Chapter

Novel Treatment Strategy against COVID-19 through Anti-Inflammatory, Antioxidant and Immunostimulatory Properties of the B Vitamin Complex

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Abstract

The immune system is influenced by vitamin B complex: B1, B2, B3, B5, B6, B7, B9 and B12. The B complex insufficiency can cause significant impairment in cellular and immune function and trigger an inflammatory response. There is currently no certified SARS-CoV-2 treatment or a credible vaccine, but strengthening the immune system with B vitamins could go a long way in preventing and treating COVID-19 patients. Thus, a complete and nutritious diet must be followed before approved drugs and potential good vaccine research results are available to boost the normal functioning of the immune system. In order to activate adaptive and inborn immune responses, reduce cytokine levels such as proinflammatory cytokines, decrease oxidative stress, preserve endothelial homogeneity, improving pulmonary function, prevents hypercoagulable conditions and shortening the length of hospital stay; B-Complex vitamins play a significant role. Thus, the role of B complex in patients with COVID-19 needs to be evaluated and additional non-drug B vitamins can be used in existing treatments.

Keywords: vitamins, immunity, COVID-19, inflammation, cytokines, anti-oxidant

1. Introduction

The severe acute respiratory syndrome coronavirus 2 SARS-CoV-2 virus is the cause of COVID-19. The World Health Organisation reported that COVID19 became an international global health crisis in January 2020 and that COVID19 has become a global epidemic, causing more than 20 million infections and 7 million deaths by March 2020. COVID-19 clinical signs include arthromyalgia, cough, diarrhoea, fevers, headache, lethargy, multiorgan disorder, severe interstitial pneumonia and septic coagulomas [1]. The severe development of COVID-19 also leads to a cytokine storm and excessively pro-inflammatory cytokine secretion [2]. In 2002–2004 and 2012–2014, epidemics of similar β-caronaviral virus (SARS) and Middle East Respiratory Syndrome (MERS), have previously taken place [3, 4].

2. Food supplements to improve immune quality, antioxidants and anti-inflammation

Today, most states all around globe are working to develop corona vaccines, with a number entering human studies while most of them are being studied and developed in various stages. Furthermore, there are no specialised COVID-19 drugs, nor are there any meaningful statistics on the impacts of nutritional additives on COVID-19 risk or seriousness at both national and international levels. Developing new antiviral medications for COVID-19 is a major challenge that requires significant time and resources in the development and evaluation of this product. Several scores of proof signify, in particular in people with insufficient food resources as well as through their free radical scavenging, anti-inflammatory or viricidal capabilities, that many supplements from various vegetables, fruits, spices, herbs and root sources can decrease the hazard or intensity of a diverse variety of viral infections. These nutrients may be recycled to reduce the disease effects of SARS-CoV-2 infection. Thus the utilisation of natural compounds, together with the treatment for COVID-19, can propose new preventative and treatment support. The positive effects of certain nutrients are discussed in the following section [5].

3. Vitamin B and its biological roles

Vitamin B complex are the main vitamin of the brain function, eyes, gastrointestinal tract, liver, hair, muscular tone, nervous system, skin, and are critical to the health of the nervous system. These vitamins next to each other help to detoxify the organ, promote good metabolism, release enzymes from the food, stabilise the functions of your nervous system, provide cells with plenty of oxygen, maintain healthy skin and hair, protect faulty vision and have also been utilised in weaknesses [6]. **Table 1** provides an overview of the vitamin B complex with its cellular roles, scientific name, recommended male and female dose.

4. Vitamin B and pandemic

Due to anti-inflammatory and immunomodulatory properties of vitamin C and vitamin D in this era of pandemic they are getting much attention. Low vitamin D and C levels lead to coagulopathy and suppression of the immune system causing lymphocytopenia. The data showed that in corona virus patients with low levels of vitamin D have high mortality rate. In corona virus patients, the consumption of vitamin C increases the oxygenation index [9]. Accordingly, a lack of vitamin B can seriously alter the function of a cell and immune system that leads to hyperhomocysteinemia inflammation. Vitamin B must be stressed because it plays a key role in proper immune function, energy metabolism and cell function [10]. Vitamin B helps to reduce inflammation, strengthens respiratory functioning, preserves endothelial homogenity, inhibits hypercoagulation, activate innate and adaptive immune responses properly, and can decrease hospitalisation for long periods of time [11]. Thus, the role of B complex in patients with COVID-19 needs to be evaluated and additional non-drug B vitamins can be used in existing treatments.

5. Food supplements to counteract COVID-19

Phase 1 is critical from the point of view of prevention because individuals are carriers and can unintentionally propagate the infection. The organisation and

Vitamin	Scientific name	Coenzymes	Groups transferred	For women daily recommended dose	For men daily recommended dose	Physiological/cellular role
B1	Thiamine	Thiamin pyrophosphate (TPP)	Aldehydes	1.1 mg	1.2 mg	Energy releasing, tissue growth
B2	Riboflavin	Flavin Mononucleotide (FMN)	H Atoms	1.1 mg	1.3 mg	Energy releasing, nucleotide synthesis
B3	Niacin	Nicotinamide Adenine (NAD+), Nicotinamide adenine dinucleotide phosphate (NADP+)	H atoms	14 mg	16 mg	Energy releasing, lipid breakdown and synthesis
B5	Pantothenic acid	Coenzyme A (CoA)	Acyl groups	5 mg	5 mg	Energy production from food stuff Synthesis of fatty acids
B6	Pyridoxine	Pyridoxal-5-phosphate (PLP), pyridoxine-5-phosphate (PNP), pyridoxamine-5′-phosphate (PMP)	Amino groups	1.3 mg	1.3 mg	Amino acid and glycogen breakdown
B7	Biotin	Biotin	CO_2	30 μg	30 μg	Fatty acid, glucose and leucine synthesis
B9	Folic acid	Tetrahydrofolate (THF)	One carbon group except CO_2	400 μg	400 μg	Amino acid and nucleotide synthesis
B12	Cobalomine/ Cyanocobalomin	methylcobalamine	Methyl groups, hydrogen atoms	2.4 μg	2.4 μg	Amino acid metabolism Nucleotide synthesis Breakdown of fatty acids Folic acid regeneration

Table 1.
Summary of Vitamin B complex [7, 8].

mounting of specific adaptive immune responses in persons and the utilisation of antivirals in phase 1 is vital for preventing entry of virus, disease progression and replication to phase 2. Global strategies can thus include administering external antivirals and food supplements that increase immune levels. In addition to retaining the overall status of the patient, phase 2 of the infection can be adapted for treatment to protect damage and malfunction to tissue in the course of the treatment by using nutritional supplements that can repress continuing oxidative stress, acute inflammation and cytokine storms. In short, in order to improve the immune response in phase one and eliminating it in the second phase, approaches to counter SARS-CoV-2 are effective, in addition to symptomatic treatment [5, 12].

6. Pathogenesis of COVID-19

The information provided shows that infection pathogenesis can be divided into two components. Phase 1: an asymptomatic phase of detectable viruses or not. Phase 2: High viral load symptomatic phase [13]. After binding the S protein into the ACE2 receptors and then initiating cellular transmembrane protease, serine 2 (TMPRSS2) and then the virus enters the airway epithelium. After the virus enters the host, innate interferon (IFN) immune response will be inhibited or delayed [14]. Ubiquitation and breakdown of RNA sensor molecules interrupts with downstream signalling [5, 15]. After an impairment of the IFN viral replication system, activation is generated of the granulocytes macrophages and monocytes that lead to the description of the "cytokine storm." The activation of proinflammatory cytokines, which involves interleukin IL-12, IL-8, IL-6 and IL-1 are described, involves massive secretions of the tumour necrosis factor (TNF-α). Tissue fibrosis, pneumonia and hyperinflammation of tissues is associated with this [16]. Research has suggested that oxidative stress is involved in COVID-19 pathogenesis. The evidence seems to indicate that SARS-CoV-2 actually causes oxidative stress by improving reactive oxygen species (ROS) production and indirectly suppressing host defence [17]. Moreover, granulocytosis also contributes to superoxide ions, a kind of of ROS

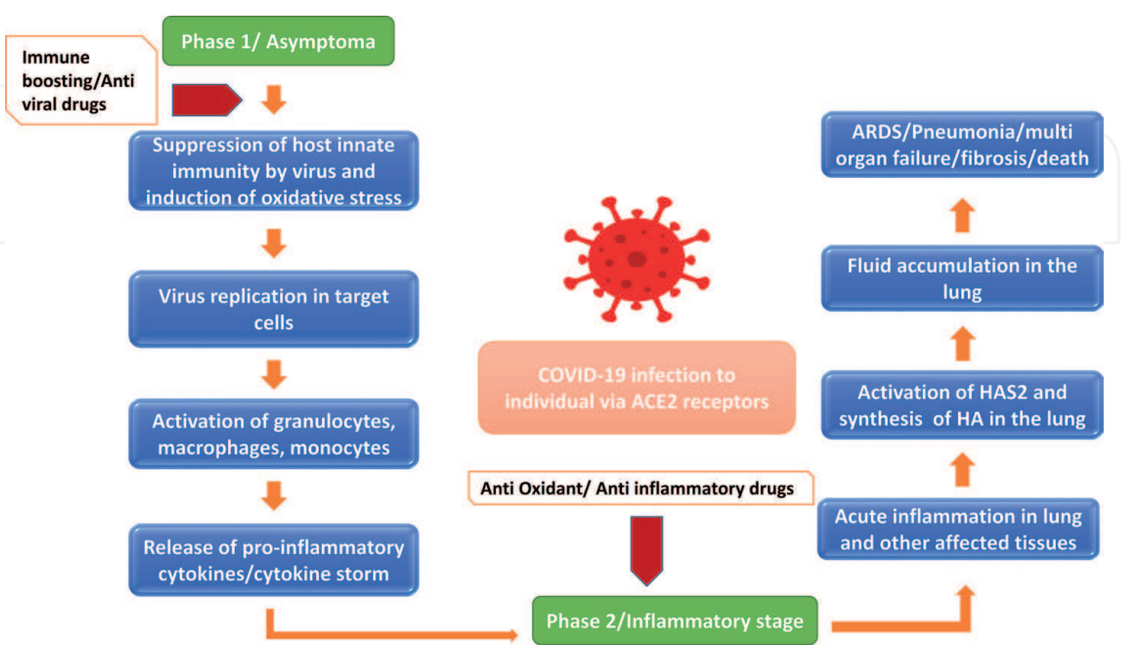

Figure 1.
Schematic representation of pathogenesis of COVID-19. Phase 1 which is asymptomatic includes dysregulation of host innate immune system, elevation of oxidative stress and phase 2 is acute inflammatory harmful phase [12, 24].

and an extra development of proinflammatory cytokines in response to SARSCoV-2 infections [16, 18, 19]. High levels of cytokines also cause HA-synthase-2 (HAS2) endothelial inductions in alveolar and fibroblast epithelial cell (Type 2) [20–23]. Lungs of patients with corona virus have increased cytokine (IL-1, TNF-α) inflammatory levels. This is related to higher HAS2 activity and successive corona virus lung pathophysiology. The clinical and scientific study results above therefore recommend that corona virus pathogenesis consists of two stages: Stage 1, dysregulation of host innate immune system, elevation of oxidative stress and phase 2 is acute inflammatory harmful phase (**Figure 1**).

7. Cross-discussion of immunity, inflammation and oxidative stress with vitamin B complex

In 1936 R.R. Williams and his coworkers defined their chemical structure and were able to synthesise the Vitamin B1 (thiamin) as the oldest vitamin. Vitamin B1 has an impact on anti-inflammatory characteristics, cytochrome C release, mitochondrial membranes, oxidative stress-induced, NF-kappaβ and protein kinases, P38-MAPK. Over expression of proinflammation cytokines like TNF, IL-1, IL-6, and arachidonic acid products, nervous system malfunction, T-cycle infiltration, neuroinflammation, expression CD40 by the microglia and CD40L, causing the loss of astrocytes, beriberi, CL2 chemokine over expression all are the outcomes of deficient vitamin B1 [25].

Therapies with vitamin B complex reduced proinflammatory expression and enhanced anti - proliferative cytokine activity, thereby making a contribution to neuroinflammatory resolution. Macrophages are usually grouped into two major subtypes: (i) macrophages (M1) that are involved as principal phagocytic cells in the inflammatory sites; and (ii) macrophages (M2) which carry out the process of tissue reshaping following inflammatory cellular activity. At the same time, B vitamins reduced the macrophage count for M1 and improved the macrophage count of M2. Thus, B vitamins have the potency for neuroinflammatory and neuroregenerational treatments and could be an excellent remedy for human peripheral nerve injury (PNI) [26].

Vitamin B-6 played an important role during the last decades in the mechanism for inflammatory and antioxidant activities [27]. PLP may interact with peroxy radicals and sequester free radicals and, through its group of hydroxyls, prevent lipid peroxidation on the pyridine ring [28]. PLP plays the role as a coenzyme in the manufacturing, throughout inflammation, of cytokines as well as other multipeptide intermediaries [29]. Therefore insufficient vitamin B-6 may diminish its antioxidant potential directly or interfere with inflammatory reactions [30].

8. COVID-19 patients: thiamine in hypoxia

Thiamine inadequacy impairs inflammatory profile through neuroinflammation by affecting cardiovascular system [31]. As the corona virus needs antibodies, mainly T cells, thiamine deficiencies can result in insufficient antibody responses and consequently in more serious symptoms. Thus, the correct immune responses to corona virus infection are effective to assist with sufficient thiamine levels. Moreover, COVID-19 symptoms seem to be much related to the disease of altitude and pulmonary edema of high altitude. By inhibiting carbonic anhydrase enzymes and consequently increasing oxygen level, for prevention of high altitude sickness and pulmonary edema acetazolamide is commonly prescribed. Thiamine also works as

an inhibitor of the carbon anhydrase enzyme, hence the potential of hypoxia limitation and lowered hospitalisation at high concentrations of thiamine administered in early COVID-19 people. Research is still needed on the possibility of helping to heal COVID-19 patients by administering of increased thiamine doses [11].

9. Riboflavin-UV for inhibition of COVID-19 replication

Riboflavin with UV light is responsible for irreparable destruction to nucleic acids such as RNA and DNA, which makes it impossible to replicate microbial pathogens. The effectiveness of Riboflavin and UV light against MERS-CoV was demonstrated and it may also be of assistance with SARS-CoV-2 [32]. In fact, riboflavin-UV reduced the SARS-CoV-2 infective titre below the human blood and plasma and platelet identification limit [33]. It may ameliorate the risk of COVID-19 transfusion and reduce other pathogenic organisms in blood products in patients critically ill with COVID-19.

10. Vitamin B3 (Nicotinamide, Niacin) for blocking cytokine storm in inflammation

Niacin is a component of NAD and NADP, which are both essential during chronic systemic inflammatory responses [34]. NAD^+ works as a coenzyme in a broad variety of metabolic pathologies, and its elevated concentrations are crucial for dealing with a range of scenarios. NAD+ has immunomodulatory effects that are proven to affect proinflammatory cytokines throughout initial inflammatory periods [35, 36]. Current proof shows that IL-6 can regulate inflammatory storm in COVID-19 patients [37]. Niacin also decreases neutrophil infiltration and has an anti-inflammatory impact in ventilator-induced patients. Nicotinamide and niacin in hamsters minimise injury to the lung tissue [38]. Nicotinamide also minimises replication of virus and reinforces body mechanisms of protection. It can be used as an additional treatment for COVID-19 patients with a view to the lung protective and immune bolstering role of niacin [39].

11. Vitamin B5 (pantothenic acid) as anti-inflammatory agent

Vitamin B5 has a variety of functions, such as lipids and triacylglycerols reduction, improve wounds recovery, reduces inflammation, and enhances mental health [10]. Although there is scarce research which shows vitamin B5's effects on the immune system, it is a feasible vitamin for scientific investigations.

12. PLP supplementation as immunodulatory and anti-inflammatory agent

Pyridoxal 5′ phosphate (PLP) is an active component of pyridoxine and is a cofactor vital for several inflammatory disorder processes that contribute to immune disorder. In chronic inflammatory diseases, PLP has a reverse relation with plasma TNF-α and IL-6. Throughout inflammation, PLP use enhances its depletion, which means that COVID-19 can be deficient in patients with high inflammatory response. In patients with type-2 diabetes and cardiovascular disorder, groups at greater risk for relatively poor COVID-19 outcomes were reported with low levels

of PLP [40, 41]. Elevated incidence of coagulopathy between many COVID-19 patients was also observed as a result of immune disregulation. In a recent manuscript, PLP intake was associated to ameliorate COVID-19 symptoms by regulate immune functions, lower pro-inflammatory cytokines, preserve endothelial stability and avoid hypercoagulability [42]. Indeed, it was found 30 years ago that platelet accumulation and blood coagulation defects were reduced by PLP amounts [43]. Vitamin B6 (along with B2 and B9) prediculated IL 10, a potent anti-inflammatory and immune suppressant cytokine which can disable monocytes and prevent T cells as well as cells present with the antigen [44]. Patients with COVID-19 often frequently react to the virus by implementing a pro-inflammatory T cell response and secretion. PLP may help dampen the cytokine storm and inflammatory processes suffered by a few patients with COVID-19.

13. Vitamin B9 (folic acid, folate) as furin inhibitor

For DNA, synthesis of protein and adaptive immune reaction, folate seems to be essential vitamin. Furin is a bacterial and viral infections-related enzyme and a good potential goal for infection treatment. Folic acid has recently been noted for being capable of inhibiting furin by avoiding binding of the spike protein SARS-CoV-2 and trying to prevent cell input and virus retention. Follic acid was thus recommended to be helpful for COVID-19-associated early phase respiratory disease management [44]. A latest publication shows the strength and stability of folic acid and its derivatives tetrahydrofolic acid and 5 methyl tetrahydrofolic acid, via structure-based molecular docking, in connection with SARS-CoV-2. Follic acid can thus be used as a treatment strategy for COVID-19 management [45].

14. Vitamin B12 (cobalmin) as antioxidant and gut modulatory agent

For the synthesis of erythrocytes, safety of the nervous system, myelin production, angiogenesis and rapid production of DNA, vitamin B12 is critical. Adenosyl-, h ydroxo- and methyl cobalamin are active forms of vitamin B12. As modulator for intestinal flora and low B12 concentrations, vitamin B12 increases homocysteine

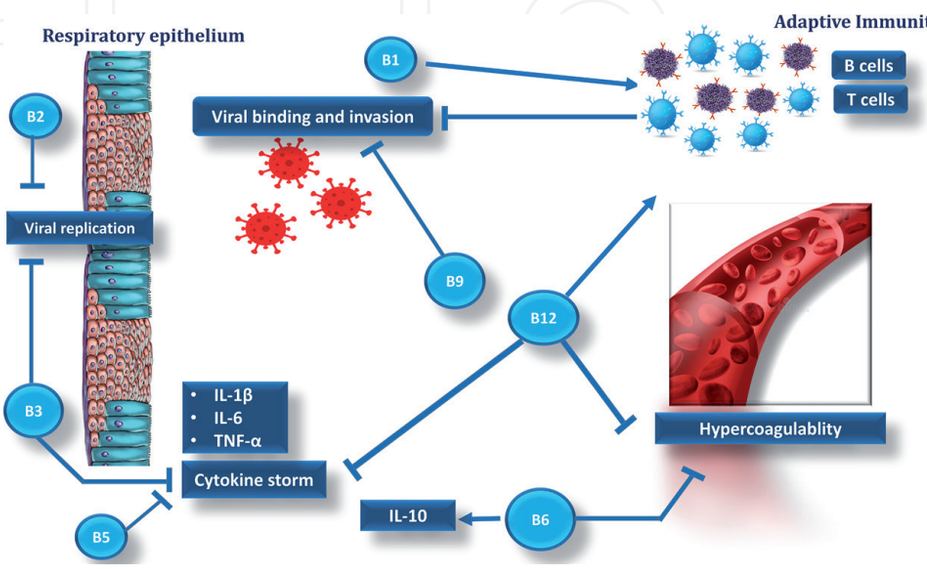

Figure 2.
Summary of Vitamin B complex as anti-COVID-19 agent for inhibition of viral replication, viral binding and invasion, cytokine storm and hypercoagulabity [9].

and methyl malonic acid, leading to increasing inflammatory process, ROS and oxidative stress [35]. Reduced immune response, endothelial dysfunction, myelin sheathing integrity interruption, megaloblastic anaemia, platelets and coagulation activation and are caused by hyperhomocysteinemia [46–48]. SARS-CoV-2 may perhaps interact with the metabolic activities of vitamin B12 which may affect microbiological bowel propagation. Provided that symptoms such as vasoconstriction, increased oxidative stress, cascade-activation of clotting, lactate dehydrogenase, renal and pulmonary vascular disorder and hyperhomocysteinemia are feasible [47, 49]. Furthermore, B12 insufficiency can lead to CNS, gastrointestinal and respiratory and abnormalities [48]. Remarkably, a new study shows that additional methylcobalamine may minimise damage to the organs and symptoms associated with COVID 19 [50]. A Singapore diagnostic research demonstrates that the intensity of COVID-19 in patients receiving magnesium, vitamin D (1000 IU) and vitamin B12 supplements (500 μg), reduced considerably the need for COVID-19 symptoms [51]. **Figure 2** shows a summary of the anti-viral vitamin B complex.

15. Conclusion and future perspective

Besides building and maintaining a stronger immune system, vitamin B can actually prevent or alleviate the symptoms of COVID-19 and / or treat infectious diseases with SARSCoV2. Inadequate nutritional conditions are much more susceptible to infections. Therefore, a balanced diet is needed to enhance immunity. Complementary or safe and cost-effective treatments are needed to reverse abnormal activation of the immune system that can lead to cytokine storms and as an antiplatelet agent. An adequate intake of vitamins is essential for the normal functioning of the body and the boosting of the immune system. B vitamins help control the immune response by decreasing pro-inflammatory cytokines and inflammatory conditions, minimising respiratory and gastrointestinal disease, preventing hypercoagulability, and possibly improving outcomes and shortening the hospital stay for COVID-19 patients.

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Conflict of interest

Authors declare no conflict of interest.

Notes/thanks/other declarations

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Abbreviations

COVID-19	Coronavirus disease of 2019
SARS-COV-2	Severe acute respiratory syndrome coronavirus 2

ACE2	Angiotensin-converting enzyme 2
CCL2	C-C Motif Chemokine Ligand 2
CD40	Cluster of differentiation 40
HAS2	Hyaluronan Synthase 2
IFN	Interferon
IL	Interleukin
MAPK	Mitogen-activated protein kinase
MCG	Microgram
MERS	Middle East respiratory syndrome
NAD	Nicotinamide adenine dinucleotide
NADP	Nicotinamide adenine dinucleotide phosphate
NFKB	Nuclear Factor kappa-light-chain-enhancer of activated B cells
P38	Type of mitogen-activated protein kinases
PLP	Pyridoxal-5′-phosphate
TMPRSS2	Transmembrane Serine Protease 2

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