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Vitamin deficiency as risk factor for SARS-CoV-2 infection: correlation with susceptibility and prognosis

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Abstract. – OBJECTIVE: In 2019, an infection provoked by SARS-CoV-2 virus arose in Wuhan, China. Currently, there is still no definite and efficacious therapy for SARS-CoV-2 infection. Moreover, our understanding of the physiopathology of the infection, and risk elements for severity and mortality, is incomplete.

PATIENTS AND METHODS: One largely neglected element that could affect prognosis of SARS-CoV-2 infection is the vitamin status of population. The purpose of this review is to evaluate whether a vitamin insufficiency could provoke an augmented risk of SARS-CoV-2 infection or the appearance of major complications. In particular, we evaluated the presence of studies related to the state and effects of vitamin D, C, B, and A in subjects with SARS-CoV-2 disease.

RESULTS: Although, actually, the interest in a possible use for vitamin supplementation in SARS-CoV-2 patients is essentially based on indirect data, we tried to examine the evidence about a favorable effect of vitamin supplementation in the therapy of the infection and its complications.

CONCLUSIONS: Supplements with vitamin A, B, C, D, and E could represent an inexpensive and sufficiently safe approach, and a useful therapeutic complement. However, solid clinical research data are expected to support such claim.

Key Words:
SARS-CoV-2 infection, COVID 19, Vitamin D, Vitamin C, Vitamin B, Vitamin A, Supplementation, Prognosis, Susceptibility, Clinical trials.

Introduction

The ongoing epidemic outbreak of 2019 new betacoronavirus (COVID-19), identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first described in Wuhan, China in 2019, and endures to threaten global health and to hinder the global economy. Regrettably, presently, there is still no definite and efficacious therapy for SARS-CoV-2 infection[1]. Nevertheless, our understanding of the physio-pathology and clinical manifestation of the infection, and risk elements for severity and mortality, although incomplete, is quickly expanding. Several data demonstrate that elderly subjects and those with preexisting medical issues, including chronic respiratory disease, diabetes, cardiovascular diseases, and cancer are more prone to manifest severe illness with SARS-CoV-2 infection[2].

In spite of problems in comparing findings across countries, mortality from SARS-CoV-2 infection is evidently greater in some countries than in others. Several elements could have a responsibility in this difference, including variances in percentage of old people in a country, availability and value of healthcare, global health, and socio-economic condition[3].

One largely neglected element that could affect prognosis of SARS-CoV-2 infection is the vitamin status of population.

The purpose of this review is to evaluate whether a vitamin insufficiency could provoke an increased risk of SARS-CoV-2 infection or the appearance of major complications and whether a vitamin supplementation could represent a useful therapeutic complement in infected patients.

In particular, we evaluated the presence of studies related to the state and effects of vitamin

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D, C, B, and A in subjects with SARS-CoV-2 disease. Finally, we also attempted to examine some of the ongoing clinical trials assessing the effects of vitamin supplementation, either alone or in association with other treatments in the therapy of the infection and its complications.

Vitamin D and COVID-19

Vitamin D is a fat-soluble vitamin, introduced into the organism in two manners: *via* sunlight and *via* food or supplementation. In the skin, vitamin D precursor 7-dehydrocholesterol is made active via ultraviolet B (UVB) rays converting it into vitamin D3. Vitamins D2 and D3 can be attained directly from food, such as milks, cereals, fatty fish or through supplementation. Vitamin D2 and D3 are then transformed in the liver into 25-hydroxyvitamin D [25(OH)D3], which is present in the serum attached to vitamin D binding proteins (DBPs). 25(OH)D3 in the serum is the more appropriate indicator for evaluating vitamin D deficiency. This type of vitamin D is converted in an activated form in kidneys by 25-hydroxyvitamin D-1-alpha-hydroxylase (1-OHase, induced by PTH), and transformed in 1,25-dihydroxyvitamin D [1,25(OH)2D, Calcitriol][4,5].

Several direct and indirect evidence seem to confirm the existence of a close correlation between vitamin D and SARS-CoV-2. For instance, different recent preprint-posted reports[6] stated a relationship between low vitamin D and SARS-CoV-2 infection occurrence.

A retrospective observational research was executed on SARS-CoV-2-infected subjects hospitalized from March 1, 2020 to April 7, 2020 to evaluate the degree of vitamin D deficiency in Belgium and its correspondence to severity of SARS-CoV-2 infection. Authors evaluated 25(OH)D concentrations in 186 COVID-19 subjects and 2717 age/season-matched health controls. SARS-CoV-2 infected subjects presented lower median 25(OH)D and greater vitamin D deficiency rates. Unexpectedly, this variance was limited to male SARS-CoV-2 subjects who presented a greater deficiency rates than male controls. Then, Vitamin D deficiency could be a risk factor for COVID-19[6].

Furthermore, reduced Vitamin D levels seem to be also correlated with a more severe outcome. In a report, twenty SARS-CV-2 infected patients with known concentrations of serum 25OHD levels were studied; 13 subjects (65.0%) needed Intensive Care Unit (ICU) admission. Among ICU patients, 11 (84.6%) presented vitamin D insufficiency *vs.* 4 (57.1%) of the other patients. Surprisingly, 100% of ICU subjects aged less than 75 years old presented vitamin D insufficiency. Among these, 64.6% had critically low 25OHD concentrations [7].

Nevertheless, a different report performed at the University of Glasgow examined the vitamin D status of SARS-CoV-2 patients employing UK biobank data and found no correlation between the status of the vitamin D and SARS-CoV-2 infection proneness, after correcting for confounding elements[8]. Coherent with this, a prospective cohort study found no positive relationship between low serum vitamin D levels and SARS-CoV-2 infection[9]. In any case, several other investigations that have evaluated the correlation between vitamin D deficiency and SARS-CoV-2 infection are underpowered and have not yet been peer-reviewed.

Furthermore, some authors reported that findings retrieved to date revealed that there is not sufficient direct confirmation for a causal correlation between vitamin D status and infection, yet[10], although the same authors point out the relevance of a normal vitamin D status and suggest supplementation to subjects who are quarantining[11]. Finally, a meta-analysis[12] of 15 randomized controlled studies examining the usefulness of vitamin D supplementation in diminishing the risk of developing respiratory infections among healthy subjects found no relevant risk decrease.

Nevertheless, numerous indirect elements make it possible to hypothesize a correlation between vitamin D deficiency and SARS-CoV-2 infection.

Ilie et al[13] suggested that there is a possible correlation between mean levels of vitamin D in different nations with occurrence, morbidity and mortality provoked by COVID-19. Negative correlations between mean concentrations of vitamin D in each country and the incidence of SARS-CoV-2 infections, as well as related mortality, were detected. Vitamin D levels were particularly reduced in the aging population in Italy, Spain, and Switzerland. This is also the most susceptible population in relation to SARS-CoV-2 infection[13].

The allotment of community pandemics exhibits seasonal patterns along specific temperature, latitude, and humidity similarly to the behavior of seasonal viral respiratory tract infections. SARS-CoV-2 infection shows important diffusion in Northern midlatitude countries with a median temperature of 5-11°C and low humid-

ity. A quadratic correlation was demonstrated between the occurrence of vitamin D deficiency in most frequently affected countries and their latitudes[14].

Moreover, a hypothesis that has been formulated to justify why ethnic populations with darker skin are more vulnerable to SARS-CoV-2 infection is because these subjects are more prone to have low serum levels of 25-hydroxyvitamin D, especially those residing at higher latitudes[15]. In Chicago, more than half of SARS-CoV-2 cases and about 70% of SARS-CoV-2 deaths were reported in African-American subjects[16] who are at higher risk for vitamin D insufficiency[17].

Another aspect that can be taken into account is that Vitamin D has an action in several cellular-mediated reactions to pathogens and could decrease the risk of acute respiratory tract infections[18,19]. This protecting action of vitamin D has been also described in several situations correlated with pneumonia[20-22], and influenza A H5N1 virus-caused lung damage[23]. Furthermore, some experimentations propose the efficacy of vitamin D as an adjuvant treatment along with antiretroviral agents in HIV-infected subjects[24]. The effect of vitamin D in the setting of viral diseases is also sustained by findings of specific vitamin D receptor gene (*VDR*) alleles that are correlated with increased predisposition to respiratory infections[25], as well as with the progress of HIV infection[26].

Vitamin D has several ways by which it decreases the risk of infections and death (Figure 1).

Vitamin D helps preserving tight junctions, gap junctions, and adherents junctions participating to the preservation of cell physical barrier integrity[27]. In fact, it is well-known that viruses alter junction integrity, augmenting the possibility of infection by the virus and other pathogens[28-30].

However, there are other processes through which vitamin D supplementation could decrease risk of different respiratory infections, including COVID-19[31].

Vitamin D increases action of innate immunity *via* an effect on monocytes and macrophages, and modifies response of cells such as dendritic and T-cells, toward a more anti-inflammatory pattern[32]. In experimental models, it reduces the immune responses due to T helper (Th) 1 cells, thus decreasing the generation of pro-inflammatory cytokines, such as IL-2, IL-6, and Interferon-γ (IFN-γ). It has also been proposed that vitamin D act as an immunomodulatory substance not only by reducing Th1 cells stimulation, but also modifying Th2 cells. An *in vitro* study[33] indicates that $1,25(OH)_2D_3$ upregulates Th2 cells activity, modifies T regulatory (Tregs) cells activity, and Th17 cells function. Vitamin D is able to reduce Th17 activity and to increase Treg cells activity. Th17 cells generate IL-17 and have been involved in the pathogenesis of several diseases. Some experimental models propose that $1,25(OH)_2D_3$ reduces Th17 growth and function by stopping Nuclear Factor of Activated T-cells (NFAT) and Runt-related Transcription Factor 1 (RUNx1) connecting to the IL-17 promoter and stimulating Forkhead box P3 (FOXP3), and by blocking RAR-related Orphan Receptor Gamma2 (RORγt) which is the transcription factor of IL-17[33].

Moreover, Vitamin D improves cellular innate

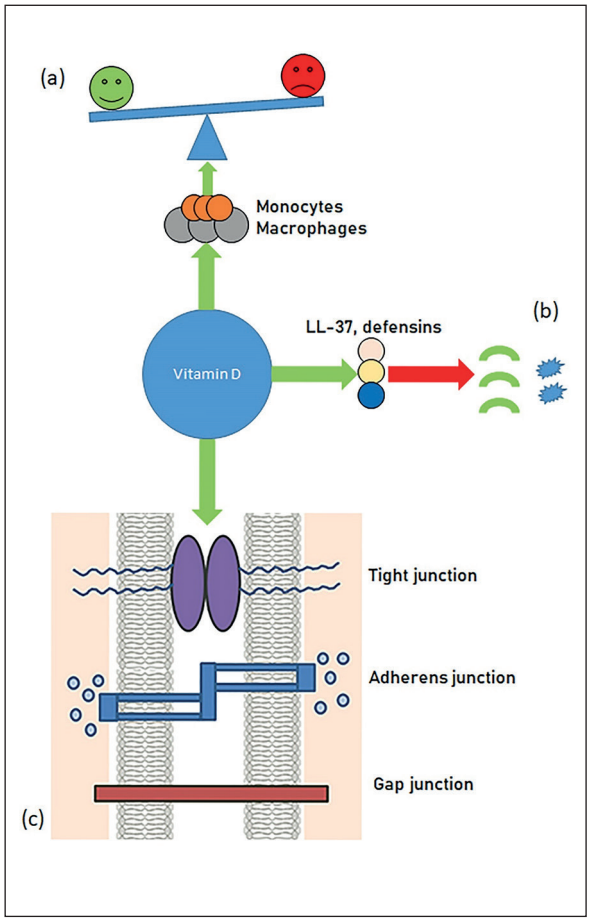

Figure 1. Mechanisms of action of Vitamin D in decreasing risks of infection and death: **(a)** stimulating monocytes and macrophages, and modifies response of cells such as dendritic and T-cells, toward a more anti-inflammatory pattern; **(b)** stimulating the delivery of antimicrobial peptides, such as human cathelicidin, LL-37 and defensins, in turn displaying direct antimicrobial function; **(c)** preserving tight junctions, gap junctions, and adherens junctions participating to the preservation of cell physical barrier integrity.

immunity partially *via* stimulating the delivery of antimicrobial peptides, including human cathelicidin, LL-37[34,35], and defensins[36].

Cathelicidins display direct antimicrobial function against a wide spectrum of microbes, including Gram-positive and Gram-negative bacteria, fungi, enveloped and nonenveloped viruses[37]. Those host-originated peptides destroy the infecting pathogens by altering their cell membranes and can reduce the damaging and biological effects of endotoxins[38].

A vitamin D deficiency could intervene at different times of the SARS-CoV-2 infection, worsening the prognosis of patients through different mechanisms.

Vitamin D may disturb the activities of 70% of the SARS-CoV-2 proteins by modifying expression of 25% of human genes encoding protein targets of SARS-CoV-2. Genes required for SARS-CoV-2 entry into human cells, ACE2 and FURIN, were employed as baits to build genomic-guided molecular maps of upstream regulatory elements, their expression and functions in the human body. Repressors and activators of the ACE2 and FURIN genes were identified based on the analyses of gene silencing and overexpression experiments as well as relevant transgenic mouse models. Employing this approach, vitamin D has been recognized as putative SARS-CoV-2 mitigation agent[39].

Moreover, vitamin D deficiency may combine "inflame-aging" to cytokine storm in elderly subjects with SARS-CoV-2. Vitamin D can reduce the expression of pro-inflammatory genes [such as monocyte chemotactic protein1 (MCP-1), and IL-12β)] in immune cells *via* decreasing disproportionate reactive oxygen species (ROS) delivery, increasing intracellular glutathione concentrations, reducing NF-κB and p38 MAP kinase expression. Overabundance of ROS production can enhance NF-kB expression in immune cells, causing an increased production of pro-inflammatory factors, including iNOS, and COX-2. Stimulation of p38 MAP kinase pathway can also increase IL-6 and MCP-1 generation in immune cells by activating the signal transducer and activator of transcription1/5 (STAT1/5)[40,41].

Furthermore, vitamin D pretreatment was advantageous in mouse models of acute respiratory syndrome (ARDS), decreasing lung permeability by change of renin-angiotensin system action and ACE2 expression[42]. In patients with kidney disease and in animals with diabetes mellitus, increased ACE2 expression was established. Vitamin D supplementation was demonstrated to reduce ACE2 expression in the kidney. 1,25-(OH)2D3 displayed reno-protective action by reducing ACE1 and ACE1/ACE2 ratio in streptozotocin-provoked diabetic nephropatic rats. In this way, Vitamin D supplementation could prevent SARS-CoV-2 entrance into the cell in infected patients[43,44].

The vitamin D binding protein (DBP), the principal transportation protein of vitamin D, may also have an undervalued role in the onset of ARDS due to SARS-CoV-2 infection.

DBP is a multifunctional plasma protein with a molecular weight of 52-59 kDa. Besides high-affinity vitamin D binding, DBP can bind actin, CD44, and annexin A2. This α2-globulin has a central role during inflammation, as it can considerably increase the action of neutrophil chemoattractants[45].

During ARDS, a situation characterized by a massive tissue injury and cell death, actin is discharged into extracellular fluids, provoking lung inflammation. An increased blood neutrophil adhesion and migration, together with an increased generation of inflammatory elements by pulmonary monocytes are involved in this condition[46]. Furthermore, in the extracellular compartment, monomeric globular actin (G-actin) polymerizes the polymerized filamentous actin (F-actin), together with coagulation factor Va, which may provoke vascular obstruction and multiple organ failure. To respond to the procoagulant action of F-actin, the two elements of the intravascular actin scavenging system, gelsolin, and DBP, slice actin and block repolymerization of G-actin[47]. DBP bound to G-actin, and not free DBP, operates as an indirect, but fundamental chemotactic cofactor for complement activation peptide C5a and for several leukocyte chemoattractants[48]. Employing an animal model, the complement system has been recognized as a central mediator of COVID-19 disease. As 25(OH) vitamin D3 and 1,25(OH)2 vitamin D3 block the chemotaxis by contending for the same binding site on DBP, reduced vitamin D levels could be correlated with a worsened outcome of SARS-CoV-2 infection[49].

Furthermore, vitamin D deficiency is related to increased thrombotic complications[50], which are commonly detected in SARS-CoV-2 infection[51].

Current studies[52,53] aim to assess the correlation between vitamin D concentrations and prognosis in subjects with SARS-CoV-2 infection as well as usefulness of vitamin D supplementation as part

of the therapy. As of June 27, there are currently 28 clinical trials listed in the clinical trial registry of the National Institutes of Health (NIH) (clinicaltrials.gov) designed at investigating vitamin D supplementation in combination with other drugs and comparing high doses versus standard doses[52,53] (Table I).

Among these protocols, two current prevention trials assess the consequence of vitamin D supplementation, alone (1600 IU on day 1 and 800 IU on days 2-5) or in combination with Zinc and Plaquenil, on SARS-CoV-2 infection risk in health care providers, or institutionalized subjects[53]. A third study assesses vitamin D3 1000 IU/day given for 2 months, to placebo, on infection and complication percentages. Three controlled trials[53] evaluate the action of vitamin D supplementation in SARS-CoV-2 positive subjects on death rates, as a primary outcome, with complication rates, time to recovery and inflammatory markers as secondary outcomes. The vitamin D arms consist of vitamin D (25,000 IU, single oral dose), the active vitamin D (Calcifediol 266 μg, 2 capsules day 1 and 1 capsule on days 3, 7, 14, 21, 28), or 2 vitamin D doses (400,000 IU or 50,000 IU in a single oral dose) compared to each other. A different research compares a vitamin D analogue (Ergocalciferol 1.25 μg daily) to vitamin D3 1000 IU daily, for 3weeks, while a protocol explores the effectiveness of vitamin D 50,000 IU weekly for 2 weeks, with or without aspirin, in decreasing the risk of hospitalization for SARS-CoV-2 infected subjects[54].

Although we have no conclusive data in place, it has been argued that vitamin D supplementation could be an easy and cheap way to reduce respiratory damage in fragile population[55].

Nevertheless, in spite of a multiplicity of interventional research, few have sustained vitamin D treatment for modifying clinical outcomes for subjects with inflammatory pathologies[56]. Changeable study methodology, including dosage and way of vitamin D administration, or target concentrations, may have participated to the negative results[57].

Then, the efficacy of high-dose supplementation of vitamin D3 in decreasing risk of SARS-CoV-2 infection is a mere extrapolation of presently existing evidence, which is often contradictory, about the efficacy of vitamin D3 in decreasing risk of other respiratory tract infections[58]. Without studies specific to SARS-CoV-2 infection, assuming whether vitamin D improves prognosis is debatable.

For the objective of the overall general health and in a population with high occurrence of vitamin D deficiency, subjects should keep on following suggestions for daily vitamin D assumption consistent with 600 or 800 IU to 4000 IU. Patients should avoid disproportionate dosages of vitamin D in the perspective of preventing SARS-CoV-2 infection[59].

In conclusion, it might be premature to propose extensive vitamin D supplementation with the target to treat SARS-CoV-2 infection. It would be logical, however, to evaluate vitamin D supplementation to safeguard musculoskeletal health in patients at risk of deficiency due to being housebound, as suggested by the UK National Health Service. Physical movements and sunlight exposure may be better for global health throughout this global crisis [60].

Vitamin C and COVID-19

Vitamin C (ascorbic acid) has several characteristics making it interesting to prevent and cure viral infections. The antiviral action of ascorbic acid has been known for at least 80 years, when its activity on poliomyelitis was described. Moreover, the use of ascorbic acid as a drug against several infectious diseases was also well reported, including rabies virus, Venezuelan equine encephalitis, human lymphotropic virus type 1 (HTLV-1), human immunodeficiency virus (HIV), influenza and herpes virus[61-69].

Pauling[70] stated that vitamin C in high doses is virucidal. This was justified *via* the generation of hydrogen peroxide and other radical initiators. Furthermore, the low pH value of the system was responsible for the *in vitro* antiviral actions of vitamin C[71,72].

Uesato et al[73] observed that vitamin C can reduce the viral load of the Ebstein-Barr virus, and the viral load was also decreased after treatment of human foreskin fibroblast and endothelial cells with vitamin C before cytomegalovirus infection[74]. These findings indicate that several mechanisms are involved in vitamin C antiviral activity. The immunomodulatory actions of Vitamin C are responsible for these actions. Ascorbic acid is present in leucocytes, lymphocytes, and macrophages[75,76]. Chemotaxis is increased by Vitamin C[77-79], and neutrophil phagocytic activity is also increased, while lymphocyte growth is augmented, too[77-79].

Meta-analyses of clinical trials propose a reduction in common cold extent by 8% with vitamin C intake[80]. However, in spite of these hypo-

Table I. Clinical studies related to COVID-19 and Vitamin D.

Study title	Interventions	Status
Vitamin D and COVID-19 Management	Dietary Supplement: Ddrops® products, 50,000 IU, Oral Dietary Supplement: Vitamin D3	Not yet recruiting
Vitamin D on Prevention and Treatment of COVID-19	Dietary Supplement: Vitamin D	Not yet recruiting
VITACOV: Vitamin D Polymorphisms and Severity of COVID-19 Infection	Other: Exposure	Not yet recruiting
Vitamin D Testing and Treatment for COVID 19	Dietary Supplement: Vitamin D3	Recruiting
Investigating the Role of Vitamin D in the Morbidity of COVID-19 Patients		Not yet recruiting
Randomized Proof-of-Concept Trial to Evaluate the Safety and Explore the Effectiveness of Resveratrol for COVID-19	Drug: Resveratrol Dietary Supplement: Vitamin D3	Not yet recruiting
International ALLIANCE Study of Therapies to Prevent Progression of COVID-19	Dietary Supplement: Vitamin C Drug: Hydroxychloroquine Drug: Azithromycin	Not yet recruiting
Impact of Zinc and Vitamin D3 Supplementation on the Survival of Aged Patients Infected With COVID-19	Dietary Supplement: Zinc gluconate Dietary Supplement: 25-OH cholecalciferol	Not yet recruiting
Increased Risk of Severe Coronavirus Disease 2019 in Patients With Vitamin D Deficiency		Recruiting
Do Vitamin D Levels Really Correlated With Disease Severity in COVID-19 Patients?	Dietary Supplement: vitamin D	Enrolling by invitation
The LEAD COVID-19 Trial: Low-risk, Early Aspirin and Vitamin D to Reduce COVID-19 Hospitalizations	Drug: Aspirin 81 mg Dietary Supplement: Vitamin D	Not yet recruiting
Cholecalciferol to Improve the Outcomes of COVID-19 Patients	Drug: Vitamin D Drug: Placebo	Not yet recruiting
A Study of Hydroxychloroquine, Vitamin C, Vitamin D, and Zinc for the Prevention of COVID-19 Infection	Dietary Supplement: Vitamin C Dietary Supplement: Vitamin D Dietary Supplement: Zinc	Not yret recruiting
COvid-19 and Vitamin D Supplementation: a Multicenter Randomized Controlled Trial of High Dose Versus Standard Dose Vitamin D3 in High-risk COVID-19 Patients (CoVitTrial)	Drug: cholecalciferol 200,000 IU Drug: cholecalciferol 50,000 IU	Recruiting
Evaluation of the Relationship Between Zinc Vitamin D and b12 Levels in the Covid-19 Positive Pregnant Women	Serum zinc, vitamin D vitamin B12 levels	Completed
Covid-19 and Vitamin D in Nursing-home		Completed
Hydroxychloroquine as Post-Exposure Prophylaxis Against COVID-19 Infection	Drug: Hydroxychloroquine Dietary Supplement: Vitamin D	Active, not recruiting
A Study of Quintuple Therapy to Treat COVID-19 Infection	Drug: Hydroxychloroquine Drug: Azithromycin Dietary Supplement: Vitamin C Dietary Supplement: Vitamin D Dietary Supplement: Zinc	Not yet recruiting
Oral 25-hydroxyvitamin D3 and COVID-19	Drug: Oral 25-Hydroxyvitamin D3	Recruiting
The Effects of Standard Protocol With or Without Colchicine in Covid-19 Infection	Drug: Colchicine Tablets	Recruiting
Prevention and Treatment With Calcifediol of COVID-19 Induced Acute Respiratory Syndrome	Drug: Best available therapy (BAT) + Calcifediol Drug: BAT	Not yet recruiting

Table Continued

Table I *(Continued)*. Clinical studies related to COVID-19 and Vitamin D.

Study title	Interventions	Status
Use of UC-MSCs for COVID-19 Patients	Biological: Umbilical Cord Mesenchymal Stem Cells + Heparin along with best supportive care. Other: Vehicle + Heparin along with best supportive care	Recruiting
REassessement After Hospitalization for Sars-COV-2 disordER	Assessment of the sequelae after hospitalization for Sars-COV-2	Not yet recruiting
Lessening Organ Dysfunction With VITamin C- COVID-19	Drug: Vitamin C Other: Control	Not yet recruiting
Proflaxis Using Hydroxychloroquine Plus Vitamins-Zinc During COVID-19 Pandemia	Drug: Plaquenil 200 mg tablet	Recruiting
Pharmacologic Ascorbic Acid as an Activator of Lymphocyte Signaling for COVID-19 Treatment	Drug: Ascorbic Acid	Not yet recruiting

thetical advantages, while the common cold can be provoked by a human coronavirus, COVID-19 is determined by a new coronavirus with a different genome sequence. It cannot be supposed, therefore, that effects of vitamin C on the common cold can be converted to the treatment of SARS-CoV-2 infection.

Nevertheless, beyond its anti-infective effect, vitamin C could exert positive effects on several features of the SARS-CoV-2 disease. For instance, late trials have evaluated vitamin C as part of a treatment for ARDS and septic shock[81-82].

In a randomized trial, subjects with sepsis-provoked acute respiratory distress syndrome were randomized to be treated with intravenous infusion of high-dose vitamin C or placebo. Vitamin C did not appreciably correct organ failure or modify markers of inflammation and vascular damage. However, the study did ascertain a substantially minor risk of death when the subjects were given high-doses vitamin C as compared to placebo. Fowler et al[83] have recognized vitamin C supplementation to reduce the risk of pneumonia.

A meta-analysis of 12 studies with 1,766 patients in ICU found that vitamin C reduced ICU stay by 8%[84]. A different research[85] of 8 studies demonstrated that vitamin C reduced the period of mechanical ventilation in subjects who needed for prolonged ventilation. Moreover, there is proof that vitamin C concentrations drop markedly in seriously ill subjects[86].

Nevertheless, it was reported that vitamin C supports the preservation of the alveolar epithelial barrier and transcriptionally increases the protein channels (aquaporin-5, ENaC, CFTR, and Na+/K+ ATPase) controlling the alveolar fluid clearance[87]. Vitamin C has also been involved in decreasing plasma cell-free DNA generated from the neutrophil extracellular trap (NET), which is the initiator of systemic inflammation in sepsis-caused multi-organ failure[88,89].

Remarkably, increased concentrations of syndecan-1 in the plasma are correlated with augmented death rate in severe infection and ARDS, and this endothelial glycocalyx can be decreased drastically by high dosage of vitamin C[89]. Moreover, vitamin C is able to reduce the cytokines storm *via* other, unknown systems (Figure 2)[83].

Researchers from China have reported to have effectively cured more than 50 subjects with moderate or severe SARS-CoV-2 infection with high dosage of IV vitamin C (10,000-20,000 mg/d), administered over a period of 8-10 h. Supplementary vitamin C bolus might be needed among subjects in critical conditions, causing a shorter mean hospital period of stay with respect to untreated subjects with SARS-CoV-2 infection. The oxygenation index was enhanced in real time and all the subjects treated were discharged[90,91].

Specifics of this evidence are unobtainable as these data have not been published in either preprint or peer-reviewed journals. It is also relevant to observe that the high dosages employed in this study are not attainable when using orally available versions of vitamin C.

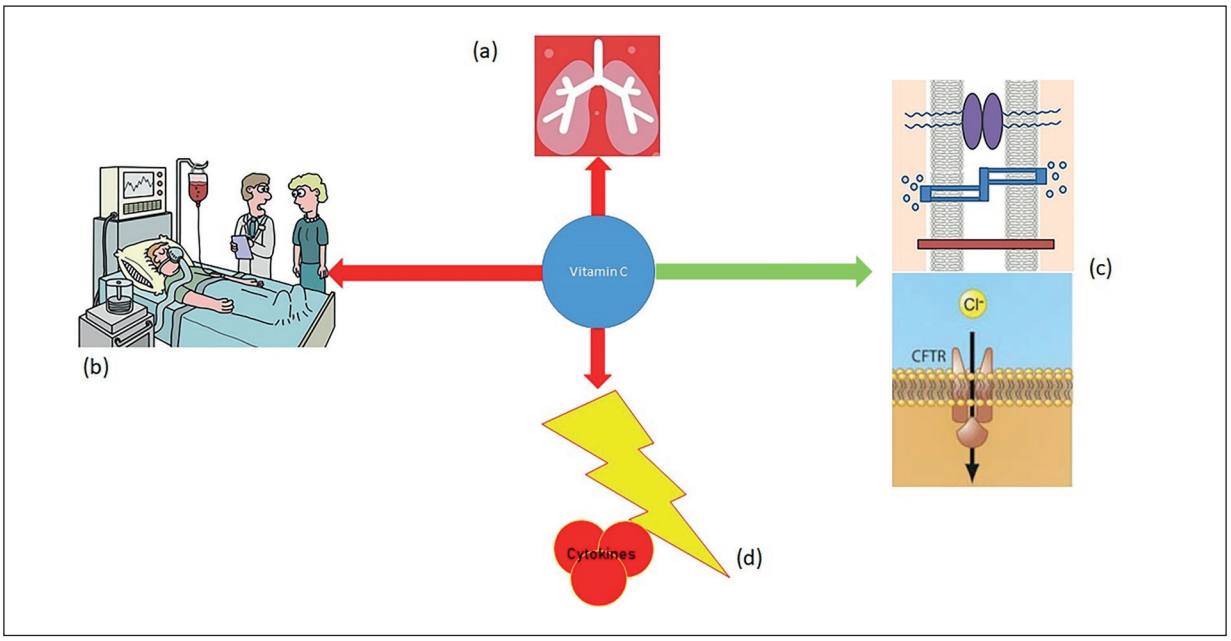

Figure 2. Mechanisms of action of Vitamin C useful for COVID-19: **(a)** reducing the risk of pneumonia; **(b)** reducing ICU stay and the period of mechanical ventilation in subjects who needed for prolonged ventilation; **(c)** supporting the preservation of the alveolar epithelial barrier and increasing the protein channels controlling the alveolar fluid clearance; **(d)** reducing the cytokine storm.

Moreover, the gastrointestinal adverse events (vomiting, abdominal cramps, nausea) could be dose limiting, and high doses of vitamin C may be correlated with development of kidney stones, especially in patients with high oxalate concentrations[92].

As of June 26, there are 25 clinical trials programmed in the clinical trial registry of the National Institutes of Health (NIH) (clinicaltrials.gov) targeted at experimenting vitamin C supplementation in SARS-CoV-2 infected patients (Table II).

Some of these protocols are controlled trials on vitamin C examining monotherapy (NCT04264533, NCT04344184, NCT03680274, NCT04357782) for acute SARS-CoV-2 treatment. Other trials use vitamin C in combination with hydroxychloroquine to treat (NCT04328961) or prevent (NCT04326725, NCT04335084) SARS-CoV-2 infection and with other supplements for prevention (NCT04342728). The dosages of vitamin C in these trials largely differs, oscillating from 250 to 500 mg orally daily to 24 g IV daily[93-95].

A different randomized controlled trial was started at the Zhongnan Hospital (NCT04264533) aiming at analyzing the clinical effectiveness and safety of vitamin C in pneumonia from SARS-CoV-2 infection. They hypothesize that vitamin C i.v. administration could improve the outcome of grave acute respiratory tract infections. The treatment arm foresees a 12 g vitamin C infusion (q12h) for seven days and the primary outcome measures the ventilation-free days. The estimated completion time is September 2020[96].

Thus, there is a need to promptly examine the uses of i.v. vitamin C, pre-infection and post-infection, and all over the different stages of the infection.

Vitamin B and COVID-19

The B vitamin complex itself consist of 8 vitamins (B1, B2, B3, B5, B6, B7, B9 and B12), which show no chemical correspondences to one another but were mainly grouped due to their similar capacity to operate as coenzymes.

Thiamine is an organo-sulfur compound including pyrimidine and thiazolium heterocycles linked by a methylene bridge. Six vitamer forms of thiamine are presently known, differing in their phosphorylation and adenosylation condition.

Vitamin B12, also identified as cobalamin, is a water-soluble vitamin with a central role for

Table II. Clinical studies related to COVID-19 and Vitamin C.

Study title	Interventions	Status
Pharmacologic Ascorbic Acid as an Activator of Lymphocyte Signaling for COVID-19 Treatment	Drug: Ascorbic Acid	Not yet recruiting
Preventing COVID-19 in Healthcare Workers With HCQ: A RCT	Drug: Hydroxychloroquine Other: Vitamin C	Not yet recruiting
Use of Ascorbic Acid in Patients With COVID 19	Dietary Supplement: Vitamin C	Recruiting
International ALLIANCE Study of Therapies to Prevent Progression of COVID-19	Dietary Supplement: Vitamin C Drug: Hydroxychloroquine Drug: Azithromycin Dietary Supplement: Zinc Citrate Dietary Supplement: Vitamin D3 Dietary Supplement: Vitamin B12	Not yet recruiting
Lessening Organ Dysfunction With VITamin C - COVID-19	Drug: Vitamin C Drug: Control	Not yet recruiting
A Study of Hydroxychloroquine, Vitamin C, Vitamin D, and Zinc for the Prevention of COVID-19 Infection	Drug: Hydroxychloroquine Dietary Supplement: Vitamin C Dietary supplement: Vitamin D Dietary Supplement: Zinc	Not yet recruiting
Clinical Application of Methylene Blue for Treatment of Covid-19 Patients	Drug: MCN (Methylene blue, vitamin C, N-acetyl cysteine)	Recruiting
Hydroxychloroquine in Patients With Newly Diagnosed COVID-19 Compared to Standard of Care	Drug: Hydroxychloroquine Dietary Supplement: Vitamin C	Suspended
Hydroxychloroquine for COVID-19 Post-exposure Prophylaxis (PEP)	Drug: Hydroxychloroquine Sulfate Drug: Ascorbic Acid	Recruiting
Vitamin C Infusion for the Treatment of Severe 2019-nCoV Infected Pneumonia	Drug: VC Drug: Sterile Water for Injection	Recruiting
A Preventive Treatment for Migrant Workers at High-risk of Covid-19	Drug: Hydroxychloroquine Sulfate Tablets Drug: Ivermectin 3Mg Tab Drug: Zinc Drug: Povidone-IodineDietary Supplement: Vitamin	Recruiting
Coronavirus 2019 (COVID-19)- Using Ascorbic Acid and Zinc Supplementation	Dietary Supplement: Ascorbic Acid Dietary Supplement: Zinc Gluconate Dietary Supplement: Ascorbic Acid and Zinc Gluconate Other: Standard of Care	Enrolling by invitation
Treatment for COVID-19 in High-Risk Adult Outpatients	Drug: Ascorbic Acid Drug: Hydroxychloroquine Sulfate Drug: Azithromycin Drug: Folic Acid	Recruiting
A Study of Quintuple Therapy to Treat COVID-19 Infection	Drug: Hydroxychloroquine Drug: Azithromycin Dietary Supplement: Vitamin C Dietary Supplement: Vitamin D Dietary Supplement: Zinc	Not yet recruiting
Proflaxis Using Hydroxychloroquine Plus Vitamins-Zinc During COVID-19 Pandemia	Drug: Plaquenil 200Mg Tablet	Recruiting
Phase II, Controlled Clinical Study Designed to Evaluate the Effect of ArtemiC in Patients Diagnosed With COVID-19	Drug: ArtemiC Drug: Placebo	Recruiting
Mesenchymal Stem Cell Infusion for COVID-19 Infection	Drug: Mesenchymal stem cells Other: Placebo	Recruiting

Table Continued

Table II *(Continued)*. Clinical studies related to COVID-19 and Vitamin C.

Study title	Interventions	Status
Evaluation of Additional Treatments for COVID-19: a Randomized Trial in Niger	Drug: Lopinavir-Ritonavir Drug Combination Combination Product: Standard Care	Not yet recruiting
Anti-inflammatory/Antioxidant Oral Nutrition Supplementation in COVID-19	Dietary Supplement: oral nutrition supplement (ONS) enriched in eicosapentaenoic acid, gamma-linolenic acid and antioxidants Dietary Supplement: isocaloric/ isonutrigenous ONS	Not yet recruiting
The Effects of Standard Protocol With or Without Colchicine in Covid-19 Infection	Drug: Colchicine Tablets	Recruiting
Lessening Organ Dysfunction With Vitamin C	Drug: Vitamin C Other: Control	Recruiting
Isotretinoin in Treatment of COVID-19	Drug: Isotretinoin Only Product in Oral Dose Form	Not yet recruiting
Host-pathogen Interactions During SARS-CoV-2 Infection	Biological: Blood sample Biological: Low or upper respiratory tract sample Biological: Stool collection or fecal swab Genetic: Blood sample for whole genome sequencing Other: phone call	Recruiting
Assessment the Activity Value of 13- Cis-Retinoic Acid (Isotretinoin) in the Treatment of COVID-19 (Randomized)	Drug: Drug Isotretinoin (13 cis retinoic acid) capsules + standard treatment Drug: Isotretinoin (Aerosolized 13 cis retinoic acid) +standard treatment Drug: Standard treatment	Not yet recruiting
In-vitro Diagnostic Test to Predict COVID-19 Mortality and Disease Severity	Diagnostic Test: CAG length <24 Diagnostic Test: CAG length >=24	Recruiting

maintaining the state of health, being implicated as a coenzyme in several chemical reactions of paramount importance for human biochemistry. Vitamin B12 is one of the most complex coenzymes present in nature. The molecule is composed by a corrin ring and a dimethylbenizmidazole moiety. The font of vitamin B_{12} is mainly animal-derived food. Then, its administration is suggested for subjects on a vegetarian/vegan diet.

Given the action of cobalamin human metabolic pathways, it is frequent to find low vitamin B12 concentrations correlated to several different physio-pathological situations, including pregnancy, older age, bariatric surgery, gastrointestinal diseases, drug treatments, and uremia-related malnutrition. It controls hematopoietic processes and the performance of the nervous system, including myelin synthesis. Moreover, it contributes to the synthesis of nucleic acids. Deficiency of cobalamin provokes megaloblastic anemia, alterations in peripheral nerves, pursued by degenerative alterations of the spinal posterior cords and cortical spinal ducts.

The interest in a possible use for B complex vitamins in SARS-CoV-2 patients is essentially based on indirect data. Vitamins B are recognized to stimulate the immune system[97]. Especially, vitamin B2, together with ultraviolet light, has been demonstrated in *in vitro* studies to decrease the titers of MERS coronavirus under the limit of detection after inoculation of the virus into human plasma[97]. Likewise, vitamin B3 is also noticed in previous *in vivo* experiments

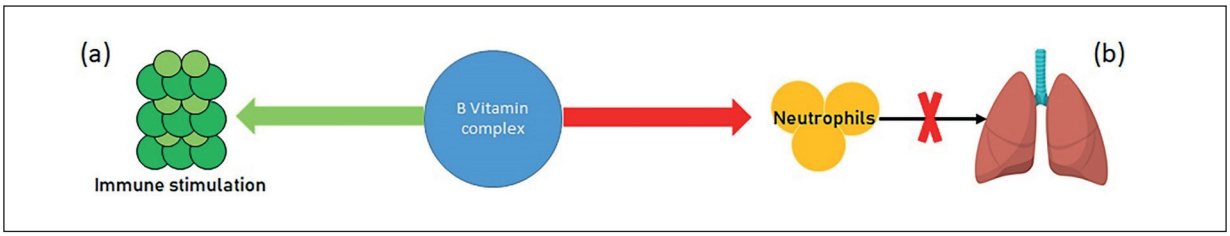

Figure 3. Mechanisms of action of Vitamins of the B complex potentially useful for COVID-19: **(a)** immune system stimulation; **(b)** neutrophil infiltration into the lungs blockade.

on mice undergoing mechanical ventilation to be able to drastically block neutrophil infiltration into the lungs throughout ventilator-provoked lung damage (Figure 3)[97].

Moreover, virtual screening and other computational techniques are widely used methods to understand the phylogenetics, molecular aspects of proteins and protein-ligand interactions during drug discovery process. Virtual screening has been employed in drug discovery against emerging diseases, including SARS CoV proteases, dengue virus and Ebola virus. In a research, the first resolved COVID-19 crystal structure was targeted in a virtual screening study by FDA approved drugs dataset. After a virtual screening capmain against SARS-CoV-2 Mpro, a set of antivirals, vitamins, antimicrobials, and other systemically acting drugs were more potent binding with COVID-19 Mpro, compared with curcumin (known Mpro inhibitor). In this work, the use and the repurposing of vitamin B12 is proposed[98].

As of June 27, there are 5 clinical trials registered in the clinical trial registry of the National Institutes of Health (NIH) (clinicaltrials.gov) aimed at evaluating vitamin B supplementation in SARS-CoV-2 subjects (Table III).

These studies aimed at testing vitamin B supplementation in combination with other drugs, such as Hydroxychloroquine, azithromycin or Vitamin D3.

Vitamin A and COVID-19

In the case of Vitamin A, the role of its possible supplementation in patients with SARS-CoV-2 is also based on purely theoretical assumptions.

Retinoids are a group of molecules that hold qualitative actions relative to all-trans retinol (vitamin A), that includes retinyl-esters, all-trans retinal and all-trans-retinoic acid (RA). RA is

Table III. Clinical studies related to COVID-19 and Vitamin B.

Study title	Interventions	Status
International ALLIANCE Study of Therapies to Prevent Progression of COVID-19	Dietary Supplement: Vitamin C Drug: Hydroxychloroquine Drug: AzithromycinDietary Supplement: Zinc Citrate Dietary Supplement: Vitamin D3 Dietary Supplement: Vitamin B12	Not yet recruiting
Evaluation of the Relationship Between Zinc Vitamin D and B12 Levels in the Covid-19 Positive Pregnant Women	Other: Serum zinc, vitamin d vitamin b12 levels	Completed
Effects of Nicotinamide Riboside on the Clinical Outcome of Covid-19 in the Elderly	Dietary Supplement: Nicotinamide riboside Dietary Supplement: Placebo	Recruiting
Vitamin D Testing and Treatment for COVID 19	Dietary Supplement: Vitamin D3	Recruiting
Treatment for COVID-19 in High-Risk Adult Outpatients	Drug: Ascorbic Acid Drug: Hydroxychloroquine Sulfate Drug: Azithromycin Drug: Folic Acid	Recruiting

the biologically active retinoid metabolite that, operating *via* its cognate receptors RA receptors (RAR α, β and γ), controls the expression of genes implicated in several biological pathways, including both adaptive and innate immune responses[98,99].

Retinoic acids have a relevant action in the control of the differentiation, growth, and function of neutrophils[100,101], stimulate a fast response to pathogen infection by phagocytosis and stimulation of natural killer (NK) T-cells[102,103]. Retinoic acid can also influence the differentiation of dendritic cell precursors, specialized cells of the immune system, able to coordinate innate and adaptive immune responses. It is consequently not surprising that low vitamin A concentrations have been demonstrated to be linked with an altered activity of neutrophils, macrophages, T-and B-cells (Figure 4). For this reason, vitamin A deficiency has usually been correlated with increased risk of infection[107,108], and a central role has been reported in the occurrence of influenza. Moreover, subjects with low vitamin A levels present histopathological modifications to the pulmonary epithelium and lung parenchyma,

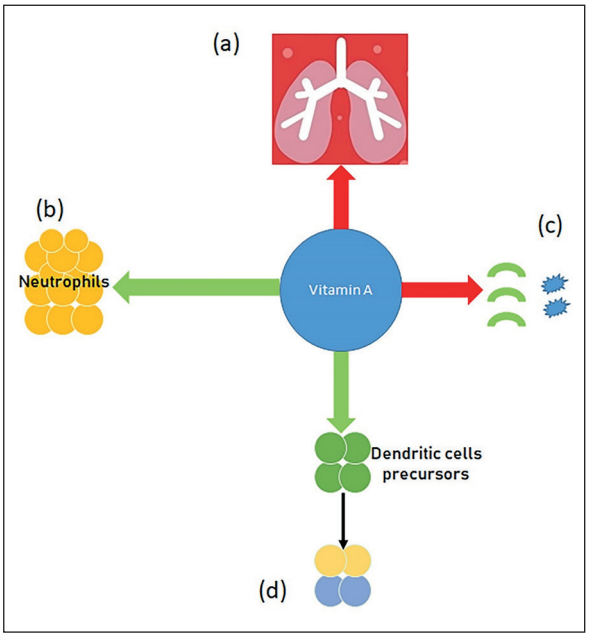

Figure 4. Mechanisms of action of Vitamin A useful for COVID-19: **(a)** reducing the risk of lung failure and respiratory diseases; **(b)** controlling the differentiation, growth, and function of neutrophils, leading to the stimulation of a fast response to pathogen infection; **(c)** directly inhibiting the proliferation of several types of viruses; **(d)** influencing the differentiation of dendritic cell precursors.

causing an increased risk of lung failure and respiratory disease[109]. This is remarkably significant taking into consideration the effects that SARS-CoV-2 has on lung function[110].

Soye et al[111] reported that RA blocks the measle virus (MeV) growth in U9370 and Huh-7 infected cells. This happens *via* IFN-I mediated pathways guided by RA:RARα promoter activation of the RIG-I gene and its downstream effectors. Analogously, Chen et al[112] stated that the anti-viral actions of RA against enterovirus 71 was due to an IFN-α and RIG-I effect. Retinoids also have direct inhibitory action on proliferation of several types of viruses, including influenza, hepatitis B virus, norovirus, cytomegalovirus, and MeV[113-116]. There are also suggestions that stimulation of retinoid signaling can powerfully block coronaviruses[117]. Through a library screen, Yuan et al[117] determined that Am580, a specific agonist for RARα, is an effective inhibitor of SARS-CoV and MERS-CoV viruses *via* alteration of SREBP-mediated lipogenic pathways.

As coronaviruses SARS-CoV and MERS-CoV can block IFN-I provoked antiviral effects and probably hamper treatments[118], the findings supporting the fact that retinoids can increase host IFN-I signaling justify the pre-clinical experimenting of combinations of IFN-I and retinoids in cell and animal models of SARS-CoV-2 infection.

However, as of June 27, there are 5 clinical trials registered in the clinical trial registry of the National Institutes of Health (NIH) (clinicaltrials.gov) aimed at evaluating vitamin A supplementation in SARS-CoV-2 subjects (Table IV).

Conclusions

In addition to direct operating drugs, increasing amounts of data demonstrated some possible adjuvant treatments with encouraging effectiveness against SARS-CoV-2 infection. These treatments include estrogen modulating drugs, immunomodulators (tocilizumab, thymosin α-1, intravenous immunoglobulin, fingolimod, cyclosporine, and thalidomide), Chinese medicines (baicalin, glycyrrhizin, Xuebijing), anti-vascular endothelial growth factors, such as bevacizumab, and statins[119]. Moreover, the pharmacological effects of natural substances have acquired growing consideration in the field of alternative and coadjutant therapeutic methods to various diseases[120,121]. These substances are dis-

Table IV. Clinical studies related to COVID-19 and retinoids.

Study title	Interventions	Status
Assessment the Activity Value of 13- Cis-Retinoic cid (Isotretinoin) in the Treatment of COVID-19 (Randomized)	Drug: Drug Isotretinoin 13 cis retinoic acid) (capsules+standard treatment Drug: Isotretinoin (Aerosolized 13 cis retinoic acid) +standard treatment Drug: Standard treatment	Not yet recruiting
Combination With Inhibitor of Neutrophil Elastase (All-trans Retinoic Acid) and Isotretinoin May Enhances Neutralizing Antibodies in COVID -19 Infected Patients Better han COVID-19 Inactivated Vaccines	Drug: Aerosolized 13 cis retinoic acid Drug: Aerosolized All trans retinoic acid Other: Placebo	Not yet recruiting
Combination of Recombinant Bacterial ACE2 Receptors -Like Enzyme of B38-CAP and Isotretinoin Could be Promising COVID-19 Infection- and Lung Injury Preventing Drug Better Than Recombinant Human ACE2	Combination Product: Recombinant Bacterial ACE2 receptors -like enzyme of B38-CAP (rbACE2) plus Aerosolized 13 cis retinoic acid	Not yet recruiting
Combination Therapy With Isotretinoin and Tamoxifen Expected to Provide Complete Protection Against Severe Acute Respiratory Syndrome Coronavirus	Drug: Drug: Isotretinoin plus Tamoxifen Drug: Aerosolized Isotretinoin plus Tamoxifen	Not yet recruiting
Isotretinoin in Treatment of COVID-19	Drug: Isotretinoin Only Product in Oral Dose Form	Not yet recruiting

tinguished by minor side effects in comparison with traditional pharmacological treatments[122].

In this framework, supplements with vitamin A, B, C, D, and E could represent an inexpensive and sufficiently safe approach for patients with SARS-CoV-2 infection[123].

However, while diet, nutritional supplements, and similar procedures show great potential for preventing and treating SARS-CoV-2 infection, it is also correct that solid clinical research data are expected to support any such claim.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contribution

Conceptualization, A.A and S.G; methodology, C.M.; A.T. and G.P.; software, A.T.; formal analysis, A.A.; resources, G.P.; data curation, A.A., A.T; writing-original draft preparation, A.A..; writing-review and editing, A.A. and A.T.; supervision, A.A.; S.G. and C.M. All authors have read and agreed to the published version of the manuscript.

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