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European Journal of Medicinal Chemistry 232 (2022) 114175

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Antioxidant, anti-inflammatory and immunomodulatory roles of vitamins in COVID-19 therapy

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ARTICLE INFO

Article history:
Received 20 November 2021
Received in revised form
27 January 2022
Accepted 2 February 2022
Available online 4 February 2022

Keywords:
Viral infection
Coronavirus
Cytokine storm
Vitamins
Antioxidants
Immunomodulation

abstract

oxidative stress is caused by an abundant generation of reactive oxygen species, associated to a diminished capacity of the endogenous systems of the organism to counteract them. Activation of pro-oxidative pathways and boosting of inflammatory cytokines are always encountered in viral infections, including SARS-CoV-2. So, the importance of counteracting cytokine storm in COVID-19 pathology is highly important, to hamper the immunogenic damage of the endothelium and alveolar membranes. Antioxidants prevent oxidative processes, by impeding radical species generation. It has been proved that vitamin intake lowers oxidative stress markers, alleviates cytokine storm and has a potential role in reducing disease severity, by lowering pro-inflammatory cytokines, hampering hyperinflammation and organ failure. For the approached compounds, direct antiviral roles are also discussed in this review, as these activities encompass secretion of antiviral peptides, modulation of angiotensin-converting enzyme 2 receptor expression and interaction with spike protein, inactivation of furin protease, or inhibition of pathogen replication by nucleic acid impairment induction. Vitamin administration results in beneficial effects. Nevertheless, timing, dosage and mutual influences of these micronutrients should be carefullly regarded.

Contents

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https://doi.org/10.1016/j.ejmech.2022.114175
0223-5234/

1. Introduction

According to WHO, "coronaviruses are a large family of viruses that can be pathogenic in animals or humans. Several coronaviruses in humans can cause respiratory infections ranging from the common cold to more serious illnesses, such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). The last coronavirus that was discovered is responsible for coronavirus disease 2019. COVID-19 is now pandemic and affects many countries around the world. The most common symptoms of COVID-19 are fever, dry cough, and fatigue. Other less common symptoms may also appear in some people, such as body aces and pain, nasal congestion, headache, conjunctivitis, sore throat, diarrhea, loss of taste or smell, rash, or discoloration of fingers on the hand or foot. These symptoms are generally mild and appear gradually. Some people, although infected, have very mild symptoms" [1].

The COVID-19 pandemic, caused by SARS-CoV-2, unfortunately led to significant life losses. The SARS-CoV-2 is classified as a Betacoronavirus. It is a single-stranded RNA virus, representing the etiological agent of the Coronavirus Disease 2019 in humans and animals [2].

A series of comorbidities have been identified as risk factors for negative prognosis in the evolution of COVID-19 patients. The prevalent comorbidities affecting the evolution of COVID-19 patients are, among other, cardiovascular disease, hypertension, diabetes mellitus type 2, malignancy and chronic obstructive pulmonary disease [3].

It has been proved that oxidative stress, understood as the lack of balance between the generation of reactive oxygen/nitrogen species and the organism's endogenous ability to counteract them, is the source involved in the same pathologies that favor a critical outcome in COVID-19, and these include cardiovascular disease and diabetes mellitus type 2 [4]. Oxidative stress was linked to the occurrence of cardiovascular complications in COVID-19 [5].

In conjunction with the treatments administered in various medical institutions and the accelerated research that led to the introduction of a vaccine, antioxidants are also studied, for their relevance in the treatment, by combating oxidative stress.

Oxidative stress was described by Sies as "a disturbance in the prooxidant-antioxidant balance in favor of the former", being subsequently redefined as "an imbalance between oxidants and antioxidants in favor of the oxidants, leading to a disruption of redox signaling and control and/or molecular damage" [6–9].

Oxidative stress is caused by an abundant production of reactive oxygen species (ROS), associated to a reduced capacity of the endogenous systems of the organism to counteract them. Reactive oxygen species are represented by free radicals or molecules possessing one or more unpaired electrons. In excess amount, they can affect cells and can represent the source of many diseases. The main aggressive reactive oxygenated species are superoxide radical anion ($O_2^{\bullet -}$), hydroxyl radical (•OH), nitric oxide radical (•NO), hydrogen peroxide (H_2O_2). Numerous reports link oxidative stress to various pathologies [10–18].

2. Antioxidants - definition and concept

A biological antioxidant can be defined as a compound that can retard or impede the oxidation of a key biomolecule, acting at much lower concentration than that of the oxidizable substrate [12].

The importance of counteracting cytokine storm in COVID-19 is essential to counterbalance the immunogenic damage of the endothelium and alveolar membrane. So, the antioxidant defense system acts against oxidative decay, comprising compounds able to trap radical species formed. These systems (enzyme-based or nonenzyme-based), are active in aqueous and membrane cell compartments. Another significant antioxidative system of the cell is constituted by repair systems, that eliminate the impaired biomolecules, before their aggregation induces modifications in cell metabolism [19].

The complete description of lines of defense includes in the first category compounds that suppress free radical species' generation, impacting either free radical species or free radical species initiators. The second line of defense is constituted by antioxidants that exert their scavenging ability namely by electron donation, suppressing chain initiation, or breaking chain propagation. The third line of defense includes the repair antioxidants that act after the occurrence of free radical injuries. Antioxidants belonging to the fourth line of defense exploit adaptation mechanisms: the signal produced by a free radical species determines the synthesis of an antioxidant species to the appropriate site [18].

A source-based classification of antioxidants considers exogenous and endogenous antioxidants [12,18,20]. The main types of exogenous antioxidants are:

- vitamins: vitamin C, vitamin E;
- carotenoids (beta-carotene, lycopene, lutein, zeaxanthin);
- phenolic antioxidants: non-flavonoids such as phenolic acids (chlorogenic acids, gallic acid, cafeic acid, etc.) or stilbene derivatives (resveratrol) and flavonoids-flavonols (quercetin, kaempferol, myricetin), flavanols: (proanthocyanidins, catechins), flavanones (naringenin, eriodictyol, hesperetin), flavones (luteolin, apigenin), isoflavones (genistein, daidzein, glycitein). Anthocyanidins (malvidin, cyanidin, pelagonidin) present as main structure a flavylium cation and their glycosides are known as anthocyanins;
- trace elements: zinc, selenium.

The category of endogenous antioxidants includes enzymatic antioxidants (superoxide dismutase, catalase, glutathione reductase, glucose-6-phosphate dehydrogenase), as well as nonenzymatic ones (coenzyme Q, uric and lipoic acids, glutathione, melatonin, bilirubin, NADPH-nicotinamide adenine dinucleotide phosphate reduced form).

In COVID-19, immunocytes, mainly macrophages and neutrophils, can become sources of reactive oxygen species (ROS) including superoxide anion radical, hydroxyl radical, hydrogen peroxide [21–23]. The role of antioxidants is to block these reactive oxygen species.

Cytokine storm is noticed in both viral and bacterial infections and results in increased oxidative stress, endothelial cell activation, neutrophil infiltration. Nuclear factor erythroid 2 (nfe2)-related factor 2 (nrf2), has been identified as main transcription factor regulating antioxidant response-driven cytoprotective protein expression. Nrf2 signaling is activated, to hamper cell and tissue injury, caused by oxidative stress. So, oxidative stress lowering by antioxidant intake, can become an approach applied to COVID-19 treatment [24,25].

Though the correlation between oxidative stress markers and the severeness of viral diseases such as hepatitis C has been well recognized and documented, for SARS-CoV-2 clinical data are not so numerous. Experimental animal models of severe acute respiratory syndrome have shown high reactive oxygenated species amounts and impairment of the antioxidant defense system, during SARS-CoV infection.

The overproduction of ROS, by both the mitochondrial electron transport chain and NADPH oxidases, can lead to lung cells' impairment and induce pulmonary dysfunction.

Impairment of glucose 6-phosphate dehydrogenase (G6PD) results in enhanced oxidative decay, as this enzyme is responsible for NADPH generation, an essential reducing agent in the cell. Previous studies have proved that G6PD deficiency promotes sensitivity to even moderate oxidative stress, whereas G6PD altered profile has been classed as an inflammation marker. Alongside enhanced oxidative burst, G6PD-deficient cells are found at a higher risk to be subject to protein glycosylation [26], a step majorly involved in viral pathogenesis - including COVID-19 - by inducing folding, circulation and viral spread, whereas host cell and viral glycans behave as attachment factors [27–29].

The beginning of severe lung injury in SARS-CoV infected patients is linked to the activation of the oxidative stress components that are coupled with hereditary immunity, as well as to the activation of transcription factors, such as NF-kB, resulting in an enhanced proinflammatory host response.

Activation of NF-kB signaling pathways via toll-like receptors (primarily TLR4), that are targeted by viral pathogens such SARS-CoV, can promote the host inflammatory response, eventually leading to severe lung injury. TLR4-TRIF-TRAF6 signaling was described as major pathogenic pathway mediating the acute lung injury severeness. Oxidative stress and inborn immunity influence the degree of severity in lung acute injury, elicited by respiratory viruses. Aging leads to increased damage caused by oxidative stress, resulting in changes in the immune response and presence of a pre-inflammatory state [30]. SARS-CoV2, like other RNA viruses, can enhance the oxidative stress.

It is thought that the inborn immune system recognizes SARS-CoV-2 virus via pattern recognition receptors (PRR) like cytosolic RIG-I like receptors (RLRs) and toll-like receptors (TLRs), with subsequent cytokine release: tumor necrosis factor α (TNF-α), IL-1, IL-6, and IL-18, as interferon-gamma inducing factor. Imbalance in the function of myeloid cells such as monocytes, macrophages, and dendritic cells becomes source of cytokine release and acute respiratory distress syndrome. The mediating cytokine most involved in the "cytokine storm" in COVID-19 is IL-6, which determines the acute phase response, but also B-cell differentiation, and thermoregulation [31].

SARS-CoV-2 essentially enters type II pneumocytes using angiotensin-converting enzyme 2 receptor and replicates with the support of transmembrane serine protease 2. After replication, SARS-CoV-2 gives rise to cytokine storm, leading to hyper-inflammation, alveolar edema, and eventually acute respiratory distress syndrome. The SARS-CoV spike protein binding to ACE2 induces subsequent interleukin-8 (IL-8) release from lung cells by activating AP-1 (activation protein 1) [32,33].

The viral pathogen - toll like receptor interaction favors prooxidant pathways, resulting in TNF-α-induced activation of nicotinamide adenine dinucleotide phosphate oxidase, an important source of ROS generation, in macrophages. Moreover, macrophages produce ferritin, protective against deleterious effects of reactive oxygenated species. This enhanced ROS production proved able to target both the virus and the infected cells [34].

Alongside oxidative cell damage induced by SARS-CoV-2, inflammatory markers such as D-dimers, C-reactive protein, ferritin, neutrophil count in a complete blood count, inflammatory cytokines, and chemokines increase in the serum of severe COVID-19 patients [35,36].

When coronaviruses enter cells, they lead to apoptosis and promote inflammatory responses, encompassing activation of pro-inflammatory cytokines that attract inflammatory cells, such as CD+ and T helper 1 (Th1) cells. SARS-CoV-2 infects immune cells and promotes the apoptosis of lymphocytes leading to lymphocytopenia. During the acute phase of SARS-CoV, especially $CD4^+$ and $CD8^+$ T cell counts decrease, these lymphocytes playing protective role in infection [37,38].

The overproduction of pro-inflammatory cytokines results in hyperinflammation and organ failure. The major reported cytokines induced by SARS-CoV-2 include IL-2, IL-4, IL-6, IL-7, IL-10, granulocyte colony stimulating factor (G-CSF), inducible protein-10 (IP-10), monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein 1 alpha (MIP1A), tumour necrosis factor alpha (TNF-α), and interferon-gamma (IFN-γ), which were noticed at elevated amounts in cases of COVID-19 severeness [33,39–42].

The importance of counteracting cytokine storm in COVID-19 is essential to hamper immunogenic damage of the endothelium and alveolar membranes [43].

Vitamin impairment is linked to illness severity, as it will be revealed for most compounds reviewed in detail in section 3. So, a balanced diet, consisting in an intake of these micronutrients mainly from food or from supplements (when needed to support the endogenous antioxidant defense) is essential [18].

In Table 1, the main food sources are given, for the compounds approached in the present review. Cooking may lead to the decay of some vitamins, especially vitamin C.

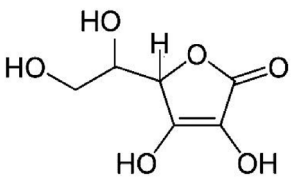
In the following sections, we aim at investigating the role of vitamins in the immune response against COVID-19. Hydrosoluble and liposoluble vitamins are reviewed in separate subsections, in order of their relevance (abundance) in the treatments applied: vitamin C is more extensively included than group B vitamins, and vitamin D is the liposoluble vitamin most largely employed. Antioxidant, anti-inflammatory and immunomodulatory activities are detailed.

3. Role of vitamins against Covid-19 pathology

3.1. Hydrosoluble vitamins

3.1.1. Vitamin C

Vitamin C (L-ascorbic acid) is an essential nutrtient for humans (structurally, a γ lactone) involved in various cellular processes, being a hydroxylation cofactor in the synthesis of collagen and neurotransmitters.



The adult fasting reference level of vitamin C is comprised between 23 and 114 μmol/l (0.4–2.0 mg/dl). Concentrations smaller than 11.3 μmol/l (0.2 mg/dl) are linked to pronounced deficiency.

The role of vitamin C against oxidative stress is largely documented [12,13,18]. Vitamin C is a powerful antioxidant, an efficient scavenger of reactive oxygenated and nitrogenated species: hydroxyl radical, alkoxyl radical, superoxide radical anion, hydrogen peroxide, singlet oxygen [18]. It stops the production of new free

Table 1
Main vitamin food sources.

Vitamin	Plant sources/fungi	Animal sources	Recommended Dietary Allowances (according to National Institutes of Health)
C	Fruits: especially citrus fruits, strawberries, sea buckthorn, rosehip, blackcurrants, papayas, mangoes, kiwifruit, pineapple, cantaloupe, fruit juices; Vegetables: red and green bell peppers, broccoli, cauliflower, parsley, tomatoes, potatoes, spinach, fortified cereals; Dietary supplements.	Chicken and lamb liver, calf and beef liver, pork liver, human breast milk, shells, cod roe.	Adults (men)90 mg Adults (women)75 mg
B1	Fresh fruits (banana, orange), peas, nuts, pistachios, black beans, lentils, brown rice, fortified breakfast cereals, whole grain breads.	Pork products (cured ham, pork tenderloin, salami), fish (tuna, trout, catfish).	Adults (men) 1.2 mg Adults (women) 1.1 mg
B2	Mushrooms, asparagus, artichokes, nuts, fortified cereals.	Meat (chicken, beef, turkey), fish, eggs, milk, plain yoghurt, cheese.	Adults (men) 1.3 mg Adults (women) 1.1 mg
B3	Peanut butter, brown rice, wheat flour, whole grain foods, enriched breads and cereals, nuts, bananas, vegetables (asparagus, leafy green vegetables, mushrooms).	Red meat (beef, pork), liver, poultry, fish.	Adults (men) 16 mg Adults (women) 14 mg
B5	Whole grains, broccoli, lentils, cauliflower, tomatoes, avocados, mushrooms, nuts, bananas, sunflowers seeds.	Chicken (liver), tuna, salmon, eggs, milk, yogurt, buttermilk.	Adults 5 mg
B6	Leafy green vegetables, peanuts, beans, soya beans, wheatgerm, oats, bananas, some fortified breakfast cereals.	Meat: pork, poultry (chicken, turkey), beef liver, some fish (salmon, tuna), milk.	Adults 1.3 mg
B7	Avocados, sweet potato, nuts, seeds, wheat bran, baker's yeast.	Organ meats, whole eggs, oysters, salmon.	-
B9	Broccoli, Brussels sprouts leafy green vegetables (cabbage, kale, spring greens and spinach), peas, chickpeas and kidney beans, rice, breakfast cereals fortified with folic acid, orange juice.	Beef liver, seafood.	Adults 400 mcg
B12	Fortified breakfast cereals.	Meat, fish (salmon, trout), clams, poultry, eggs, milk, cheese, yogurt.	Adults 2.4 mcg
D	Fortified cereals, fortified juices, mushrooms.	Egg yolks, beef liver, fish liver oils, fatty fish, sardines, fortified milk, fortified margarine; the skin can make vitamin D (exposed to sunlight).	Adults 15 mcg (600 IU)
A	Beta-carotene sources - leafy, dark green vegetables (lettuces, broccoli, spinach), other vegetables (carrots, winter squash, sweet potatoes, pumpkin), dark orange fruits (apricots, cantaloupe), and other fruits (mangoes), squash.	Retinol sources- milk, butter, fortified margarine, cheese, cream fortified milk, eggs, liver.	Adults (men) 900 mcg of retinol activity equivalents Adults (women) 700 mcg of retinol activity equivalents
E	Polyunsaturated plant oils (soybean, corn, cottonseed, safflower), leafy green vegetables (broccoli, spinach, etc.), whole-grain products, nuts (like peanuts and almonds) and seeds, wheat germs, red bell pepper, asparagus, mango, avocado.	Goose meat, egg yolks, rainbow trout, Atlantic salmon.	Adults 15 mg
K	Green leafy vegetables - leaf cabbage, collard greens, and spinach; Green vegetables - broccoli, Brussels sprouts, and asparagus; cereal grains, vegetable oils; Carot juice, pomegranate juice; Also produced in the intestinal tract by bacteria (K2 form).	Chicken breast, ham, cheese, ground beef.	Adults (men) 120 mcg Adults (women) 90 mcg
F	Oils: flaxseed, corn, soybean, canola, sesame, mustard; Nuts (pecan, Brasil, pine); Leafy green vegetables (spinach, broccoli, and Brussels sprouts).	Fish (salmon, tuna), meat.	Adults (men) 1.6 g Adults (women) 1.3 g

radicals, via suppression exerted on the NADPH oxidase pathway. Can replenish the antioxidative (reduced) form of tocopherol, the major membrane protector, by reducing tocopheroxyl radicals. Nevertheless, it can exert a prooxidant activity, in the presence of transition metal cations [12].

Two families of transport proteins are responsible for the whole-body vitamin C levels and its distribution to various compartments: sodium-dependent vitamin C transporters (SVCT1 and SVCT2, that transport ascorbic acid) and glucose transporters (GLUT1, GLUT3, and GLUT 4, that transport the oxidized form, dehydroascorbic acid). The ability of vitamin C to hamper sepsis-induced immunosuppression was linked to a decrease of apoptosis of lymphocytes and monocytes. Given the increased metabolic requirements of critically ill patients with sepsis, counteracting low levels of plasma vitamin C (under 23 μmol/l) may necessitate a dose of around 6 g/day, a total daily level 30 times higher, than in the case of healthy subjects [44].

Intracellular accumulation of vitamin C in leukocytes and neutrophils is dependent on its plasma availability. In neutrophils, vitamin C can influence chemotaxis, as well as phagocytosis. Given its antioxidant (ROS scavenging) ability, vitamin C exerts protective effect from the impairment suffered upon oxidative burst in neutrophils and phagocytes. Vitamin C promotes a caspase-dependent cascade, enabling both programmed apoptosis and necrosis inhibition [45–47]. An analogous protective effect from oxidative injury is noticed in lymphocytes. Other involvement of vitamin C against inflammation encompass modulation of nuclear transcription factor kappa B (NF-kB) and lowering of pro-inflammatory cytokines production [47].

Diminution in the generation of IL-6 and TNF-α, induced by vitamin C, takes place in a dose dependent manner [31,48,49]. Reduction of granulocyte-macrophage colony-stimulating factor signaling, which modulates redox-signal transduction of cytokines in host immune cells, impacts inflammatory responses [50].

It was reported that vitamin C exerts antiviral properties by promoting lymphocyte activity, boosting interferon-α production, modulating cytokines, lowering inflammation, counteracting endothelial dysfunction, and improving mitochondrial function [51–53]. High doses of vitamin C control the proliferation and functioning of T lymphocytes (responsible for cytokine release) and B lymphocytes (that secrete antibodies), as well as the activity of natural killer cells, impeding the progression of cytokine storm and boosting the host's immune system [54,55].

Tanaka and colab. reported that ascorbic acid (in the ascorbic acid 2-glucoside form) has the capacity to promote immunoglobulin production. The phytohemagglutinin-induced proliferative

response of human peripheral blood lymphocytes was also enhanced by ascorbic acid 2-glucoside [55,56].

Vitamin C promotes chemotaxis of neutrophils and macrophages, enhances phagocytosis and inhibits necrosis [31]. Subjects with sepsis-related acute respiratory distress syndrome present low ascorbate levels [57].

Vitamin C is involved in the epigenetic and transcriptional activation of protein channels that modulate alveolar fluid clearance, resulting in improvement of lung epithelial barrier function, lowering acute respiratory distress symptoms [58,59].

Hemilä and Chalker [60,61] have analysed 18 publications, which reported 19 trials on the influence of vitamin C on the length of intensive care unit (ICU) period, or on the period required for mechanical ventilation. The length of intensive care unit stay was analysed in seventeen trials, and the period required for mechanical ventilation in six. Patients that underwent cardiac surgery were analysed in thirteen trials, patients with sepsis in two, patients with lung contusion in two, and patients with burns, in one. Eight trials were performed in Iran, four in the USA, two in Egypt, one trial in China, the same for Greece, Japan, and Slovenia. The total number of patients considered for the eighteen trials was 2004, with 1835 patients in studies dealing with cardiac surgery and 169 patients in other conditions. Vitamin C was given orally in seven trials and intravenously in eleven trials. All oral intake trials dealt with cardiac patients and the dose was comprised between 1 and 3 g/day. All the eleven intravenous administration trials encompassed five non-cardiac studies and the dose was comprised between 0.5 and 110 g/day. In three trials, vitamin C was administered for one day only, and in eleven trials, for four days or more. A meta-analysis of twelve trials with 1766 patients in intensive care unit, reported that vitamin C could reduce the intensive care unit period by 8%. It was also asserted that vitamin C may lower the duration of mechanical ventilation in critically ill subjects.

Preclinical research focused on early sepsis and acute respiratory distress syndrome showed that vitamin C compared to placebo did not lead to a significant amelioration of organ dysfunction, or of inflammation biomarkers and vascular injury. In a preliminary study focused on the effect of vitamin C on inflammation and vascular injury in patients with sepsis and severe acute respiratory distress syndrome, it was shown that intravenous infusion of high-dose vitamin C for 96 h gave no significant differences, versus placebo, in the modified Sequential Organ Failure Assessment score at 96 h, or in the levels of C-reactive protein and thrombomodulin at 168 h. The incapacity of vitamin C to impact C-reactive protein and thrombomodulin amounts was assigned to the advanced sepsis, existing before acute respiratory distress syndrome. Later quantification of the above-mentioned biomarkers in CITRIS-ALI when compared to early vitamin C administration in serious sepsis, could explain the discrepancy with respect to the results of previously published studies regarding the role of vitamin C in severe sepsis [62]. Nevertheless, although an improvement of all parameters followed could not be noticed versus placebo, an important reduction in 28-day all-cause mortality, a diminution of ICU period, and an increase of hospital-free days were shown for vitamin C-infused patients [57].

Administration of ascorbic acid alone or in combination with thiamine and corticosteroids could ameliorate hemodynamics, end-organ function and survival in critically ill patients. Factors like timing, dose and vitamin C administration are important, as direct radical scavenging depends on vitamin C plasma concentrations higher than 175 mg/l (1.0 mmol/l). The intravenous route is preferred, ensuring a more rapid increase of plasma vitamin C concentration [63].

Intravenous vitamin C at high doses has been used with good results in treating 50 moderate to severe COVID-19 patients in China. The doses employed varied between 10 g and 20 g daily, given for a period of 8–10 h. It was asserted that additional vitamin C dose may be required for patients found in critical conditions. This led to an oxygenation index improvement in real time, and all the patients finally cured and did not need further hospitalization [64].

High-dose (1.5 mg/kg body weight) vitamin C has been employed clinically for several decades. NIH panel also clearly showed that this amount is safe, being not accompanied by significant side effects [65,66]. The reactive oxygen species generated by the cytokine storm could be counteracted by administering 30–60 g vitamin C, while relatively high amounts of vitamin C can trigger chemotaxis of white blood cells (neutrophils, macrophages, lymphocytes, B cells, NK cells) [66]. Vitamin C proved its efficacy in SARS-CoV-2 treatment, due to its antioxidant ability, its antiviral and anti-inflammatory features, and capacity to trigger the immune response. Vitamin C can also help in elimination of the alveolar fluid that builds up during acute respiratory distress syndrome by preventing neutrophil activation and accumulation, and by lowering the impairment of the alveolar epithelium. An amount of 100 g in intravenous infusion proved safe [66]. A diminution of oxidative stress-induced acute inflammatory lung injury in mechanically ventilated patients was obtained by dietary antioxidant administration: both ascorbic acid and sulforaphane can lower hyperoxia-induced inflammatory acute lung injury by amplifying macrophage phagocytosis, via inhibition of airway high-mobility group box 1 protein (HMGB1) accumulation [67].

In a minireview approaching micronutrient combination, it was proved that vitamin C, vitamin D and selenium, result in prevention of virus spread, and reduce the disease progression towards severe stages [68]. High dose vitamin C administration can lower the required doses of corticosteroids, antibacterials and antiviral drugs. Vitamin C can also be efficacious in primary prevention of viral infections by triggering the inborn immune response, and may also prevent disease severity [69,70].

Vitamin C has the potential to alleviate immune response overactivation in COVID-19 patients. It was reported that inhibition of glyceraldehyde 3-phosphate dehydrogenase by high vitamin C doses, may reduce the hyperactivation of immune cells by low adenosine triphosphate production in the cells [71].

Using vitamin C against SARS-CoV-2 infections proved good results, in both prevention and treatment.

Another trial (ClinicalTrials.gov Identifier: NCT04335084), entitled A study of hydroxychloroquine, Vitamin C, Vitamin D, and Zinc for the prevention of Covid-19 infection (HELPCOVID-19), with 600 participants, will have as estimated completion period December 2021.

In conformity to U.S. National Library of Medicine, in June 2021, there were 65 ongoing trials regarding vitamin C treatment against SARS-CoV-2, of which only one has been finished, but the results have not been published yet [ClinicalTrials.gov Identifier: NCT04264533 *Vitamin C Infusion for the Treatment of Severe 2019-nCoV Infected Pneumonia: a Prospective Randomized Clinical Trial*]. 14 studies can be classed as “Not yet recruiting Studies”, 26 as “Recruiting Studies“, 4 as “Active, not recruiting Studies“, one as “Suspended Studies“, one as “Terminated”, 16 as “Completed“ and 3 are retired [72].

One of the studies (ClinicalTrials.gov Identifier: NCT04342728) has as main results: a total number of 214 patients were randomized, having a mean age of 45.2 (SD of 14.6) years and encompassing 132 (61.7%) women. For patients who were given a usual care without supplementation, a 50% reduction in symptoms was noticed, at a mean duration of 6.7 days (SD of 4.4), compared with 5.5 days (SD of 3.7) for the ascorbic acid group, 5.9 days (SD of 4.9) for the zinc gluconate group, and 5.5 days (SD of 3.4) for the group

that received both supplementations (overall P = 45). In this investigation, no significant difference in secondary results was obtained between the treatment groups. It was concluded that, in this clinical randomized trial focused on ambulatory SARS-CoV-2 patients, treatment with high-doses ascorbic acid, zinc gluconate, or combination of these two supplements did not significantly lower the duration of symptoms, when compared to standard. Several limitations were identified for this clinical trial, performed in a single health system: the absence of a placebo group, under-representation of elderly and of patients from ethnic groups, the open label characteristic of supplementation administered, the subjects being completely aware of the therapy administered. Ascorbic acid and zinc administered doses, although well tolerated, could be smaller than those required for reducing symptom duration; zinc requires ionophores to exhibit antiviral potential. Thus, it was inferred that the results cannot be generalized (extrapolated) to other health care environments/locations [73].

Another investigation (ClinicalTrials.gov Identifier: NCT04570254), encompassing 110 participants, focused on the administration of N-acetylcysteine, vitamin C, melatonin, and vitamin E. Antioxidant administration influence on the increase of the intracellular content of glutathione, reactive oxygenated species sequestration, membrane lipid protection, cytosol proteins, nuclear DNA and lipoprotein oxidation decrease was followed. The results have not yet been published.

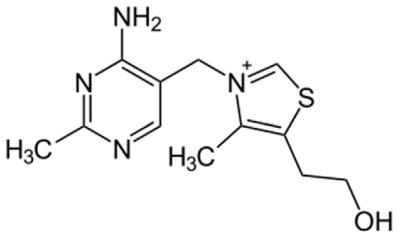
A study entitled Micronutrient status involved in immunity in elderly patients with COVID-19 (ClinicalTrials.gov Identifier: NCT04877509), comprising 229 subjects over 50 years age, follows the selenium, zinc, copper, vitamins A, D, E plasma concentrations during patient hospitalization. The results have not yet been published.

3.1.2. Vitamin B

B vitamins represent a class of water-soluble vitamins including B1 (thiamine), B2 (riboflavin), B3 (niacin), B5 (pantothenic acid), B6 (pyridoxine), B7 (biotin), B9 (folate) and B12 vitamin (cobalamin). These micronutrients are involved in the synthesis of erythrocytes, and function as cofactors in vital metabolic processes regarding sugar, amino-acids, fatty acid metabolism and DNA synthesis. Although their antioxidant role is not so largely documented as it the case of vitamin C and vitamin E, a series of studies report the antioxidant function, as well as immunomodulatory role of vitamin B group.

The antioxidant - prooxidant balance established by group B vitamins was assessed by the $AlCl_3$ method, based on the study of the behavior against hydroperoxide generation, in a linoleic acid peroxidation system. B1 and B2 vitamins, nicotinic acid and folic acid exhibited prooxidant activities in the early phase (one week) of the linoleic acid peroxidation reaction at concentrations comprised between 2.5 μM and 2.5 mM, but exerted significant antioxidant activities in the last phase of reaction (three weeks), in the same amounts. B12 vitamin did not have important influences during the early phases (one-two weeks), but showed enhanced antioxidant activities in the last reaction phase (three weeks). B6 vitamin showed antioxidant activity beginning with the early phase, and resulted in pronounced antioxidant influence in the last phase of reaction (3 weeks). Altogether, much more enhanced antioxidant activities of B group was noticed in the later phases of lipid peroxidation, when compared to earlier phases [74].

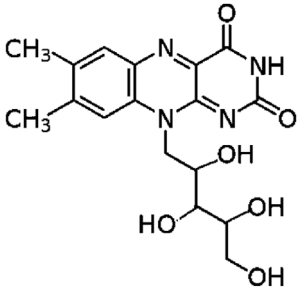
Thiamine (vitamin B1) is involved in energy release from carbohydrates, thermoregulation, fat synthesis, and is also required for appropriate functioning of the immune and nervous system [75,76]. Structurally, it presents a thiazolium ring and an aminopyrimidine ring connected by a methylene bridge.



Vitamin B1 exerts anti-inflammatory effect in macrophages, lowers oxidative stress - induced NF-kappa B activation [77] and alleviates pro-inflammatory cytokine release [78]. It has been found that thiamine deficiency impairs the immune system through enhanced inflammation, oxidative stress and metabolic imbalance [79]. By strengthening humoral and cell-mediated immunity, adequate thiamine levels can fight against SARS-CoV-2 viral infection [80].

Thiamine deficiency triggers ferritin expression in activated brain microglia, in vulnerable zones. Given its antioxidant power exerted in neutrophils, it protects −SH groups present at the cell's surface [81,82]. Vitamin B1 impairment may lead to unappropriate antibody response, and eventually more severe disease form. Therefore, appropriate thiamine supplies may promote an adequate immune response in SARS-CoV-2 infection. Thiamine also improves oxygen levels, by acting as a carbonic anhydrase isoenzyme inhibitor [83]. So, high-dose administration at early COVID-19 stages can lower hypoxia and hospitalization duration. Nevertheless, further data should be necessary to assess the beneficial role exerted by high thiamine levels in the treatment [80].

Riboflavin (vitamin B2, presenting an isoalloxazine ring linked to a ribitol moiety) is the precursor of flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), cofactors of flavoproteins [84]. Glutathione reductase, that keeps glutathione at its reduced form, essential for the endogenous antioxidant defense, is a flavoenzyme using FAD as a prosthetic group [85].



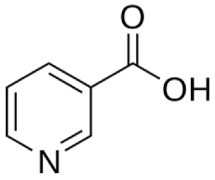
Minutious biochemical assays have proved that both riboflavin and FAD play a key role in modulating phagocytic NADPH oxidase, responsible for superoxide anion radical generation in reaction to infection [86].

Riboflavin triggers phagocytosis, as well as macrophage and neutrophil proliferation [87]. It lowers inflammatory responses by hampering neutrophil migration and infiltration, as well as aggregation of activated granulocytes at peripheral sites [88]. Inhibition of the lipopolysaccharide-induced reactive oxygen species generation and of NF-kB activation by riboflavin, leads to downregulation of TNF-α and nitric oxide in a series of experimental models [89]. Nevertheless, in a study focused on undifferentiated pro-monocytic lymphoma cells, it was proved that riboflavin did not influence cell proliferation or apoptosis [82,90].

Riboflavin in combination with UV radiation can contribute to the inhibition of pathogen replication by inducing irreversible

impairment to nucleic acids. This finding can be exploited to diminish pathogens in the blood plasma of COVID-19 patients, hampering virus transmission via transfusion [75].

Niacin or nicotinic acid (**pyridine-3-carboxylic acid**) (in its niacinamide or nicotinamide form) represents a component of NAD and NADP coenzymes, both involved in a plethora of metabolic pathways, mainly related to oxidoreductase activity.



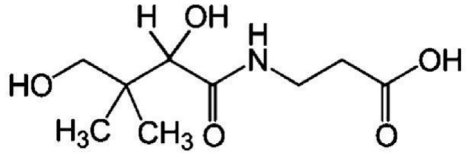
The roles exerted by niacin and nicotinamide-containing coenzymes in chronic systemic inflammatory processes linked to influenza viruses been revealed [91]. It has been reported that NAD^+ acts in the early stages of inflammation and is endowed with immunomodulatory features, including in stimulated alveolar macrophages [75], these properties encompassing diminution of pro-inflammatory cytokines, TNF-α, IL-1β and IL-6 [92–94], the latter constituting a therapeutic target enabling control on the cytokine storm in COVID-19 [82,95].

It has been found that sirtuin 1, a NAD^+-dependent deacetylase possessing anti-inflammatory features, suppresses proinflammatory cytokine generation. Sirtuin 1 overexpression or its activation by resveratrol, hampered TNF-α-induced acetylation of NF-κBp65 [96].

A series of in vitro, ex vivo and animal studies have showed the potential of nicotinamide to lower UV irradiation-induced immunosuppression, to promote DNA repair in keratinocytes and melanocytes, as well as to suppress inflammatory cytokines in keratinocytes [82,97]. Niacin lowers CXC chemokine and CXCL-8 (IL-8) induction, as well as neutrophil adherence and migration induced by leukotriene B4 lipid mediator in mice [75,98]. It diminishes monocyte chemoattractant protein 1 secretion induced by lipopolysaccharide (a Toll Like Receptor 4 agonist) [82] and lowers neutrophil infiltration, so exerts anti-inflammatory potential in ventilator-induced lung injury. In hamsters, both niacin and nicotinamide hamper lung tissue impairment [99].

Nicotinamide diminishes viral replication, as reported for human immunodeficiency virus, vaccinia virus, enteroviruses, hepatitis B virus. Considering the lung protective and immune boosting roles of niacin, it is recommended for inclusion as an adjunctive therapy against COVID-19 [80,100,101].

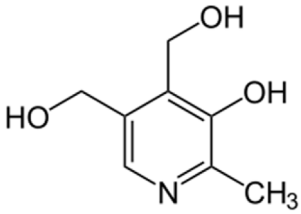
Pantothenic acid is an essential micronutrient involved in the synthesis of coenzyme A, vital for acylation reactions and participant in fatty acid and sugar (tricarboxylic acid cycle) metabolism [82].



Pantothenic acid exerts a series of functions, such as triglyceride and cholesterol-lowering properties, facilitates wound healing, lowers inflammation and has beneficial influences on mental health [79]. The role of pantothenic acid in the immune system has not been largely reviewed, as deficiency is very rare and availability in plants and animal is high, but it has been stated that this compound is worth further investigation [80,82].

Inflammatory properties of panthotenic acid have been reported, being mainly exerted indirectly, through its metabolites: coenyzme A catabolism gives rise to pantetheine that is depleted by pantetheinase, forming pantothenate and cysteamine, the latter having pro-inflammatory properties [102]. Cysteamine dissociates disulfide bonds leading to protein and γ-glutamylcysteine synthase inactivation, inhibiting the rate-limiting step in the synthesis of glutathione [82,103].

The three main forms of **vitamin B6** are pyridoxine presented below, pyridoxal and pyridoxamine, all presenting a pyridine ring as their core.



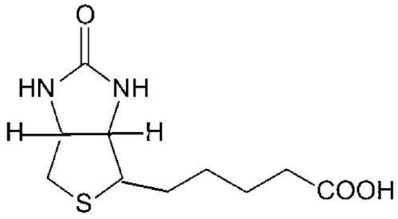
In the liver, they are converted to pyridoxal 5′-phosphate - a cofactor in a series of reactions relative to amino acid metabolism. Pyridoxal 5′-phosphate is also required for the enzyme reactions responsible for glucose release from glycogen.

The response to the virus often consists in high T cell response and secretion of pro-inflammatory cytokines [80]. In this context, vitamin B6 influences proliferation of immune cells, modulating inborn and adaptive immune function [104].

Pyridoxal 5′-phosphate is the active form of pyridoxine, and its deficiency leads to immune imbalance. It was found that pyridoxal 5′-phosphate alleviates the cytokine storm and inflammation in COVID-19. Pyridoxal 5′-phosphate level is inversely correlated with plasma IL-6 and TNF-α in chronic inflammation. During inflammation, there is an enhanced pyridoxal 5′-phosphate utilization, resulting in its depletion, pointing out that COVID-19 patients suffering from high inflammation may be exposed to deficiency [80]. Supplementation modulates immune response, lowering pro-inflammatory cytokines, preserving endothelial integrity and hampering abnormal platelet aggregation and hypercoagulability [105,106]. It has been reported that vitamin B6, as well as vitamins B2 and B9, trigger IL-10, a cytokine with strong anti-inflammatory and immunosuppressive potential, which can inactivate macrophages and monocytes, as antigen-presenting cells [90].

Vitamin B6 involvement in stimulating proliferation of blood and splenic lymphocytes has also been reported [82,107]. In conclusion, pyridoxine-based supplementation improves immune responses by lowering pro-infammatory cytokines' level, prevents hypercoagulability, sustaining endothelial integrity and leading to a relief of COVID-19 symptoms [75].

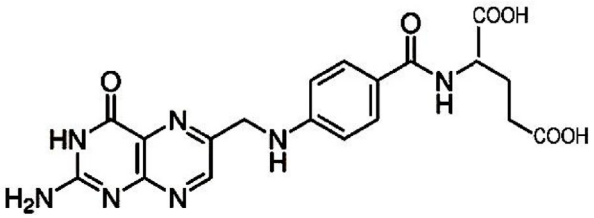
Biotin (vitamin B7) has a heterocyclic structure containing a tetrahydrothiophene cycle fused with a ureido group.



In the cellular medium, biotin is covalently bound to biotin carboxyl carrier protein, and is involved in a series of carboxylases/decarboxylase reactions important for gluconeogenesis, lipogenesis, fatty acid synthesis and catabolism of branched-chain amino acids such as valine and isovalerate [82]. As in the case of most B-group vitamins, biotin impairment is linked to a high level of inflammation [108]. Human monocyte-derived dendritic cells

cultured in a biotin-impaired growth medium, were characterized by elevated inflammatory cytokines, as response to lipopolysaccharide stimulation [108]. Biotin deficiency upregulates the expression of transcription factors such as NF-κB, proving the immunomodulatory role of biotin, alongside its involvement as cofactor in carboxylation/decarboxylation [109].

Folate (vitamin B9) is an essential micronutrient required for DNA and protein synthesis, being also involved in the adaptive immune response [75].



Folic (pteroyl-L-glutamic) acid, used as dietary supplement is converted to folate in the body. In conformity to the results of a meta-analysis, folic acid supplementation significantly lowers oxidative stress markers: an increase of serum glutathione concentrations and of total antioxidant capacity, alongside a decrease of malonyl dialdehyde concentration have been reported [110]. The improvement of antioxidant biomarkers following folic acid supplementation was explained by its directly exerted antioxidative influence, and by the diminution of homocysteine concentration [111]. Folic acid is a co-substrate in re-methylation reaction of homocysteine, which is converted to methionine [112].

Studies on primary human lymphocytes showed that folate deficiency diminishes cell proliferation and leads to DNA strand breaks, cell cycle arrest and apoptosis [113]. Folate impairment is also related to reduced human monocyte-derived dendritic cells maturation and effector functions, implying reduced TNF-α, IL-2, IL-6 and IL1-β, after lipopolysaccharide-induced inflammatory response. These alterations were associated with lowered $CD4^+$ T differentiation, and diminished T helper (Th1) and regulatory T cells (Treg) cell number [114]. Anti-inflammatory Treg cells can induce high expression of the folate receptor. Blocking this receptor eventually results in lowered Treg cell populations [82,115].

The investigation of the antiviral potential of folic acid showed its ability to inhibit furin (whose activity is responsible for bacterial and viral infections), and to subsequently block its binding by SARS-CoV-2 spike protein, so hampering viral entry and replication. In this manner, folic acid can help in the control of COVID-19-associated respiratory decay, at early stages [80,116]. Furin has become a target in antiviral therapy, due to its confirmed ability to act as promoter of coronavirus entry, by inducing sequence-specific dissociation of the spike protein, into S1 and S2 domains. Its interaction with folic acid consisting mainly in hydrogen bond formation, impacts both its structure and proteolytic ability [116]. Moreover, this nutraceutical establishes non-polar interactions with the key amino acids, that ensure interaction of spike protein with ACE-2 [117].

Detailed molecular docking studies proved that folic acid and its derivatives tetrahydrofolic acid and 5-methyl tetrahydrofolic acid have the ability to hamper viral entry. They can impede the interaction of spike protein with ACE-2 receptor, therefore, these compounds may be used as a therapeutic approach for the management of COVID-19. The computational method revealed that folic acid breaks the hydrogen bond between ASP30 residue of ACE-2, and spike protein. 5-methyl-tetrahydrofolic acid establishes hydrogen bond with ASP30 residue of ACE-2 receptor, and with LYS417 residue of spike protein [117].

Folic acid supports recycling of tetrahydrobiopterin and in this manner imparts protective effects against hypoxia-induced pulmonary hypertension. It was found that restoring the impaired function of endothelial nitric oxide synthase and subsequently the local nitric oxide generation, could protect from this complication of serious pneumonia, including in the picture of COVID-19 pathology. This observation is consistent with studies performed on human pulmonary artery endothelial cells and murine pulmonary arteries subjected to hypoxia, proving that folic acid restores uncoupled endothelial nitric oxide synthase and rehabilitates nitric oxide production [118,119].

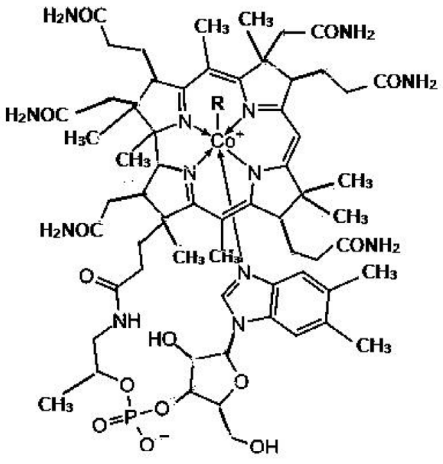
Given the significant role of folate described in cell metabolism and its pathologic implications in deficiency, studies on folate levels and on the impact of supplementation, were performed for hospitalized COVID-19 patients. It was found that diminished serum folate levels are often encountered among hospitalized patients with COVID-19 [120].

Detailed mechanistic studies have described that SARS-CoV-2 virus up-takes host folate and exploits one-carbon metabolism, following a post-transcriptional pattern, to sustain de novo purine biosynthesis, circumventing steps like viral blocking of host translation. Folate and glucose are consumed in SARS-CoV-2-infected cells, and viral replication is highly sensitive to the presence of compounds inhibiting folate and one-carbon metabolism, such as methotrexate [121].

Nevertheless, despite the above-detailed beneficial effects, in a published cohort study, no correlation could be found between seric folate amounts and clinical consequences: no significant discrepancy was noticed in the prevalence of hypoxemia, acute kidney injury, invasive ventilation, duration of hospital stay, and mortality, between subjects with lowered and adequate folate levels. The relevance of folate levels evaluation in hospitalized COVID-19 patients is stressed upon. Supplementation should be administered adequately, as to hamper a deficient status in the future. Further studies are required to assess the prevalence and consequences of folate deficiency in COVID-19 patients [120].

The most recognized adverse effect of supplementation or food fortification with folic acid, is its ability to hide B12 deficiency, especially as megaloblastic anaemia provoked by cobalamin deficiency can be repaired, but not its associated neurological effects, likely to be exerted on long term [122].

Vitamin B12 (known as cobalamin) is involved in erythrocyte synthesis, in the preservation of nervous system health, in myelin synthesis, cell growth and DNA synthesis. Its structure is one of a corrin-metal complex, encompassing a porphyrin ring with cobalt ion in its center, as presented below (R can be represented by methyl, hydroxyl, cyano or 5′-deoxyadenosyl group).



The active vitamin B12 forms are hydroxo-, adenosyl- and methylcobalamin. Vitamin B12 modulates gut microbiota, and its diminished levels increase homocysteine and methylmalonic acid amounts, leading to oxidative stress and promoting inflammation [94].

Excessive homocysteine levels associated to B12 deficiency result in endothelial dysfunction, platelet activation, coagulation, impairment of myelin sheath integrity, megaloblastic anemia and diminished immune response [123–126]. Vitamin B12 impairment may result in respiratory, gastrointestinal and central nervous systems disorders. SARS-CoV-2 impacts vitamin B12 metabolism, negatively affecting intestinal microbial proliferation [126].

High oxidative stress and lactate dehydrogenase levels, excessive homocysteine levels, coagulation cascade stimulation, vasoconstriction, pulmonary and renal vasculopathy, are symptoms associated to both vitamin B12 deficiency and COVID-19 infection [124,127].

Vitamin B12 is involved in the strengthening of colonic immune system and preservation of intestinal barrier function. Therefore, it promotes immunity, including against COVID-19 virus, as there has been reported that bifdobacteria and lactobacilli can promote immune response, also in the case of respiratory tract infections [75,128].

The ability of B12 vitamin to impart protective effects against multiple organ dysfunction was attributed to its antioxidant activity, as well as to its anti-inflammatory and immune-modulating potentials, encompassing control on cytokines and growth factors [129]. The complex mechanisms followed by B12 vitamin and transcobalamins, in lowering serious systemic inflammation that causes acute respiratory distress syndrome, have been described: quenching of reactive oxygenated or nitrogenated radicals, selective inhibition of inducible nitric oxide synthase and reduction of NO excess, protective effect exerted on reduced glutathione form, stimulation of oxidative phosphorylation, associated to the bacteriostatic role of transcobalamins during phagocytosis [129,130].

By regulating chemokine/cytokine generation and by modulating the intercommunication between immune cells that are part of pathophysiological pathways, vitamin B12 can impart protective effect against bacterial and viral infections [75,128].

Vitamin B12 decreases activation of NF-kB, a transcription factor signalling vitamin B12 deficiency. Moreover, methyl-cobalamin supresses interleukin-6 [129]. It has been reported that methylcobalamin supplementation has the potential to lower COVID-19-related symptoms and damage of organs [131].

High dose of B12 could be employed as viable therapeutical alternative to lower acute respiratory distress syndrome in COVID 19. It has been asserted that higher doses than those commonly used for routine parenteral or enteral nutrition, should be administered [132].

A cohort study performed in Singapore revealed that administering vitamin B12 (500 μg), vitamin D (1000 IU) and magnesium alleviated COVID-19 symptom severity and lowered the requirement for oxygen and intensive care support. Nevertheless, further and more extensive control trials, on large number of participants, would be necessary to establish the complete benefits of vitamin B12/vitamin D/magnesium in lowering COVID-19 severity [133].

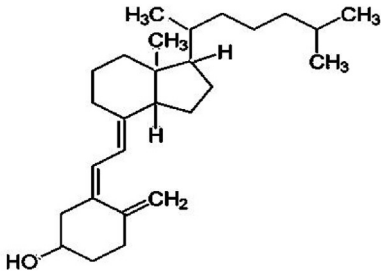
The involvement of vitamin B12 in the upregulation of immune cells, such as NK cells and $CD8^+$ T cells [134] led to the evaluation of the impact of various dietary folic acid and vitamin B12 levels on the immune response in aged rats: there was a major diminution in natural killer cell-mediated cytotoxicity for the vitamin B12 deficient group, as well as for the folic acid control group. A significant diminution was also noticed in the number of B lymphocytes (CD45 subtype) [135]. The age-induced B12 level reductions were the most enhanced after folate supplementation. It was concluded that NK cell activity was diminished by free unmetabolized folic acid, so achieving a proper balance between folate and B12 levels is highly important [82,135].

Establishing optimal dose, starting and duration of treatment, and the most efficient administration route, whether alone or combined with other micronutrients, are questions that still require optimization [129].

3.2. Liposoluble vitamins

3.2.1. Vitamin D

Posessing a structure related to that of cholesterol [136], vitamin D was described as a compound exerting an antioxidant role similar to, or even more enhanced than vitamin E [137].



Though the antioxidant character of vitamin D has been considered controversial [138], Wiseman [139] reported the ability of both secosteroids - vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol) - to act as membrane antioxidants and to achieve inhibition of iron-dependent lipid peroxidation. Ansari et al. [140] reported that vitamin D supplementation may be used to lower oxidative stress, whereas Mutlu et al. [141] revealed its neuroprotective and antioxidant properties, in a study involving neonates. Vitamin D3 improves the antioxidant defense systems, significantly decreasing oxidative stress [142].

Vitamin D deficiency was linked to the occurrence of insulin resistance and type 2 diabetes [143,144], cardiovascular complications [145], advancement of chronic kidney disease [146], and autoimmune diseases like type 1 diabetes [147]. Vitamin D can exert a significant role in the prevention of the previously-mentioned pathologies by regulating oxidative stress, inducing the expression of molecules that are part of the endogenous antioxidant defense (glutathione, glutathione peroxidase, glutathione reductase and superoxide dismutase) and suppressing the expression of NADPH oxidase, major superoxide generator [148].

Its relationship with other antioxidant compounds and aspects of oxidative stress has been studied. Vitamin D activates glutamate-cysteine ligase and glutathione reductase, increasing glutathione profile, hence endogenous antioxidant pool, lowering oxidative stress, and pro-inflammatory cytokine level, hampering harmful effects of cytokine storm [149–152].

Enhanced glutathione status after vitamin D and L-cysteine co-supplementation, proved a marked increase in vitamin D circulating form, 25(OH)D [153].

It has been concluded that glutathione presence in the treatment can attenuate vitamin D deficiency: restoring glutathione levels by L-cysteine administration can positively alter the level of methyltransferases and increase the expression of genes linked to vitamin D metabolism [154].

Glucose-6-phosphate dehydrogenase deficiency, noticed in African-American patients induces glutathione depletion and enhanced oxidative stress, as this enzyme catalyzes the rate-limiting step in the pentose phosphate pathway, which results in NADPH generation. The latter is involved in the recycling of

oxidized glutathione to its reduced (antioxidative) form. Impaired antioxidant activity and glutathione (GSH) depletion negatively affect vitamin D metabolism genes in the liver (25-hydroxylases, encoded CYP2R1, CYP27A1) and the kidneys (1-α-hydroxylase, encoded CYP27B1). This results in lowered levels of 25(OH)D (main circulating metabolite), and a diminution in the amount of active vitamin D form, 1,25(OH)2D [155].

Skin pigmentation is an essential factor regulating vitamin D3 synthesis, mainly under conditions of low solar light. Melanin absorbs UV photons, competing with 7-dehydrocholesterol, resulting in low vitamin D amounts. Although some alternative approaches do not embrace this theory, a reverse relationship has been accepted between cutaneous pigmentation and vitamin D synthesis, correlated to increased infection susceptibility [156]. It was inferred that the replenishment of glutathione and 25(OH)D can potentially lower oxidative stress, improve immunity, and alleviate adverse clinical effects of COVID-19 infection in the Afro-American population [155].

Alongside glutathione level improvement, vitamin D supplementation decreased reactive oxygen species level, monocyte chemotactic protein 1 and interleukin-8 secretion in U937 monocytes subjected to high-glucose levels [151].

The correlation between vitamin D deficiency, subsequent immune impairment and the occurrence of systemic infection has been detailed in several studies [157–160], and associated to inborn and acquired immunity, that are tuned by ligand-dependent vitamin D receptor functions [159]. Vitamin D exerts an immunomodulation role [161], increases inborn immunity by inducing antiviral peptide gene expression [161,162], and this improves mucosal defenses. Clinical studies proved that low levels of serum vitamin D were associated with acute respiratory tract infections, encompassing epidemic influenza [163–166], and correlated to impaired calcium absorbtion.

Hypocalcaemia is a status encountered in different infectious diseases, including SARS-CoV-2, as shown for 80% of hospitalized Italian patients and other study groups [167], and is associated with poor prognosis [168]. The virus uses free intracellular calcium for its replication [169] and for mediation of the fusion of its viral envelope, with the host's cellular membrane [170,171]. SARS-CoV E protein (envelope protein) generates Ca^{2+} - permeable channels in the endoplasmic-reticulum–Golgi intermediate compartment (ERGIC)/Golgi membranes. E protein ion channel activity alters calcium ion homeostasis in the cells, favoring NLRP3 inflammasome activation, which results in the overproduction of IL-1β. In this manner, SARS-CoV envelope protein Ca^{2+} channel activity plays a role in SARS-CoV-2 pathology, so it may constitute a therapeutic target [169].

Vitamin D deficiency corresponds to a 25(OH)D (25-hydroxyvitamin D) level smaller than 50 nmol/l and vitamin D-inadequacy is defined for a 25(OH)D amount comprised between 50 and 75 nmol/l. Higher blood levels of 25(OH)D are correlated to improved health status, as reported in clinical studies. A study performed on vitamin D - deficient mouse models, showed that co-supplementation with vitamin D and L-cysteine (as glutathione precursor) improved glutathione levels, also showing a significantly higher increase in the circulating 25(OH)D amount. This growth notably lowers oxidative stress, inflammatory biomarkers such as tumor necrosis factor alpha (as major pro-inflammatory cytokine released mainly from macrophages, to alert immune system) and insulin resistance, compared with supplementation with vitamin D only [149].

An independent correlation was illustrated between vitamin D sufficiency (25(OH)D greater or equal to 30 ng/mL) and lowered risk of negative clinical outcomes and mortality, in COVID-19. Patients with appropriate vitamin D levels had a diminished risk of hypoxia and unconsciousness. They had much lower blood levels of C-reactive protein inflammatory marker. This anti-inflammatory effect illustrated by low levels of C-reactive protein can prevent cytokine storm, explaining the diminished risk of severity and mortality of subjects who were vitamin D sufficient. The blood lymphocyte count in subjects with vitamin D deficiency is smaller than in case of patients with vitamin D sufficiency, these results pointing out that vitamin D appropriate levels promote immune function [172].

A series of mechanisms were described, underlying the potential beneficial effects of vitamin D on health outcomes in COVID pathology: modulation of the cytokine storm that results from activation of the renin-angiotensin system, modulation of neutrophil activity, protection of the pulmonary epithelial barrier, and promotion of epithelial repair [173–175].

Vitamin D deficiency lowers the expression of alpha-1-antitrypsin, a protease inhibitor exerting as main functions inhibition of neutrophil elastase, so leading to prevention of elastin impairment in the lungs [149].

Calcitriol, as vitamin D agonist, exerts protective effects, acting against acute lung injury by modulating the expression of components of the renin–angiotensin system such as ACE2 in lung tissue [176], these findings sustaining the significance of vitamin D deficiency as pathogenic factor in COVID-19.

Vitamin D receptors are largely distributed in immune cells (T cells, B cells, dendritic cells such as macrophages and monocytes) and epithelial cells found in the respiratory tract. 25-hydroxyvitamin D (25OHD, calcidiol or calcifediol), the main vitamin D circulating form can be transformed to the active form, 1,25-dihydroxyvitamin D (calcitrol) in the bronchial epithelium and immune cells [177]. The enzyme, D-1α-hydroxylase (encoded CYP27B1), necessary for vitamin D activation, is triggered by cytokines and toll-like receptor ligands. It was asserted that appropriate serum amounts of 25(OH)D are necessary to boost 1,25-dihydroxyvitamin D levels and promote the immune response against respiratory viral infections [160,178].

Activation of vitamin D 1-α hydroxylase in antigen-presenting cells, enables the antimicrobial mediator activity of calcitriol, in these cells [31]. Nevertheless, calcitriol lowers polymorphonuclear cells' activity [179].

Vitamin D can overcome the aggression of coronaviruses by strengthening physical barriers and promoting synthesis of antimicrobial peptides in the pulmonary epithelium [68].

1,25(OH)2D is synthesized in macrophages, following stimulation of toll-like receptors by the binding of the viral pathogen. Then it binds to the vitamin D receptor giving an increase in the synthesis of antimicrobial peptides endowed with antiviral potential [172,180].

Promotion of this synthesis of antiviral peptides such as β2-defensins and cathelicidin takes place in the respiratory epithelium, strengthening the defense ability at the level of the mucosa. Moreover, vitamin D lowers pro-inflammatory cytokine production, supports the inborn immune system and counteracts the overactivation of the adaptive immune system, subsequent to viral infection [160,181].

Recent studies describe the role of vitamin D in upregulating LL-37 (a cathelicidin endowed with antimicrobial properties, promotor of clearance of respiratory pathogens) that protects from SARS-CoV-2 infection, so it was concluded that this vitamin can help in treatment of COVID-19 disease. Surface plasmon resonance assay showed that LL-37 binds to SARS-CoV-2 spike protein, and inhibits its binding to hACE2 receptor, the viral entry in the cell [182].

The active vitamin D form also modulates the activity of invariant natural killer T cells, that are regulatory cells connecting inborn and adaptive immunity [183].

In processes linked to adaptive immunity, 1,25(OH)2D inhibits activation of B-cells [184].

Vitamin D stimulates macrophage differentiation, where it promotes CD14 and toll-like receptor expression, as well as CYP27B1 expression, required for synthesis of 1,25(OH)2D. It decreases the maturation of some types of sentinel cells (dendritic cells) that link the innate and adaptive immune systems. In this manner, it lowers dendritic cells' ability to function as antigen presenting cells, towards T and B lymphocytes. Vitamin D boosts the antimicrobial potential by tuning the inborn immune response, balancing T helper cells' defense ability against pathogens, and circumventing pro-inflammatory effects resulted from both inborn and adaptive immune responses [185–187].

Vitamin D helps in controlling T cell proliferation and differentiation, mainly discriminating between regulatory T cells and cytotoxic T cells [31]. Calcitrol activates T regulatory cells, endowed with anti-infective potential exerted by induction of IL-10 generation. This results in suppression of T helper 1 and T helper 17 cells, of γ-interferon, IL-17, IL-6, IL-23 and IL-2, and promotion of T helper 2 prevalence. Th2 cells counteract inflammatory processes by inhibiting tumour necrosis factor α, as well as Th1-mediated cytokines [87,172,183,188].

Hence, vitamin D immunomodulative activity implies lowered activity of Th1 cells and amplified Th2 response [31,189]. Vitamin D brings about a transfer from Th1 to Th2 phenotype, so it lowers Th1 cytokines but favors Th2 cytokines. As consequence, induction of anti-inflammatory cytokine synthesis such as IL-4, IL-5, IL-10 and IL-13, and inhibition of proinflammatory cytokines TNF-α, TNF-β, IL-1, IL-8, IFN-β, IFN-γ has been reported [33,179,190,191].

Studies were focused on the reduction of immune cell levels of interleukin 6, that acts both as pro-inflammatory cytokine and anti-inflammatory myokine. IL-6 is an important component of the cytokine storm, involved in B-cell differentiation, release of acute phase reactants and thermoregulation [31,192]. It represents a target in anti COVID-19 therapy. Interestingly, vitamin D lowers pro-inflammatory effects, and this takes place without targeting IL-6 receptors, thus circumventing any detrimental influence on the anti-inflammatory actions of IL-6 [192]. The anti-inflammatory potential of vitamin D also encompasses inhibitory effect on nuclear factor κB (NF-κB) activation by a mechanism involving vitamin D receptor interaction with the inhibitor of κB kinase β [193].

Vitamin D imparts protective effects against acute respiratory distress syndrome, as it suppresses renin expression and the angiotensin-converting enzyme/angiotensin II/Angiotensin II type 1 receptor axis, at the same time activating the angiotensin-converting enzyme 2/angiotensin 1–7/G protein-coupled Mas receptor 1 [171,176]. During this step, the above-described mechanism of intervention of vitamin D is highly important, as down-regulation of angiotensin-converting enzyme 2 in the viral context is detrimental, primarily in subjects with baseline ACE2 impairment linked to old age, diabetes, hypertension or cardiovascular disease [194]. This deficiency negatively affects the angiotensin-converting enzyme 2/angiotensin 1–7/G protein-coupled Mas receptor axis, impeding conversion of angiotensin II into anti-inflammatory angiotensin 1–7, at the same time activating cytokine storm, accompanied by tissue damage and acute respiratory distress syndrome [194,195].

Combining angiotensin type 1 receptor antagonists and vitamin D, has been suggested as a protective alternative against COVID-19-induced lung impairment. The mechanisms underlying beneficial effects are: the increase in angiotensin-converting enzyme 2 expression, inhibition of the renin-angiotensin system, and the suppression of the subsequent compensatory increment in renin levels. Renin inhibition decreases angiotensin I, precursor of pro-inflammatory angiotensin II and mitigates lung injury [196].

The study of directly exerted vitamin D antiviral potential revealed its ability to down-regulate furin activity and the associated transmembrane protease serine 2 precursor action, in this manner reducing the chances of coronavirus entry into the host cells. It has been described that furin expression is down-regulated via 1-α-hydroxylase, that is an important component in vitamin-D pathway, and modulates cellular calcium amounts. Moreover, in silico studies have shown that melanin intermediates are able to strongly bind to the active site of furin protease. Hence, a synergistic antiviral approach of melanin and vitamin D can be applied, by inactivating furin protease and enhancing both cellular and humoral immunity [156].

A series of trials focus on the impact of vitamin D administration. Hansdottir and Monick [197] showed that vitamin D deficiency is linked to viral respiratory tract infections and acute lung injury. High doses of 250,000–500,000 IU vitamin D proved safe in critically ill, mechanically ventilated patients, leading to increased levels of plasma 25(OH)D (>30 ng/mL, by day seven) and shortened hospital stay length [198].

Treatment with cholecalciferol, 500,000 IU, led to a major increase in hemoglobin concentrations in time, to reduction of pro-inflammatory cytokines, suppression of hepcidin transcription and improvement in circulating iron levels, to sustain erythropoiesis, in critically ill adults. However, more extended clinical trials regarding the influence of high-dose vitamin D3 on hemoglobin levels in critically ill subjects would be required, to confirm the beneficial effect of vitamin D on anemia (associated to a decrease in oxygen transport capacity), and the possibility of transfusion avoidance [199].

Ilie et al. [200] identified a negative correlation between vitamin D level and the number of COVID-19 cases in several countries: Iceland, Norway, Sweden, Finland, Denmark, the UK Ireland, the Netherlands, Belgium, Germany, France, Switzerland, Italy, Spain, Estonia, Czech Republic, Slovakia, Hungary, Turkey, and Portugal. This study also reported a negative correlation between vitamin D levels and the number of deaths provoked by COVID-19.

A series of observational studies suggest that vitamin D deficiency can have as consequence negative prognosis in COVID-19 patients. Hence, vitamin D may be applied as an adjuvant therapy. The mortality rate of hospitalized COVID-19 patients who presented serum 25-hydroxy vitamin D greater or equal to 10 ng/mL, was 5%. Patients with pronounced vitamin D deficiency (serum 25-hydroxy vitamin D lower than 10 ng/mL) had a 50% mortality rate after a hospitalization period of 10 days [201]. A positive correlation has been noticed between vitamin D deficiency and hospitalization, as well as illness severity. Vitamin D supplementation in deficient COVID-19 patients, might improve disease prognosis [202].

Cholecalciferol boosting therapy was linked to a lowered risk of COVID-19 mortality [203], and the administration of a high calcifediol dose of reduces the requirement for intensive care unit stay [204].

Nevertheless, in a systematic study, the authors opinate that vitamin D benefits illustrated in clinical reports are more linked to lowering COVID-19 severity, mortality and hospitalization length, and that richer data and more solid evidence would be required for intensive care unit admission, mechanical and non-invasive ventilation, or acute respiratory distress syndrome [175].

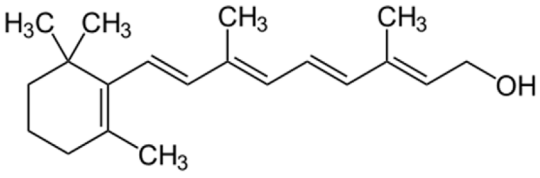
Nurshad [205] studied the correlation of vitamin D concentrations with COVID-19 cases and deaths per one million of the population in twenty European countries relying on the data present in the COVID-19 pandemic data portal, reported for 20 May 2020. The assessment showed negative correlation ($p = 0.033$) between mean vitamin D levels and COVID-19 cases per one million population in

European countries. Nevertheless, the correlation of vitamin D with COVID-19 deaths in these countries was not significant.

In a relevant review paper, it was reported that the pathophysiologic and mechanistic links between diabetes and COVID-19 are more evident when vitamin D levels are below 10 ng/ml. Diabetic patients are more exposed to "cytokine storm", in response to viral or bacterial infections. The unbalanced cellular and metabolic profile in diabetic Covid-19 patients encompasses a reduction in the peripheral counts of $CD4^+$ and $CD8^+$ T cells, with a parallel rise in proinflammatory $CD4^+$ T-helper 17 (Th17) cells. Acute phase reactants like serum ferritin, erythrocyte sedimentation rate, C-reactive protein, IL-6, are much more elevated in diabetics suffering from Covid-19 infection, compared to non-diabetic patients. This complex response to infection linked to both pathology and low vitamin D status, enhances hyperglycemia by antagonising insulin activity or by impairing the insulin secretion by beta-cells [206,207]. The presence of 1,25(OH)2D adequate levels results in control on this negative impact of cytokine storm, given the ability to trigger the native immune system (monocytes and macrophages), and to hamper the overactivation of the adaptive immune system (consisting of T-helper cells) [208]. With respect to vitamin D supplementation, it was inferred that this may be useful to attain 25(OH)D concentrations higher than 30 ng/mL, mainly in winter [209,210]. Nevertheless, vitamin D addition to foodstuffs like dairy or flour products [211,212] can elevate seric concentrations of the main circulating form by a few ng/mL, to reduce the risks of pronounced vitamin D deficiency and acute respiratory-tract infections [213,214]. Nevertheless, to obtain benefits, alongside vitamin D supplementation for deficient population, at health risk [213], the annual assay of serum 25(OH)D concentration would be recommendable [215].

3.2.2. Vitamin A

Vitamin A belongs to the class of fat-soluble retinoids that includes retinol, retinal and retinyl esters [216–218].



Retinoic acid is a key metabolite of *trans*-retinol, mediating functions necessary for growth and development, and regulating a series of aspects of immune function.

The antioxidant activity of vitamin A is imparted, just like in the case of carotenoids, by the hydrophobic structure made of polyene units, enabling singlet oxygen quenching [219].

The ability of retinol to act as an antioxidant via hydrogen atom donation has been reported. Nevertheless, a detailed mechanistic study revealed that radical adduct formation was the prevalent route involved in hydroperoxyl radical quenching by retinol [220].

15 mg/kg retinol acetate administration to intact rats resulted in improved antioxidant activity in the heart and hemolysate. Lowering in malonyl dialdehyde levels and promotion of the activity of glutathione-dependent enzymes was noticed. Nevertheless, administering retinol doses as high as 60 mg/kg resulted in subsequent tissue accumulation, associated to a prooxidant effect [221]. Pro-oxidant effects can also be induced at impaired vitamin A levels, as shown in an experimental study involving Wistar male rats. The binding activity of NF-kB proved more elevated in vitamin A-deficient rats than in controls. Including vitamin A in the diet of vitamin A-deficient rats diminished thiobarbituric acid reactive substances levels, nitrite concentration, inducible nitric oxide synthase, endothelial nitric oxide synthase and cyclooxygenase-2 expression, at the same time enhancing copper zinc superoxide dismutase and glutathione peroxidase activities [222].

Vitamin A is involved in supporting immune system, vision, and controls cell proliferation [216,223,224]. The dose recommended for children over one year and for adults with xerophthalmia is 200,000 IU, administered for two days [224]. For adults, toxicity is not common at such doses. Nevertheless, if acute toxicity occurs, it may encompass gastrointestinal problems, blurred vision, headaches and vertigo [225,226].

Retinoic acid and carotenoids act as immunomodulators, improving the acquired immune response to viruses. Moreover, vitamin A and its derivatives are endowed with antioxidant and surfactant-mediating properties, exerting protective effects in COVID-19 complications, such as acute respiratory distress syndrome [227]. Retinoids preserve epitelial cell integrity and function, boost specific and non-specific immunity, improve the level of mineral elements, being endowed with anti-infective potential [228].

Vitamin A triggers humoral immune response by controlling B-cell maturation, proliferation and differentiation, as well as immunoglobulin production [229,230]. It promotes proliferation of T cells, following a mechanism that involves increase of interleukin-2 [231]. Also, it strengthens the immune system by T cells differentiation [232–234] and by triggering immunoglobulin A synthesis required for immune response in mucosal tissues [231,235].

Vitamin A deficiency results in a diminution in the number and activity of innate lymphoid cells, including natural killer cells in peripheral blood, that play an essential role in activating the response against viral infection [236].

Ex vivo and animal studies reported that treating macrophages with retinoic acid can result in anti-inflammatory effects, lowering generation of IL-12 (promoter of IFN-γ and TNF-α secretion from T cells) and of other pro-inflammatory cytokines such as TNF-α, while promoting the regulatory cytokine IL-10 [237].

Studies performed on vitamin A-deficient mice showed decreased immunoglobulin A antibody and inconstant virus-specific $CD8^+$ T response after respiratory infection, that was correlated to a cytokine storm in the superior respiratory tract [238].

The involvement of retinoic acid in specifically modulating the pathogenesis of acute respiratory distress syndrome, encompasses impact on IL1-β and IL-1 receptor antagonist production by alveolar macrophages, as well as on lung infiltration of neutrophils [239]. In combination with simvastatin, its improves pulmonary regeneration, as shown in animal studies [240]. It could be inferred that vitamin A mediates the mechanisms related to the decrease of oxidative injury and to the regenerative capacity of the lungs [227].

The mechanism of vitamin A intervention in the treatment of COVID-19, was linked to its capacity to boost the immunity of the body, to anti-inflammatory features, that diminish the chances of cytokine storm occurrence, one factor accelerating acute respiratory distress syndrome [42]. Moreover, its ability to repair the epithelial tissue at the level of the respiratory tract, and prevention of fibrosis have also been confirmed [226,241].

A series of specific targets of vitamin A against COVID-19 were identified, their modulation leading to potentially positive effects: mitogen-activated protein kinase 1, interleukin 10, epidermal growth factor receptor, intercellular adhesion molecule 1, mitogen-activated protein kinase 14, catalase and protein kinase C - β [226,227,242–245].

So, vitamin A promotes inborn and adaptive immunity, as well as clearance of a primary infection, minimizing risks associated to secondary infections [241].

A cross-sectional study was performed in isolation centers for COVID-19 patients, involving a first group of 70 patients who were

given two doses of vitamin A (200,000 IU daily), and nebulized salbutamol and budesonide at three doses per day, from the beginning of admission. The second group of patients (also 70) did not receive vitamin A. The mean respiratory rate improved in the first group from 39.87 to 33.19 after 48 h, reaching 28.44 after 96 h. In the second group, the mean respiratory rate was 39.97 on the first day of admission, decreasing to 35.21 after 48 h, and to 34.73 after 96 h.

Regarding oxygen blood saturation (SPO2) measured for the first group of patients, the mean SPO2 ameliorated from 77.84 on the first day, to 89.53 after 48 h, and to 93.08 after 96 h. In the second group (no vitamin A), the mean SPO2 at admission was 78.57, changing at 80.72 after 48 h, but lowering to 75.31 after 96 h.

There were two reported deaths (2.86%) among the first group patients who received vitamin A and nebulizers, whereas 14 deaths (20%) were reported among the second group who did not receive vitamin A [226,246].

COVID-19 leads to inflammatory status, especially in lung, liver, and kidney, which promotes depletion of vitamin A stores. Hence, supplementation aims at restoring an appropriate status, hampering life threatening condition [247,248].

The presence of vitamin A being essential for normal lung functioning and for restoring lung tissue after injury [249], it was found that vitamin A adequate levels may be highly important during recovery from COVID-19 [241].

Under these circumstances, critical discussions were detailed and directed towards the importance of adequately timed supplementation, with important aspects stressed upon: despite the existence of an appropriate vitamin A stored amount in the organism prior to infection, the occurrence of SARS-CoV2 infection can reduce these vitamin A stores. Vitamin A deficiency caused by infection can negatively affect the ability of the lung in restoring impaired epithelial surfaces, that is likely to lead to lung fibrosis and diminished pulmonary capacity. So, vitamin A supplementation during recovery may be necessary, however, administration in early stages of infection may not be advisable, especially in the absence of vitamin deficiency prior to infection, as it has been reported that it may result in unforeseeable, and opposite outcomes. The ability of all-transretinoic acid to upregulate the expression of ACE2 [250,251] is related to increased levels of ACE2 after vitamin A supplementation, with two effects: in subjects already presenting appropriate vitamin A stores, it can increase the risk of SARS-CoV2 infection upon exposure to the virus [252]; or, this activation of ACE2 can lower the risk of sympathetic overactivation noticed in severe forms of SARS-CoV2 infection that affects obese and diabetic patients [241,253–255].

By reversing the effect induced by the virus on ACE2 expression, vitamin A not only minimizes COVID-19 adverse effects on the angiotensin system, but also minimizes medication-related adverse effects [228,241].

3.2.3. Vitamin E

The term vitamin E refers to a class of liposoluble compounds, comprising tocopherols and tocotrienols, all presenting a chromanol ring.

Alpha-tocopherol is the main protector of cell membranes' integrity against lipid peroxidation, hampering low-density lipoprotein free radical damage. It has the ability to stop the radical chain, and can quench singlet oxygen [12,18].

Vitamin E traps reactive species generated from oxidative stress [256–258], so it was asserted that vitamin E antioxidative and therapeutic features can be applied to prevent oxidative burst associated with the SARS-CoV-2 [228,259–261].

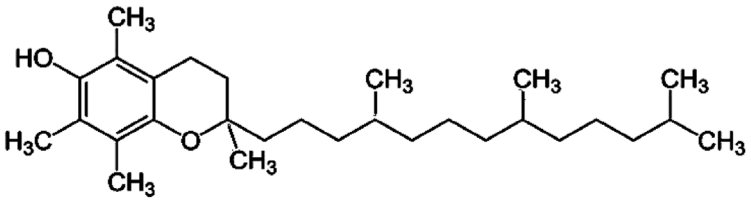
α-tocopherol interacts with lipid peroxyl radical by hydrogen donation [262]. The resulted α-tocopherol-corresponding radical form, traps another lipid peroxyl radical via radical-radical coupling, yielding a non-radical adduct [263]. Hence, two peroxyl radicals can be quenched by one α-tocopherol molecule [264].

Due to their antioxidant virtues, vitamin E and its derivatives can protect cell membranes, and can enhance the adaptive immune response to viral infections occurring in the respiratory system [227].

Vitamin E, mainly in the form alpha-tocopherol, hampers oxidation of membrane polyunsaturated fatty acids, controls reactive oxygen and nitrogen species generation, and modulates signal transduction [265]. It is involved in suppression of platelet aggregation, lowers macrophage proliferation, and diminishes superoxide level in neutrophils and macrophages. Also, it enables inhibition of protein kinase C activity by promoting protein kinase C-alpha dephosphorylation, via activation of protein phosphatase 2A [228,266]. With respect to the inhibition of protein kinase C activity, it has been reported that α-tocopherol is more efficacious than β-tocopherol, which was assigned to the interaction with a particular enzyme isoform. Moreover, the α form posesses a better ability to inhibit the lipoxygenase pathway [265,267].

The ability of vitamin E to inhibit lipoxygenase is the mechanism underlying its antiferroptotic effect, that encompasses hampering of cell death provoked by iron-dependent lipid peroxides' accumulation. The reduction of the ferric iron center present in the structure of 15-lipoxygenase, gives rise to ferrous ion, resulting in enzyme activity inhibition. Moreover, vitamin E reacts with peroxyl radicals, preventing lipid hydroperoxides' accumulation. Other antioxidants such glutathione, glutathione peroxidase (GPx4), deplete oxidized lipids, in this manner inhibiting ferroptosis activation. In case of GPx4 deficiency, vitamin E can participate in this detoxification. Alpha-tocopherol hydroquinone was reported as a more powerful antioxidant form than alpha-tocopherol [268].

Vitamin E importance in preserving the antioxidant pool and its ability to counteract endogenous antioxidant species' deficiency has been discussed: in the case of glutathione deficiency, vitamin E is involved in elimination of electrophilic compounds resulting from lipid peroxidation, and hampers the oxidation of protein cysteine residues, preserving membrane integrity. Vitamin E supplementation at a dose as high as 500 ppm may result in lipoxygenase and peroxyl radicals inhibition, hampering ferroptosis, that in COVID-19 is associated to multiple organ damage in lung, heart, kidney, liver, gut and nervous system. Its ability to lead to viral clearance and hamper inflammation through T cells modulation, has also been reported [269].



Even though no direct antiviral potential has been linked to vitamin E, this major liposoluble antioxidant lowers inflammatory cytokine production and favors T cell proliferation and differentiation [228]. The capacity of vitamin E to boost immune response in both animal and human models has been reported, relying on mechanisms such as T-lymphocyte signal initiation, lowered nitrogen oxide production resulting in prostaglandin E2 inactivation and inhibition of cyclooxygenase-2 [227,270].

As in the case of other vitamins, vitamin E deficiency negatively affects adaptive responses regarding both humoral and cellular immunity, as these compounds are involved in the proliferation and differentiation of B and T cells and maintain the balance T helper cell type 1/T helper cell type 2 [229,271].

The higher levels of lipid peroxidation noticed in vitamin E deficiency are consistent with the reported reverse relationship between plasma lipoperoxidase and vitamin E in acute respiratory distress syndrome [272–274].

Vitamin E supplementation promotes leukocyte phagocytic activity, natural killer cell and neutrophil function [275]. The direct scavenging of oxidative species, the modulation of oxidative eicosanoid pathways and prostaglandin synthesis, the inhibition of inflammatory mediators, contribute to lowering inflammatory responses in various tissues, including the lungs [228,276].

The anti-inflammatory and immunomodulatory roles of different vitamin E forms have been compared. α-tocopherol hampers interleukin-1 release from the cells by inhibition of 5-lipoxygenase, effect noticed in activated monocytes of vitamin E-supplemented subjects [261,267]. Moreover, despite a comparable anti-inflammatory potential of α and β isomers, α-tocopherol could more efficiently lower pro-inflammatory IL-β, effect ascribed to the better ability of the α form, to inhibit the lipoxygenase pathway [265,267].

Among different vitamin E isomer forms, γ-tocotrienol is a powerful inhibitor of TNF-induced NF-κB activation [277] and proved the most effective in inhibiting IL-6 in macrophages, by suppressing lipopolysaccharide-induced activation of NF-κB [278]. On the other hand, no impact has been noticed on IL-10, an anti-inflammatory cytokine [278–280].

γ-Tocopherol, as well as its metabolite (γ-gamma-carboxyethyl hydroxychromane), are endowed with anti-inflammatory features, observation confirmed by in vitro studies, showing that stimulated macrophages and epithelial cells treated with γ-tocopherol have decreased cyclooxygenase-2 activity and lowered levels of prostaglandin E2 [261,281].

Shibata et al. reported the antiangiogenic effects of δ-tocotrienol in human umbilical vein endothelial cells, and also showed that α-tocotrienol lowered δ-tocotrienol-induced cytotoxicity [282].

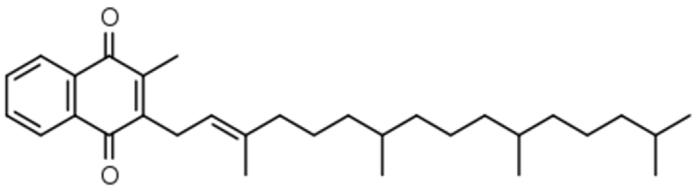
Gamma-tocopherol, delta-tocopherol and gamma-tocotrienol exert effects that result from both their antioxidant and anti-inflammatory potential. These compounds can scavenge reactive oxygenated and nitrogenates species, hinder eicosanoid formation catalysed by cyclooxygenase-2 and 5-lipoxygenase, suppress NF-kB and STAT proinflammatory signaling [283].

Moller and Lauridsen [284] proved that dietary fish oil supplemented at an amount of 5% of the diet administrated, but not mere vitamin E supplements, lowered the inflammatory responses of alveolar macrophages isolated from weaned pigs.

In a clinical study on the beneficial effects imparted by vitamins C and E in COVID-19 patients, it was concluded that, these vitamins did not result in a significant improvement compared to the control group, at all parameters followed, the significant differences being noticed only with respect to respiratory rate and lymphocyte count - lower in the supplementation (vitamin C and vitamin E) group, when compared to control. Although not classed as significant effects, diminished treatment failures and reduced hospital stay, observed in the intervention group, are worth mentioning. Future studies would be required, with appropriately established dosage and numbers of subjects, to definitely conclude about the benefits of these vitamins in COVID-19 [285].

3.2.4. Vitamin K

Vitamin K, fat-soluble vitamin, participates in the synthesis of several proteins involved in coagulation – factor II (prothrombin), factors VII, IX, and X [286]. There are two natural vitamin K forms: K1 (phylloquinone, presented below), present in green leafy vegetables, and K2 (menaquinones) [228,287]



Vitamin K and vitamin K-dependent proteins are also involved in calcification (preserving bone and cardiovascular health), energetic metabolism and inflammation [287,288]. Vitamin K exerts its powerful antioxidant ability, lowering the lipid peroxidation in the cell by producing vitamin K-hydroquinone, an efficacious radical scavenging species [289,290]. Vitamin K modulates NF-KB signaling, exerting an anti-inflammatory activity [291].

Vitamin K catalyzes γ-carboxylation reactions, converting glutamic acid moieties into γ-carboxyglutamic groups. It activates hepatic procoagulant factors II (prothrombin), VII, IX and X. Nevertheless, vitamin K also promotes the activities of anticoagulant proteins C and S, as well as of a series of extrahepatic proteins that are not involved in blood coagulation. These complex activities were discussed also in relationship with COVID-19 [292].

Patients in the intensive care unit are at risk of vitamin K deficiency, presenting high D-dimer protein levels. This deficiency lowers the functional coagulation factors II, VII, IX, and X, with predisposition towards coagulopathy, increase of hemorrhage risk [293,294] and disseminated intravascular coagulation. The latter has been confirmed as a major contributor to multi-organ system failure, because of the accumulation of thrombi in the microvasculature [295]. Also, it has been asserted that low vitamin K levels may be linked to increased elastin degradation [296,297], that prevalently affects lung tissue, resulting in breath difficulty. Comorbidities associated to COVID-19 severity such as type II diabetes, cardiovascular diseases, or hypertension, are related to impaired vitamin K levels. So, it is thought that low vitamin K levels might be linked to disease severity in COVID-19, and that supplementation might lower complication risk [228,294,298–300].

COVID-19 induces venous and arterial thromboembolic complications due to enhanced inflammation, hypoxia, and diffuse

intravascular coagulation. It results in blood clotting occurrence and the degradation of elastic fibers in the lungs [75]. Matrix Gla, a protein which is vitamin K2-dependent, inhibits degradation of elastic fibers and, given this required protective effect, its level becomes increased in the lungs of SARS-CoV-2 patients, which eventually leads to the utilization of extrahepatic vitamin K deposits [301]. Moreover, vitamin K1 activates hepatic coagulation factors, to overcome thrombotic complications [302].

In SARS-CoV-2 pneumonia, the requirement for vitamin K, to additionally carboxylate Matrix Gla protein, increases. This enhanced vitamin K utilization linked to extrahepatic vitamin K insufficiency, leads to improper carboxylation of pulmonary Matrix Gla protein and advanced pulmonary damage. Another consequence of extrahepatic vitamin K impairment is inadequate carboxylation of endothelial protein S, which promotes the risk of thrombosis [292].

Therefore, pneumonia-induced vitamin K exhaustion, leads to a diminution in activated Matrix Gla protein and protein S activities, worsening lung damage and coagulopathy. Improper Matrix Gla protein activation, results in unprotected elastic fibres, from SARS-CoV-2-induced proteolysis. Nevertheless, activated factor II is kept at normal level even in Covid-19 context, which is consistent with previous reports proving that vitamin K is mainly transported to the liver, to activate of procoagulant factors [292].

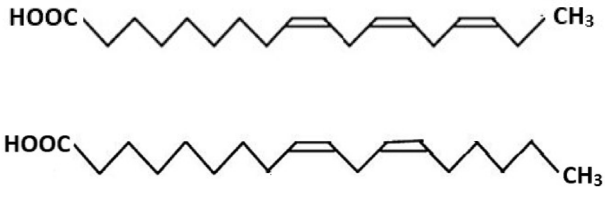
In case of COVID-19-induced coagulopathy, employing an anticoagulant is often considered. Unfractionated heparin has been reported as a better choice than low molecular weight heparin [303]. Vitamin K antagonists induce vitamin K deficiency, subsequently blocking carboxylation of hepatic procoagulant factors, which retards blood clotting. Apart from this beneficial antithrombotic function, they can also exacerbate lung fibrosis, likely by impeding anticoagulant protein C and S activation, both with confirmed antifibrotic activity [304,305]. So, this may result in negative effects on pneumonia severity in Covid-19 patients, but this reported result still needs confirmation in further studies [292].

Long term use of broad-spectrum antibiotics such as cephalosporins, can interfere with vitamin K synthesis and absorption at the gastrointestinal tract level, which should be carefully be taken into consideration during this infection [306].

Inspite of the previously explained shortcomings of vitamin K deficient amounts in COVID-19 pathology, further studies should be necessary to determine whether vitamin K administration alleviates severity [228]. Further experimental evidence is required, to establish the definite role of vitamin K inclusion in treatment protocols [292].

3.2.5. Vitamin F

This name does not refer to a traditional vitamin, and designates a mixture of two essential fatty acids: alpha-linolenic acid (omega 3) and linoleic acid (omega 6).



Even though they do not act as antivirals, these compounds are recognized for the ability to impart protective effects against lung damage.

Supplementation with conjugated linoleic acid can lower the inflammatory markers and improve the health status in chronic obstructive pulmonary disease: an increase in sirtuin and a decrease in IL-6 serum levels were noticed, both statistically significant [307].

Alpha-linolenic acid can protect against lipopolysaccharide-induced acute lung injury due to its anti-inflammatory and antioxidant features. Alpha-linolenic acid significantly lowered the infiltration of neutrophils, and improved macrophage number. Important inhibition of the secretion of proinflammatory cytokines, TNF-α, interleukin-6 and interleukin-1β and parallel increase of anti-inflammatory cytokines, have been noted. Alpha-linolenic acid decreased the levels of myeloperoxidase and malondialdehyde, and restored endogenous antioxidants' profile (glutathione and superoxide dismutase) that was impaired by lipopolysaccharide-induced acute lung injury. Alpha-linolenic acid alleviated lipopolysaccharide-induced histopathological alterations and apoptosis. Furthermore, in acute lung injury, alpha-linolenic acid majorly inhibited IκBα (nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha) phosphorylation and NF-κB p65 activation. It was suggested that alpha-linolenic acid protective effects, involve NF-κB pathway [308].

Alonside protective effects exerted on human respiratory tract, alpha-linolenic acid is likely to boost the expression of glucose transporter-4 gene, mitigating the negative impact of adipose tissue on COVID-19 prognosis. These reported results need further confirmation, nevertheless, they stress upon the importance of the diet in avoiding illness severity [309].

The next table (Table 2) summarizes the main findings relative to the intervention of each vitamin in the approached pathology, either by directly impacting the virus or by alleviating the associated hyperinflammation and oxidative stress markers.

In Table 3, the impact of each vitamin on SARS-CoV-2 infection, in either preventing or alleviating illness severity, is resumed.

4. Critical conclusions and prospects

The pathogen triggers both pro-oxidant and pro-inflammatory pathways, so infectious diseases are associated to decreased endogenous antioxidant profile, including vitamins, increase of oxidative stress markers, and boost of pro-inflammatory cytokines. Immune cells become sources of oxidative species. This type of pathology involves a vicious cycle, in which oxidative stress results in inflammatory responses by activating transcription factors linked to inflammation. In turn, cytokine storm and sepsis enhance oxidative stress through the action of inflammatory mediators and, consequently, promote endothelial dysfunction [310,311].

In this context, the antioxidant role of vitamins consists in hampering oxygenated and nitrogenated species occurrence, suppression of NADPH oxidase pathway, but also contribution to antioxidant pool replenishment, as illustrated for instance by the relationship between vitamin D supplementation and glutathione profile [148,154].

Trapping oxygenated and nitrogenated species proved beneficial, nevertheless each particular micronutrient's roles and mechanisms of intervention have to be carefully considered, under specific conditions: restoring the impaired function of endothelial nitric oxide synthase and subsequently the local nitric oxide generation by folic acid, could protect from complications of severe pneumonia including in the picture of COVID-19 pathology [118,119].

Vitamins fight against oxidative burst, this role being complemented by their anti-inflammatory activities. Suppression of pro-inflammatory cytokine release, including IL-6, IL-2, IL-8, IL-12, interferon-gamma, TNF-α, NF-kB, etc, has been reported. Thus, the overactivation of immune response leading to disease severity is counteracted. Vitamins are endowed with immunomodulatory potential, proved by their ability to tune the responses of immune

Table 2
An overview of the main findings describing each vitamin's intervention in coronavirus.

Vitamin	Specific intervention	References
C	promotion of lymphocyte activity, boost of interferon-α production, modulation of cytokines, lowering inflammation, counteracting endothelial dysfunction, and improving mitochondrial function	[51,53]
	control on the proliferation and functioning of T lymphocytes and B lymphocytes, as well as on the activity of natural killer cells, impeding the progression of cytokine storm and boosting the host's immune system	[54,55]
	promotion of immunoglobulin production	[55]
	triggering of chemotaxis of white blood cells (neutrophils, macrophages, lymphocytes, B cells, NK cells)	[33,66]
	enhancement of phagocytosis and inhibition of necrosis	[31]
	modulation of alveolar fluid clearance, resulting in improvement of lung epithelial barrier function and lowering of acute respiratory distress symptoms	[58,59]
	inhibition of glyceraldehyde 3-phosphate dehydrogenase at high doses; this leads to prevention of hyperactivation of immune cells by low adenosine triphosphate production in these cells	[71]
	promotion of the antiviral activity of other antioxidants such as quercetin, that impacts virus entry and replication	[44]
B1	anti-inflammatory effect in macrophages, lowering of oxidative stress induced NF-kappa B activation and alleviation of pro-inflammatory cytokine release	[77,78]
	strengthening of humoral and cell-mediated immunity	[80]
	improvement of oxygen levels, by acting as a carbonic anhydrase isoenzyme inhibitor	[83]
B2	modulation of phagocytic NADPH oxidase, responsible for superoxide anion radical generation in viral infection	[86]
	triggering of phagocytosis, as well as of macrophage and neutrophil proliferation	[87]
	lowering of inflammatory responses by hampering neutrophil migration and infiltration, as well as aggregation of activated granulocytes at peripheral sites	[88]
	inhibition of the lipopolysaccharide-induced reactive oxygen species generation and of NF-kB activation, resulting in downregulation of TNF-α and nitric oxide	[89]
	inhibition of pathogen replication by induction of nucleic acid impairment	[75]
B3	involvement in the incipient stages of inflammation; immunomodulatory potential, including in stimulated alveolar macrophages	[75]
	diminution of pro-inflammatory cytokines, TNF-α, IL-1β and IL-6 (a therapeutic target allowing control on the cytokine storm in COVID-19)	[82,92–95]
	lowering of CXC chemokine and CXCL-8 (IL-8) induction, as well as of neutrophil adherence and migration induced by leukotriene B4 lipid mediator in mice	[75,98]
	diminution of monocyte chemoattractant protein 1 secretion induced by lipopolysaccharide and lowering of neutrophil infiltration, hence anti-inflammatory potential in ventilator-induced lung injury	[82,99]
	lung protective and immune boosting roles	[80,100,101]
B5	essential micronutrient involved in counteracting inflammation	[79]
B6	impact on proliferation of immune cells, modulating inborn and adaptive immune function	[104]
	triggering of IL-10, endowed with strong anti-inflammatory activity, enabling inactivation of antigen-presenting cells	[90]
B7	immunomodulatory potential proved by reported elevated inflammatory cytokines and NF-κB upregulation, at biotin-impairment	[108,109]
B9	furin inhibition with subsequent hindrance of its binding by SARS-CoV-2 spike protein, resulting in circumvention of viral entry and replication	[80,116]
	cleavage of the hydrogen bond between ASP30 residue of ACE-2, and spike protein	[117]
B12	lowering systemic inflammation that causes acute respiratory distress syndrome	[129,130]
	decrease of NF-kB activation	[129]
	suppression of interleukin-6 by methylcobalamin	[129]
	upregulation of immune cells, such as NK cells and $CD8^+$ T cells	[134]
D	activation of glutamate-cysteine ligase and glutathione reductase, increasing reduced glutathione profile, hence endogenous antioxidant pool, lowering oxidative stress and pro-inflammatory cytokine level, hampering cytokine storm	[149–152]
	modulation of neutrophil activity, protection of the pulmonary epithelial barrier, and promotion of epithelial repair	[173–175]
	prevention of elastin impairment in the lungs	[149]
	modulation of the expression of the components of the renin–angiotensin system such as ACE2 in lung tissue	[176]
	promotion of antiviral peptide gene expression	[161,162]
	upregulation of LL-37, promotor of clearance of respiratory pathogens	[182]
	control on T cell proliferation and differentiation, mainly discriminating between regulatory T cells and cytotoxic T cells	[31]
	induction of anti-inflammatory cytokine synthesis such as IL-4, IL-5, IL-10 and IL-13, and inhibition of proinflammatory cytokines TNF-α, TNF-β, IL-1, IL-8, IFN-β, IFN-γ	[33,179,190,191]
	inhibitory effect on NF-κB activation	[193]
A	control on B-cell maturation, proliferation and differentiation, as well as on immunoglobulin production	[229,230]
	promotion of T cells proliferation, following a mechanism that involves increase of interleukin-2	[231]
	promotion of inborn and adaptive immunity, as well as clearance of primary infection, minimizing risks associated to secondary infections	[241]
	strengthening of the immune system by T cells differentiation and by triggering immunoglobulin A synthesis required for immune response in mucosal tissues	[231–235]
	lowering generation of IL-12 (promoter of IFN-γ and TNF-α secretion from T cells) and of other pro-inflammatory cytokines such as TNF-α, while promoting the regulatory cytokine IL-10	[237]
	the ability to counteract severe effects by modulation of: mitogen-activated protein kinase 1, interleukin 10, epidermal growth factor receptor, intercellular adhesion molecule 1, mitogen-activated protein kinase 14, catalase and protein kinase C-β	[226,227,242–245]
E	direct scavenging of oxidative species such as peroxyl radicals and inhibition of the lipoxygenase pathway, modulation of oxidative eicosanoid pathways and of prostaglandin synthesis, inhibition of inflammatory mediators, lowering inflammatory responses in the lungs	[228,265,267]
	boosting of immune response relying on mechanisms such as T-lymphocyte signal initiation, lowered nitrogen oxide production, resulting in prostaglandin E2 inactivation and inhibition of cyclooxygenase-2	[227,270]
	promotion of leukocyte phagocytic activity, of natural killer cell and neutrophil function	[275]
	involvement in the proliferation and differentiation of B and T cells, as well as in the balance T helper cell type 1/T helper cell type 2	[229,271]
	hampering of interleukin-1 release from activated monocytes by inhibition of 5-lipoxygenase; the α form could more efficiently lower pro-inflammatory IL-β, effect ascribed to the better ability to inhibit the lipoxygenase pathway	[261,265,267]
	γ-tocopherol confirmed as most active in inhibiting IL-6 in macrophages, by suppressing lipopolysaccharide-induced activation of NF-κB	[278]
K	lowering of lipid peroxidation by vitamin K-hydroquinone, an efficacious radical scavenging species	[289,290]
	modulation of NF-KB signaling, exerting an anti-inflammatory activity	[291]
	inhibition of degradation of elastic fibers by controlling Matrix Gla, vitamin K2 dependent protein	[301]
	activation of hepatic coagulation factors by vitamin K1, overcoming thrombotic complications	[302]
	proper extrahepatic vitamin K levels linked to adequate carboxylation of endothelial protein S, which lowers the risk of thrombosis	[292]

Table 2 (*continued*)

Vitamin	Specific intervention	References
	appropriate vitamin K levels lead to activation of both Matrix Gla protein and protein S, overcoming worsening in lung damage and coagulopathy	[292]
F	lowering of oxidative stress and inflammatory markers and improvement of the health status in chronic obstructive pulmonary disease	[307]
	increase in sirtuin and decrease in IL-6 serum levels, both statistically significant	[307]
	enhanced inhibition of IκBα (nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha) phosphorylation, as well as of NF-κB p65 activation by alpha-linolenic acid	[308]

cells and to inactivate antigen-presenting cells [90].

Direct antiviral activities mainly include synthesis of antiviral peptides [68,172,180], modulation of angiotensin-converting enzyme 2 receptor expression and interaction with spike protein [171,176,196], inactivation of furin protease to hamper virus entry into the host cell [116,156], or inhibition of pathogen replication by

Table 3
A summary of the impact of vitamins on SARS-CoV-2 infection.

Vitamin	Impact	References
C	reduces the intensive care unit period by 8% and lowers the duration of mechanical ventilation in critically ill subjects	[60,61]
	boosts the intracellular content of glutathione, improves reactive oxygenated species sequestration, membrane lipid protection, cytosol protein content	ClinicalTrials.gov Identifier: NCT04570254)
	reduction of immune cells' hyperactivation	[71]
	in combination with zinc, is involved in reducing symptom duration	[73]
	proved its efficacy in SARS-CoV-2 treatment, due to its antioxidant, antiviral and anti-inflammatory potentials, and to the ability to trigger the immune response	[45–47] [51–53]
B	high-dose administration of B1 vitamin at early COVID-19 stages can lower hypoxia and hospitalization duration	[80]
	thiamine promotes an adequate immune response in SARS-CoV-2 infection and improves oxygen levels	[83]
	riboflavin in combination with UV radiation can contribute to the inhibition of pathogen replication	[75]
	nicotinamide diminishes viral replication, as reported for human immunodeficiency virus, vaccinia virus, enteroviruses, hepatitis B virus; it is recommended for inclusion as an adjunctive therapy against COVID-19	[80,100,101]
	the active form of pyridoxine (pyridoxal 5′-phosphate) lowers the cytokine storm and inflammation in COVID-19	[80]
	pyridoxine-based supplementation prevents hypercoagulability, sustains endothelial integrity and leads to a lowering in COVID-19 symptoms	[75]
	folic acid can help in the control of COVID-19-associated respiratory decay, at incipient stages	[80,116]
	reported correlation between vitamin B12 deficiency and susceptibility to COVID-19 infection	[124,127]
	methylcobalamin supplementation lowers COVID-19-related symptoms and organ damage	[131]
	administering vitamin B12 (500 μg), vitamin D (1000 IU) and magnesium alleviated COVID-19 symptom severity and lowered the requirement for oxygen and intensive care support	[133]
D	overcomes the aggression of coronaviruses by strengthening physical barriers and by promoting synthesis of antimicrobial (antiviral) peptides in the pulmonary epithelium	[68]
	correlation reported between vitamin D sufficiency (25(OH)D higher or equal to 30 ng/mL) and lowered risk of negative clinical outcomes and mortality, in COVID-19	[172]
	modulation of the cytokine storm that results from activation of the renin-angiotensin system, modulation of neutrophil activity, protection of the pulmonary epithelial barrier, and promotion of epithelial repair	[173–175]
	sustains the inborn immune system and counteracts the overactivation of the adaptive immune system, subsequent to viral infection	[160,181]
	antiviral potential by modulation of the expression of ACE2 in lung tissue and by impacting furin protease	[156,176]
	doses of 250,000–500,000 IU vitamin D proved safe in critically ill, mechanically ventilated patients, leading to increased levels of plasma 25(OH)D (>30 ng/mL, by day seven) and shortened hospital stay length	[198]
	a negative correlation between vitamin D level and the number of COVID-19 cases in several countries	[200]
	patients with enhanced vitamin D deficiency (serum 25-hydroxy vitamin D lower than 10 ng/mL) had a 50% mortality rate after 10 days hospitalization	[201]
	supplementation in deficient COVID-19 patients, might improve disease prognosis	[202]
A	involved in supporting immune system, vision, and control on cell proliferation	[216,223,224]
	together with its derivatives, is endowed with antioxidant and surfactant-mediating properties, protective effects in COVID-19 complications, such as acute respiratory distress syndrome (ARDS)	[227]
	promotor of adaptive and inborn immunity; endowed with anti-inflammatory features, leading to diminution of cytokine storm occurrence, one factor accelerating ARDS	[42,241]
	ability to repair the epithelial tissue at the level of the respiratory tract, and involvement in prevention of fibrosis;	[226,241]
	involved in reduction of mortality	[226,246]
	improvement of oxygen blood saturation	[226]
	essential for normal lung functioning and for restoring lung tissue after injury	[249]
	adequate levels may be highly important during recovery from COVID-19	[241]
	minimizes COVID-19 adverse effects on the angiotensin system and medication-related adverse effects	[228,241]
E	prevents oxidative burst associated with SARS-CoV-2	[228,259–261]
	anti-inflammatory and immunomodulatory roles	[261,267]
	protects cell membranes, and enhances the adaptive immune response to viral infections occurring in the respiratory system; lowers inflammatory responses in various tissues, including the lungs	[227]
	boosts immune response in both animal and human models	[227,270]
K	reduces hemorrhage risk but also thrombotic complications	[293,294,302]
	low levels might be linked to disease severity in COVID-19, and supplementation could lower complication risk	[228,294,298–300]
F	alleviates oxidative stress and inflammatory markers	[307]
	alpha-linolenic acid boosts the expression of glucose transporter-4 gene, mitigating the negative impact of adipose tissue on COVID-19 prognosis	[309]

inducing irreversible impairment to nucleic acids [75]. Recently, in vitro studies, reported that L-ascorbate inhibits 3C-like protease (3CLpro), a cysteine protease on which replication of the SARS CoV-2 is dependent. The binding of vitamin C to 3CLpro active site, may potentially lead to the development of low-cost antiviral therapy [312].

High dose vitamin administration, as proved by the case of vitamin C, can lower the required doses of corticosteroids, antibacterials and antiviral drugs [69,70].

A series of clinical trials report beneficial role exerted by vitamin administration, but there are also several studies that conclude that these results cannot be generalized [62,175]. So, not all reported data with respect to antioxidant intake benefits, show consistency. Or, supplementation benefits cannot be extrapolated to all subjects, and for all parameters followed [57,175]: disease severity, mortality, hospitalization length, intensive care unit admission, mechanical and non-invasive ventilation, or acute respiratory distress syndrome alleviation.

Nevertheless, vitamin impairment is always associated to weakened immune response and illness severity [57,80,149,201,236]. Appropriate timing and dosage, as well as particular mechanistic aspects characterizing each micronutrient, should be carefully monitored and optimized, to obtain beneficial effects, and the activation of angiotensin-converting enzyme 2 has to be critically considered. For instance, in the case of all-transretinoic acid, its ability of to up-regulate the expression of ACE2 [250,251] and the increased levels of ACE2 after vitamin A supplementation, may exert antithetical effects: they can increase the risk of SARS-CoV2 infection in subjects already presenting proper vitamin A levels [252], but can diminish the risk of sympathetic overactivation noticed in severe SARS-CoV2 infection, affecting obese and diabetic subjects [253–255]. It was inferred that ensuring vitamin A adequate levels may be highly important during recovery [241].

The relationship between these micronutrients, as well as their complex relationship with other antioxidant species, are also essential factors that should be considered: for instance, the age-induced B12 level reductions proved most pronounced after folate supplementation [82,135]; ascorbic acid plays a key role in preserving the levels of glutathione [313], and, in turn, the latter has ability to reduce dehydroascorbate, keeping vitamin C at its reduced form. This results in oxidized glutathione, that is eventually reduced at the expense of glutathione reductase [13]. Moreover, vitamin C enhances the antiviral potential of quercetin, that lowers pathogen virulence by impacting virus entry (impedes viral membrane fusion) and replication (inhibition of reverse transcriptase) [44].

SARS-CoV-2 infection is assimilated to a multisystem disorder, targeting multiple organs, and in this pathology, oxidative stress and inflammation play key roles. The intake of antioxidants (food-sourced antioxidants from a balanced diet, as well as antioxidant and metal-chelating agents included in supplements and nutraceuticals) represents a viable alternative in prevention, and for inclusion in therapy [314]. Although the potential of such nutrients to strengthen the immune system has been largely documented, no all the research results converge with respect to the real impact of their deficiency, their ability to lower disease incidence and mortality, that should be confirmed by large randomized studies performed at extended scale [315,316]. Nevertheless, vitamins positively impact the recovery from infection, and the antioxidant features of micronutrients remain a pivotal component of the strategy in the fight against COVID 19 infection [75].

Vitamin administration is not meant to replace classical antiviral and anti-inflammatory treatments, but it should be considered as adjuvant therapy, at least to prevent deficiencies linked to weakened immune response.

Declaration of competing interest

The authors declare that they have **no** known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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