add to public skepticism and resistance to accepting vaccination.

The need for safe and effective strategies to control the coronavirus and end the pandemic

Impaired immunity is a major risk factor for infection with and death from coronavirus. Based on multiple reports, the elderly and individuals with pre-existing health conditions such as hypertension, diabetes, cancer and obesity are more severely affected by COVID-19 and suffer more complications.[15-17] All these risk factors are associated with micronutrient deficiencies caused by inadequate diet, genetic predispositions, the intake of various pharmaceutical drugs, smoking, environmen-

tal pollution and other external factors. Collectively, they culminate in metabolic impairments, compromising the health status of affected individuals, and, in particular, weakening the immune system.

At the beginning of the COVID-19 pandemic, the correlation between low vitamin D levels, zinc deficiency and a risk of infections was established.[18] Zinc undernutrition or deficiency was shown to impair important immune functions such as the elimination (phagocytosis) of pathogens, the activity of the so-called "natural killer" (NK) cells, and others.[19] By contrast, its combination with vitamin C (ascorbic acid) showed immune-enhancing effects.[20]

Vitamin D also affects the cellular immune system by suppressing the overproduction of biological signaling molecules known as "cytokines", triggered by viral infections, including COVID-19. It can also decrease tissue damage induced by an explosion of cytokines in the context of inflammation and infection, a process known as a "cytokine storm".[21]

Significantly, a combination of vitamin C with amino acids, green tea extract and other micronutrients showed benefits in decreasing the expression of cellular ACE2 receptors – the entry ports of the coronavirus – in lung cells and vascular endothelial cells, two of the cell systems most affected by coronavirus infections. This effect was particularly pronounced in the context of inflammatory processes.[22,23]

It is well established that vitamin C has strong antiviral effects, and that it alleviates an inflammation process known to be aggravated in coronavirus infections resulting in the above-mentioned life-threatening cytokine storm.[24,25] Vitamin C interacts synergistically with vitamin D and zinc in protecting the integrity of barrier cell systems, including those of the skin, vascular walls, lungs and intestines, which constitute the first line of defense of the human body against pathogen entry. This micronutrient combination also has a positive effect on the cells of the immune system.[26]

Among other nutrients, B vitamins are needed for an optimum functioning of the immune system to fight off viral infections and to support antibody production.[27] It has been shown that vitamin B6 deficiency weakens both humoral and cell-mediated immunity, impairing the formation of new lymphocytes, their maturation (differentiation), and antibody production.[28,29] Elderly people, in particular, are prone to vitamin B12 and folate (vitamin B9) deficiency, which also negatively affects their immunity.[30,31]

Various plant extracts and active plant components have meanwhile shown beneficial effects on immune-system function.[32] Among these substances, fucoidan, for example, a sulfur-rich, complex sugar molecule from brown algae, has a positive influence on immunity, especially in the defense against viral infections. It optimizes the function of various cell systems involved in immune defense, including the body's "police cells" (macrophages) and NK cells. This plant compound also positively influences the signaling substances discussed above, the cytokines.[33,34]

Fucoidan is not, however, uniquely beneficial. Polyphenol- and vitamin-C-rich fruit and vegetables in general – tart cherries, lychees, ginger root and others – have similarly shown strong anti-inflammatory and antioxidant effects in numerous studies.[35]

Advantages of micronutrients against coronaviruses

Since the onset of the COVID-19 pandemic, there has been an increasing interest in applying safe and effective natural approaches that would support immune-system function and have direct antiviral effects on the coronavirus.

Micronutrients, especially when applied in specific combinations, can both protect against infectious pathogens directly and improve immune-system functions, thus increasing efficacy in the elimination of viruses and other pathogens. Since their key target is to strengthen body cells in their defense against viral attacks in general, micronutrients are no less effective against mutated coronaviruses. What is more, micronutrients have a large margin of safety, and support multiple cellular functions in the body.

Since the onset of COVID-19, various studies have searched for individual compounds that could prevent the first step of cellular infection – the binding of the viral spike protein to its natural cellular receptor on the cell surface. Many of these studies applied molecular modelling methods by attempting to match the structure of the viral spike protein (the "key") to the structure of the ACE2 cell receptor (the "lock").[17] Furthermore, theoretical evaluations were conducted based on the known efficacy of individual compounds in other types of infections.[36] A limited number involved experimental tests evaluating which micronutrients interfere with the binding of the COVID spike protein to its specific receptor on the cell surface.[37,38]

Clinical applications of micronutrients against coronaviruses

Many studies recommend the consumption of vitamin C to control lower-respiratory-tract infections. Vitamin C supplementation represents one of the most compelling therapeutic interventions against coronaviruses.[39-42]

A clinical trial in the USA reported that intravenous (IV) doses of vitamin C decreased sepsis-induced acute respiratory distress syndrome (ARDS) death rates. ARDS is a lung injury that allows fluid to leak into the lungs, impairing breathing and decreasing oxygen supply to the body. The development of ARDS in patients with COVID-19 is a critical complication that often has a deadly outcome.[43]

A recently published randomized, placebo-controlled clinical intervention study documented that high-dose vitamin C can cut the death rate in patients with advanced stages of COVID-19 almost in half.[44] This multi-center clinical study, coordinated by the University Hospital of Wuhan, the site of the outbreak of the current pandemic, included COVID-19 patients confined to intensive care units, owing to the severity of the life-threatening stage of their infections. Severely ill patients were randomly assigned to high-dose intravenous vitamin C or a placebo.

Patients receiving 24 grams of vitamin C daily had a significantly better oxygenation of their blood, indicating that oxygen could better move to the red blood cells across the lung tissue. That in turn, meant that the lung tissue was less inflamed, a fact that was confirmed in this study by much lower levels of inflammatory markers (interleukin-6) in the vitamin C patients.

Particularly significant for these severely ill patients, however, was their much improved chance of surviving COVID-19 when they received high dose vitamin C. When compared with the patients in the study group that received only a placebo, those patients receiving vitamin C were twice as likely to survive. In other words, every second life – even at this advanced stage of coronavirus infection – could be saved. These data stand in stark contrast with study results from conventional pharmaceutical drugs used in advanced COVID-19 patients. Remdesivir, for example, was officially approved for use to treat COVID-19 patients but failed to live up to its promise. A November 2020 statement by WHO concluded that there is no evidence that remdesivir improves survival and other outcomes in COVID-19 patients.[45]

Since the emergence of the COVID-19 pandemic, several clinical trials with vitamins C, D, A and B3, as well as zinc, have been initiated in different countries, as listed in WHO records.[46]

The scientific publication reporting on the clinical efficacy of vitamin C in COVID-19 patients, however, did not specifically address the underlying cellular mechanisms for this therapeutic effect. In general, vitamin C is known for its high benefits for the immune system as well as its strong antioxidant properties. It is a cofactor for various biocatalysts (enzymes) involved in the regulation processes of cell metabolism as well as genetic molecules (DNA, RNA). Vitamin C is also an essential factor in collagen synthesis and integrity, thereby optimizing natural biological barriers against infectious agents.

Our studies show that vitamin C specifically inhibits several key mechanisms of coronavirus infections. It is effective in inhibiting the production (expression) of ACE2 receptors on the surface of human body cells.[22] Moreover, we have shown that, by combining vitamin C with certain other micronutrients, these effects can be significantly enhanced.[23]

Designing micronutrient combinations against SARS-CoV-2 to gain natural control of the coronavirus pandemic

By combining specific micronutrients that have different cellular functions we can achieve enhanced antiviral efficacy. Such nutrient combinations can simultaneously control a variety of cellular processes associated with infection, and are effective at lower doses than when used individually. This principle of "nutrient synergy"– the mutually enhancing effects of the individual micronutrient components – has formed the backbone of our scientific research for more than two decades, with clinical evidence of its efficacy in other viral and bacterial infections.[47-49]

In a recent study we evaluated the effects of a composition of plant extracts and active plant components, including curcumin, resveratrol, green tea extract, cruciferous plant extracts and quercetin, on key cellular mechanisms involved in SARS-CoV-2 infectivity (Figure 4).

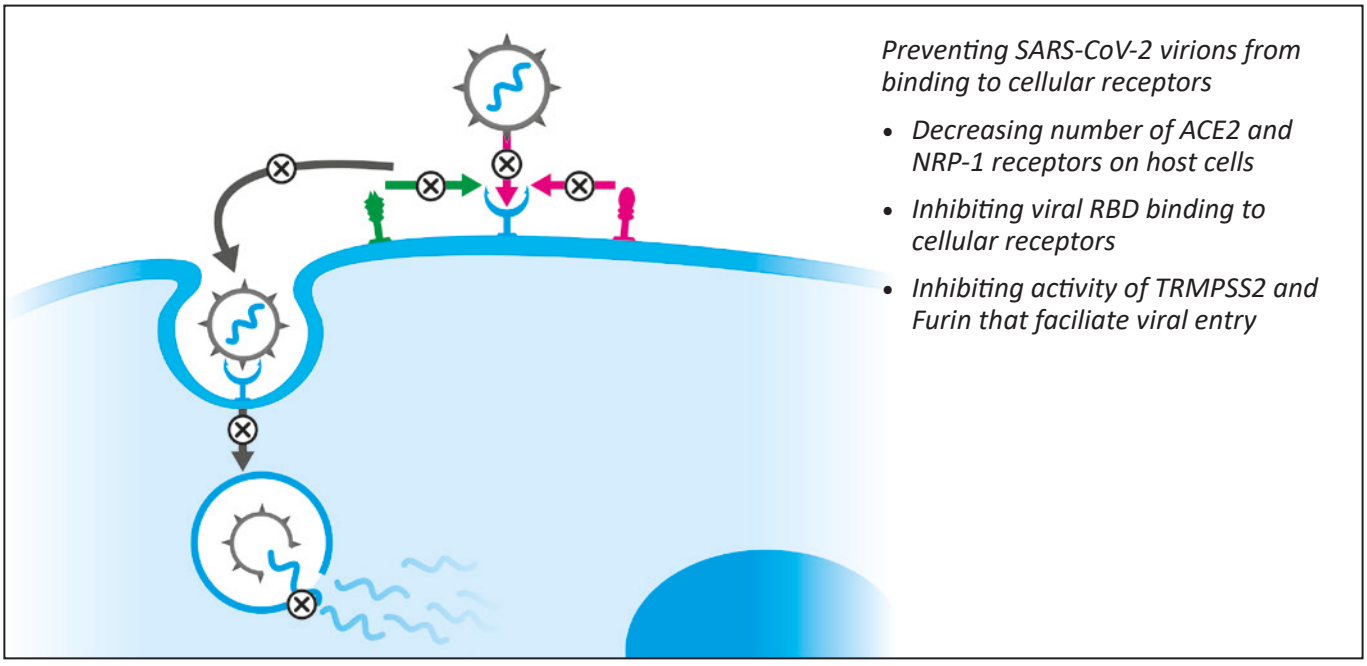

Figure 4: *Micronutrients affect key mechanisms involved in SARS-CoV-2 infection of human cells*

A. Micronutrients' role in decreasing ACE2 and NRP-1 receptors

Decreasing ACE2 and NRP-1 receptors (SARS-CoV-2 "docking stations") presents an important therapeutic goal for decreasing viral infectivity. Our previous studies demonstrated that a specific combination of micronutrients can inhibit the expression of ACE2 receptors on human alveolar epithelial cells by 90%.[22,23] In a more recent study, we demonstrated that these micronutrients can also decrease the expression of a second type of viral cell surface receptor, NRP-1.[38]

In addition, we observed that vitamin C used at high (up to 10 mM) concentrations can significantly decrease ACE2 production at the protein and RNA levels. Furthermore, vitamin C can enhance the efficacy of other natural compounds (green tea extracts/EGCG, baicalein, curcumin and others) in decreasing the production (expression) of cellular ACE2 receptors (Ivanov et al, submitted for publication).

As for the inhibitory effect of the essential trace element zinc on the SARS-CoV-2/ACE2 interaction,[50] our studies showed that the efficacy of zinc in decreasing ACE2 expression can be significantly enhanced by its combination with vitamin C. For example, zinc aspartate applied at a concentration of 33 µM results in ACE2 inhibition by 22%. When combined with vitamin C in the form of ascorbate, this inhibitory effect more than doubled and results in a 62% ACE2 inhibition.[23]

In September 2020, a clinical randomized study with 4,500 participants was initiated at the Mayo Clinic to test the role of zinc versus multivitamin supplementation in supporting immune health in the context of the COVID-19 pandemic. The results are expected in September 2021.[51]

B. Micronutrients inhibit the RBD binding to cellular ACE2 receptors

As stated above, the interaction of the receptor binding domain (RBD), a component of the viral surface protein (spike protein), with its binding site on the surface of somatic cells (ACE2 receptors), provides the framework for the development of "blockers" (inhibitors) that can potentially prevent viral entry, thus preventing infection.

Our studies also show that various natural components, such as vitamins and fatty acids, can directly interfere with viral RBD binding to ACE2 receptors on human cells.38 We were further able to demonstrate that a specific combination of plant-derived compounds can inhibit SARS-CoV-2 pseudo virus from binding to cells expressing ACE2 receptors, when applied both before and after this virus enters the cells.[38] These data confirm the high efficacy of natural compounds in the prevention of this key step in the viral infectivity of new cells, as well as their efficacy in already-infected cells.

C. Micronutrients' role in inhibiting TMPRSS2, furin and cathepsin L activities

Various biocatalysts (enzymes) are required both for the entry of the virus into the cells and for its replication. Cathepsin L, a protein-splitting enzyme (endosomal protease), type II transmembrane serinprotease (TMPRSS2), and the enzyme furin enable the coronavirus (SARS-CoV-2) to enter the cells and replicate.[52]

Therefore, inhibition of the activity of these enzymes is essential to effectively reduce the risk of infection. In addition to the role in SARS-CoV-2 (COVID-19) infection, binding between the spike protein, furin and the ACE2 receptor is also a danger in the context of the occurrence of adverse cardiovascular events.[53]

Our studies showed that natural compounds can inhibit the activity of these enzymes when tested directly and in the cells.[38]

D. Micronutrients' role in inhibiting RdRp polymerase

In vitro experiments demonstrate that zinc possesses antiviral activity through inhibition of SARS CoV-2 RNA polymerase. Specifically, zinc (Zn2+) cations – especially in combination with zinc ionophore pyrithione – were shown to inhibit SARS-coronavirus RNA polymerase (RNA-dependent RNA polymerase, RdRp) activity by decreasing its replication.[54]

Our studies showed that the combination of specific micronutrients was able to inhibit RdRp activity by 100%. In other words, it achieved a complete blockade of this enzyme crucial for virus replication.[38]

CONCLUSIONS

In summary, these findings confirm the significant potential of micronutrients, especially when applied in a specific combination, as a new therapeutic strategy in controlling the COVID-19 pandemic. This direction shows superiority to other currently applied measures by simultaneously affecting key infection mechanisms used by SARS-CoV-2 and other coronaviruses: the expression of cellular ACE2 receptors, viral binding and entry, as well as its replication potential inside the cells. The general safety of natural compounds makes this approach a safe and effective alternative that can be used by the general public.

Health practitioners, in particular, should consider micronutrient deficiencies as a key factor when evaluating patients with existing COVID-19 conditions. A targeted micronutrient supplementation should be implemented in strategies to control the COVID-19 pandemic.

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