Role of Vitamins' Supplement in Fighting against Covid-19 infection: A review

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Abstract

COVID-19 is a highly-transmissible, newly emerged, and pathogenic virus in humans which has caused economic disasters as well as global public health issues. To date, millions of mortalities and infections were reported globally and the numbers are continuing to rise. Due to the continual improvements in medical science, various vaccine types were identified and able to reduce the disease's virulence to some extent. However, there is currently no effective treatment for the disease. Enhanced nutrition, including vitamin supplementation to enhance the immune system, was discovered as a viable therapy for alleviating and preventing the severity of COVID-19. To lower the mortalities related to acute respiratory distress, various dietary therapies and alternate supportive treatments are being utilized and tested in patients experiencing COVID-19. A systematic literature review was conducted to uncover nutritional therapies which might assist individuals to recover from COVID-19. Furthermore, electronic databases Science Direct, Google Scholar, PubMed, Scopus, and Web of Science have been searched from February 2020 to April 2021. The purpose of the presented work was give a vision how successful early micronutrient intervention, with an emphasis on vitamin C, vitamin D, and zinc, was at decreasing the escalation of COVID-19, along with the impact of other vitamins in boosting the immune system as well as preventing further complications and improving death rates.

Keywords : COVID-19, immune system, Vitamin supplements (D, C, Zinc)

Abbreviations: coronavirus disease : (COVID-19), World Health Organization (WHO), acute respiratory distress syndrome (ARDS), Angiotensin II (Ang II), vitamin D receptors (VDR), nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB).

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الخلاصة

إن كوفيد-19 هو فيروس كورونا متطور حديثًا وسريع الانتشار بين البشر وقد تسبب في مشاكل صحية عامة عالمية وكوارث اقتصادية. تم تسجيل ملايين الإصابات وآلاف الوفيات في جميع أنحاء العالم و الاعداد مستمرة بالازدياد لحد الان ، وقد قامت عدة شركات ومراكز بحثية بتصنيع عدد من اللقاحات الطارئة التي تم اعطاؤها في دول مختلفة.التي تمكنت من تقليل ضراوة المرض إلى حد ما ، وذلك بفضل التطور المستمر في التكنولوجيا الطبية، ولكن لا يوجد الى الآن علاج فعال للمرض . وقد تم تحديد التغذية الصحية ، والتي تشتمل على مكملات الفيتامينات لتعزيز جهاز المناعة ، كاستراتيجية مجدية للوقاية من عدوى كوفيد- 19 والتخفيف من حدة الاصابة.ومن الجدير بالملاحظة ان استخدام العديد من العلاجات الغذائية والعلاجات الداعمة البديلة و التي أعطيت للمرضى المصابين ب كوفيد- 19 ادت الى تقليل الوفيات المرتبطة بضيق التنفس الحاد. تم إجراء مراجعة منهجية لعدد من البحوث والمقالات العلمية من أجل توضيح فكرة التداخلات الغذائية التي بدورها تزيد من فرص التشافي للأشخاص المصابين بكوفيد-19 . خلال الفترة فبراير 2020 و الى أبريل 2021 ، تم البحث إلكترونيًا في قواعد بيانات PubMed و Science Direct و Scopus و Web of Science و Google Scholar . وكان الهدف من هذه الدراسة إعطاء رؤية حول فعالية التدخل المبكر للمغذيات الدقيقة ، مع التركيز على فيتامين D و C والزنك ، في الحد من تصاعد اعراض إصابة كوفيد- 19 ، وكذلك دور الفيتامينات الأخرى في تعزيز جهاز المناعة وبالتالي منع المزيد من المضاعفات والحد من الوفيات.

Introduction

In early December. 2019, some pneumonia cases from an unidentified source were indicated in Wuhan, Hubei Province, China [1]. On January 3, 2020, the Chinese Center for Disease Control and Prevention discovered a noval and enveloped RNA corona-virus in samples of broncho alveolar lavage fluid from a patient in Wuhan, confirming it as the source of the disease [2]. On January 7, 2020, WHO designated it as the 2019 new coronavirus (2019-nCoV). WHO classified the illness resulting from 2019-nCoV as the 2019 novel coronavirus disease on February 11, 2020. COVID-19 was declared a public health emergency of international concern by the WHO, following the appearance of 2019-nCoV [3].

COVID-19 Genomic Structure and Replication

Coronaviruses are positive-stranded RNA viruses with 3 major structural proteins on their surface: E envelope, M membrane protein, and S spicule. The appearance of corona (Latin: crown) is caused by a spike on the virus's surface that is projected. Cryo electron microscopy revealed a space separating the inner core from the envelope inside the virion. Those cores are formed by the interaction between genomic RNA and nucleoprotein N [4]. As in the following (figure 1).

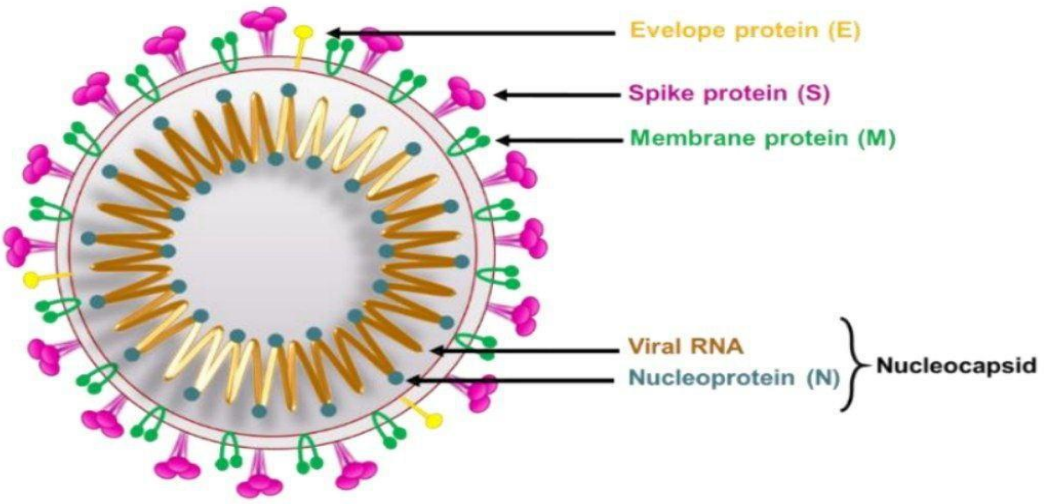

Figure1. SARS-CoV-2 structure schematic representation [4].

This virus is transmitted between persons through respiratory droplets and aerosols. As soon as this virus is inside the body, it binds to host receptors and enters the host cells via the endocytosis or membrane fusion [5]. The viral content is released when the virus reaches the pulmonary alveolar epithelial cells after membrane fusion. Now, this virus is replicated and created in the host cell thanks to the pre-existing single strand positive RNA's RNA polymerase activity (i.e. transcription). Concerning cytoplasm cell, this freshly generated negative RNA strand creates new positive RNAs, which synthesize new proteins [6].

The N protein of the virus attaches to new genomic RNA, whereas M protein facilitates cellular reticular integration. The newly synthesized nucleocapsids are then trapped in the endoplasmic reticulum membrane and transported to the lumen, where they are transferred to the cell membrane through exocytosis via Golgi vesicles, the New Viral Particles are now ready to enter neighboring epithelial cells and offer fresh infectious material to the population through the gout [7].

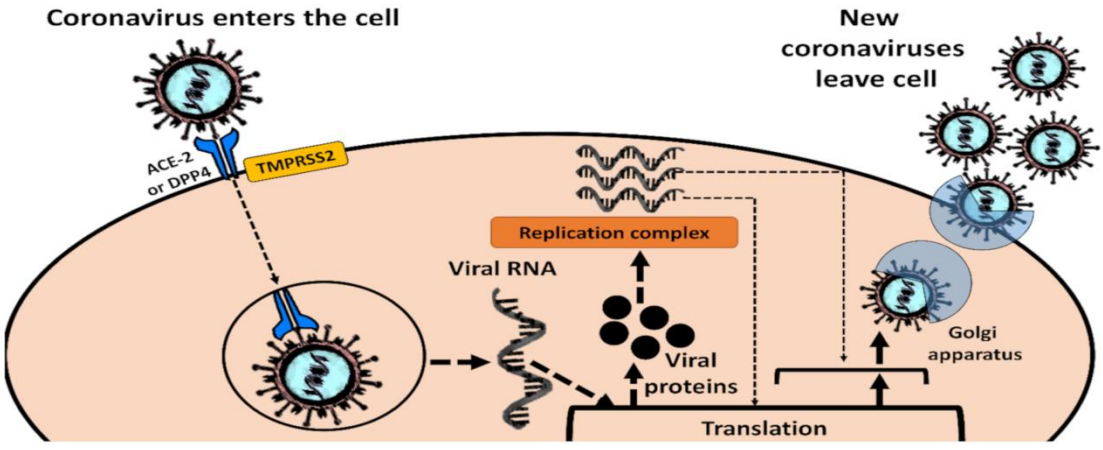

Figure 2. Replication process of Coronaviruses.

Role of vitamin supplements for fighting COVID-19 infection

The human immune system represents an effective and complicated defense system that consists of an integrated set of cells, chemical mediators, along with a number of the defensive "modular" components that modify the immune response and protect the organism from external threats [8]. Immunonutrition can be defined as the process of modulating the immune system by changing the nutrients in one's diet. The rise in antioxidant nutrient levels in the body was hypothesized for many years, given the pre-inflammatory state of ARDS. Dietary nutrient supplementation has been shown to change the clinical pattern in a range of patients, such as those with severe illnesses. A variety of parenteral and enteral formulae containing a combination of immune nutrients are commercially-available [9]; such micronutrients, which include vitamins D, C, and zinc, are recognized as crucial to supporting immune function and reducing the risk of respiratory infection [10]. Those nutrients are found in food, yet they might also be found in dietary supplements, either alone or as part of the multi-vitamin or multi-nutrient blends [11].

1. Vitamin D

Vitamin D3, a lipid-soluble vitamin recommend at higher doses such as a 5,000 IU or even 10,000 IU per day for COVID-19 patients , is produced in the skin when UVB sunlight interacts with 7-dehydrocholesterol and is converted to 25(OH)D or 25-hydroxyvitamin D, also known as calcidiol, in the liver. This is the kind of vitamin D that circulates in quantifiable amounts in the blood and might be tested to determine vitamin D status in serum. For converting 25(OH)D to 1,25(OH)D or 1,25-di-hydroxyvitamin D, also referred as calcitriol or active vitamin D, the renal use the enzyme 1-α-hydroxylase to complete a second hydroxylation [12]. Other cells, such as immune response cells and respiratory tract epithelia, have undergone such second hydroxylation to create the active form, calcitriol. Each cell in the body has vitamin D receptors (VDR), and the calcitriol form of vitamin D acts as a hormone in those cells. In addition, VDRs are nuclear transcription factors which epigenetically control the expression of up to 2,000 genes, such as almost 300 genes included in the immune response in white blood cells (WBC) [13]. Vitamin D is certainly crucial for a wide range of health issues. Along with its well-known role in bone health, it plays a significant and central role in the immunological enhancement and immune modulation. Vitamin D reduces COVID-19 mortality and infection through at least 3 mechanisms (i) adaptive immunity and cellular innate, (ii) physical barriers , and (iii) renin-angiotensin pathway modulation [14].

Renin Angiotensin System (RAS) regulation

The Renin-Angiotensin System (RAS) is required for maintaining vascular resistance and extra-cellular fluid homoeostasis. Renin is important for cleaving angiotensinogen released by the liver to inactive form angiotensin I.

(Ang I). Renin is generated largely in the juxtaglomerular apparatus of kidneys, yet also in other cells and tissues. Also, ACE on the surface of endothelial cells after cleaves such decapeptide (Ang I) into active angiotensin II (Ang II) that might be binding to either the AT2R or AT1R receptors [15]. Catecholamines are released and vasoconstriction occurs as a result of Ang II. The discovery of the ACE-2, a novel homologue of ACE, a transmembrane metallopeptidase with external ectodomain, added to our knowledge of RAS regulation function [16].

Vitamin D can be defined as one of the negative endocrine RAS modulators that inhibits renin expression and production [17] and the deficiency of vitamin D might cause an increase in RAS activity, which might result in chronic cardiovascular disease and impaired lung function. The deficiency of Vitamin D is caused by a lack of sunlight and a poor diet. Vitamin D might activate ACE2/Ang-(1–7)/MasR axis while inhibiting renin and ACE/Ang II/AT1R axis, potentially protecting against acute lung injury/ARDS by raising the concentration and expression of ACE-2, MasR, and Ang-(1–7). It has been hypothesized that vitamin D might be used as a treatment for COVID-19-induced ARDS [18]

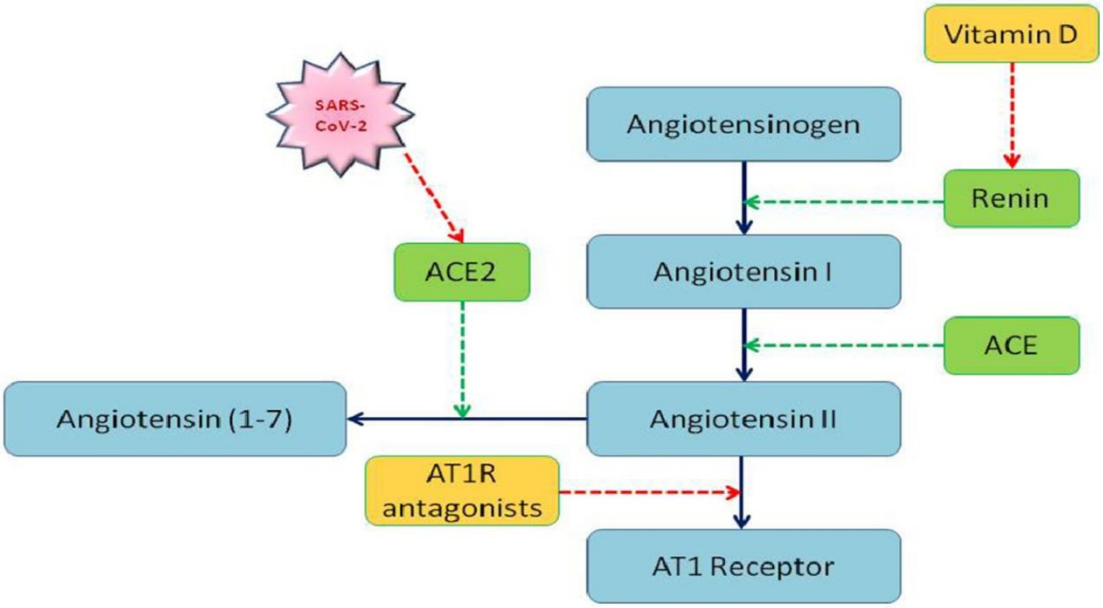

Figure (3); Vitamin D actions on the RAS [19]

Through acting on RAS, vitamin D might protect tissues against SARS-CoV2 infection. SARS-CoV2 causes tissue damage by suppressing the expression of ACE2. Vitamin D can be defined as one of the negative endocrine RAS modulators which might increase ACE2 concentration and expression in tissues, perhaps shielding them from harm [19].

Vitamin D in the Innate and Adaptive Immune Response

Following the identification of VDR in macrophages, dendritic cells, and activated T and B lymphocytes, the involvement of vitamin D in the immune system has been hypothesized. This receptor affects both adaptive and innate immunity. Also, Vitamin D increases the production regarding two antimicrobial peptides known as -defensin and cathelicidin, which play a role in innate immunity. Those compounds have antimicrobial properties, like killing bacterial cells and preventing viral reproduction [14]. Vitamin D reduces adaptive immunological responses in respiratory epithelial cells throughout viral infections, which helps to manage the immune system. Reduced T cell proliferation and the shifting from Th1 to Th2 cells are the most common symptoms. Decreased Th1 proliferation may result in decreased amounts of pro-inflammatory cytokines and weakened acquired immunological responses, both of which make establishing a powerful immune response to a virus more difficult. Vitamin D was demonstrated to influence T cell maturation, causing inflammatory Th17 cell mass for shifting to anti-inflammatory regulatory T cell (T-reg cell) populations. Vitamin D might reduce pro-inflammatory cytokines such as IL6, IL1, TNF alpha, IL-12, and IL-17, whereas raising anti-inflammatory cytokines like IL10 in this way. Reduced pro-inflammatory cytokine production protects against immune-mediated damage by reducing immune cell activation and development. Vitamin D also inhibits nuclear factor kappa-light-chain-enhancer regarding the activated B cells (NFκB) pathway, which reduces the expression of the pro-inflammatory cytokines. As a result of its opposing effects on cytokine modulation and T cell differentiation, vitamin D has a complex dual function in immuno-pathology [20].

Physical Barriers like Maintenance of Tissue Integrity

Firm intercellular connections which Vitamin D might help sustain include gap junctions, tight junctions, and adherent junctions. A few viruses disrupt junctional integrity, increasing the risk of infection by the virus and other microorganisms [14]. Strong physical barriers generated by efficient cell connections are the body's first line of defense from different infections [21]. Also, tight junctions should also be maintained for preventing immune cells from invading the lungs and other respiratory tissues [22]. Which could be crucial for COVID-19 to avoid severe pneumonia and ARDS. There is a high risk of coagulopathies, particularly thrombosis, such as microvascular thrombosis in the lungs, in severe COVID-19 cases [23] A lack of vitamin D has been related to an increased risk of thrombosis. Vitamin D or its analogs have been reported to decrease tissue factor, thrombospondin-1 expression, and pro-thrombotic plasminogen activator inhibitor-1, whereas raising thrombomodulin expression [24]. Therefore, it appears that restoring normal levels of Vitamin D could help to lower the risk of thrombosis.

2. Vitamin C

Vitamin C, which has also been referred to as the ascorbic acid, is considered as a water-soluble nutrient which serves as a cofactor in a number of enzymatic reactions, including amidation of peptide hormones, norepinephrine biosynthesis, hypoxia-inducible factor (HIF) hydroxylation, collagen hydroxylation, carnitine biosynthesis, HIF control, histone demethylation, and tyrosine metabolism. It has a broad effect on the immune system throughout infection, involving T-lymphocyte maturation and development, along with chemotax and phagocytosis. The involvement of phagocytes in the import of oxidized (Dehydroascorbic acid) and reduced (L-ascorbic acid) vitamins C is re-generated in exchange [25], and they also serve as a key homeostatic antioxidant. Vitamin C may possibly play a role in mediating adrenocortical stress response, which is especially important in sepsis [26]. Sneezing, a running or congested nose, and swollen sinuses may be relieved by vitamin C, which also works as a weak antihistamine. In three human controlled trials, vitamin C-supplemented groups had a considerably decreased incidence of pneumonia, showing that vitamin C might decrease susceptibility to lower RTIs under specific conditions. Vitamin C may be one of the most efficient treatments for COVID-19 since it was linked to a lower RTI [27].

Mechanisms of Action in Infections, Sepsis and COVID-19

Vitamin C has immunomodulatory, anti-inflammatory, antithrombotic, anti-oxidant,andanti-viral effects [26] .Through effector mechanisms, the vitamin has direct veridical activity and impacts the adaptive and innate immune systems. (27) Throughout infection, vitamin C affects T-lymphocyte maturation and development, along with the functions of phagocytosis and chemotaxis in leucocytes (28) .Phagocytes take in oxidized vitamin C (dehydroascorbic acid) and convert it into reduced vitamin C (ascorbic acid), making it an antioxidant [25]. With special reference to the critical stage of COVID-19, vitamin C contributes greatly to cytokine down-regulation, shields endothelial cells from oxidative damage, and plays a key role in tissue repair [29]. Vitamin C inhibits NF-κB activity, which decreases inflammation and ROS [30] .Vitamin C dramatically increases superoxide dismutase, glutathione, and catalase, while serum TNF-α and in the IL-1β model of rat ARDS are lowered[31].

Instead of the direct scavenging of oxidants, the epigenetic regulation related to vitamin C might come from the upregulation of the antioxidant protein and the down-regulation of the pro-inflammatory cytokines. Vitamin C might aid to avoid excessive neutrophil activation and accumulation, along with the damage to alveolar epithelial water channels, resulting in such consequences [32]. Vitamin C, a pleiotropic stress hormone, is gradually being demonstrated to be important in mediating adrenocortical stress responses, particularly in septic illness [26). The levels of Vitamin C in the adrenal glands are 3-10 times higher than in any other organ [33].

It is secreted from adrenal cortex in response to physiological stress (Adrenocorticotropic hormone stimulation), such as virus exposure, which elevates plasma levels by fivefold [34]. Vitamin C increases cortisol production, which enhances the anti-inflammatory and endothelial impacts of the glucocorticoides [35]. Exogenous glucocorticoid steroids are the only proven COVID-19 treatment modification [36]. The figure depicts the strategies for treating COVID-19 pathology of vitamin C.

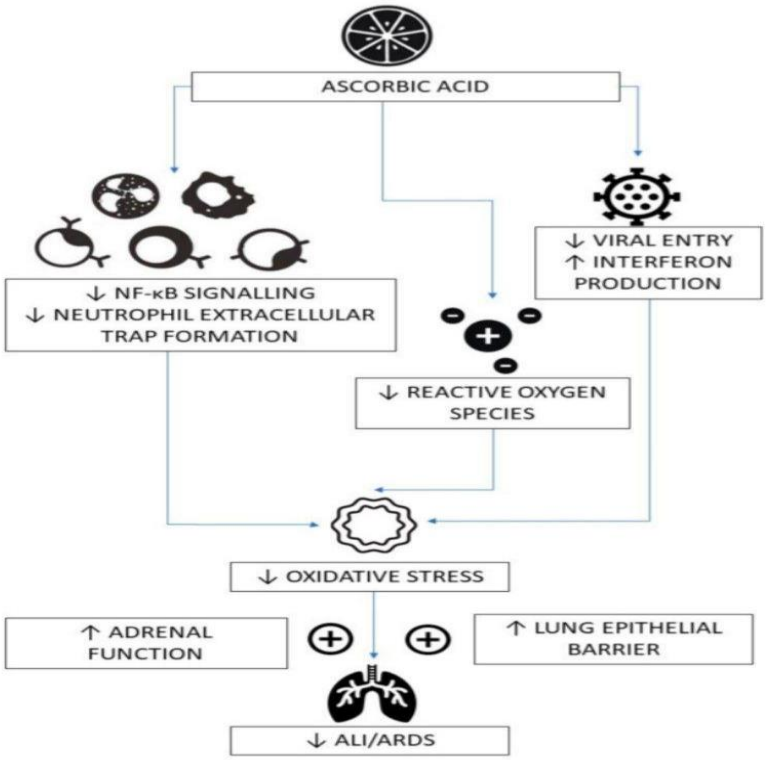

Figure (4): The mechanisms for improving COVID-19 pathology of vitamin C
Postulated mechanisms for vitamin C's amelioration of thepathologyof COVID-19. ↓—decreased; ↑—increased; ARDS—acute respiratory distress syndrome; ALI—acute lung injury; NF-κB—nuclear factor kappa B [35]

3. ZINC

Zn can be defined as one of the essential trace elements identified in considerable amounts in a variety of foods, including eggs, whole grains, various meat, and vegetables. It might also be identified in human tissues, ranging between (1.4 and 2.3) g in adult body tissue, with a wide range of distribution throughout organs and tissues, with 85% of the total quantity found in bones and muscles and approximately 11% in the skin [37].

Because Zn is typically bound to proteins like transferrin, albumin, and alpha-2-macroglobulin (A2M), the free form of Zn in plasma is extremely low (approximately 0.1% of total body), yet it remains the most significant Zn reservoir which is significant for homeostasis, and according to a few kinetic studies, just a small proportion (10%) of total body Zn is representing the functional pool which is located in the liver and other tissues [38]. Also, Zn has a role in many biological functions as it is specified as one of the multipurpose trace elements and due to its capacity for binding to approximately 300 enzymes and over 2000 transcriptional factors which can not function in its absence; therefore, Zn is significant for the function related to thymidine kinase, DNA polymerase as well as DNA dependent RNA polymerase which is vital in nucleic acid synthesis and this might explain the impacts of Zn on the proliferation of lymphoid cells [39]. Furthermore, Zn plays a role in membrane stabilization through acting at the cytoskeletal level, and this effect on membranes might indicate the decrease in phagocytosis, oxygen consumption, and bactericidal activity which is induced via Zn in phagocytic cells, implying that any change in the status of Zn will impact immune response, increasing the susceptibility to inflammation and infectious diseases such as AIDS, pneumonia, and tuberculosis [40]. Plasma Zn levels can remain stable even with low food intake because of the homeostasis in the human body, and plasma levels will only decline in the case when there is a long-term deficit. Even though plasma Zn concentrations are related to daily consumption, tests on Zn plasma levels have limited specificity since Zn plasma levels are reduced throughout inflammatory disease states, pregnancy, and might increase in acute catabolic states and other conditions. It's vital to remember that the suggested daily limit of Zn varies depending on an individual's sex, age, and health. The suggested daily amount of elemental Zn for healthy persons is generally 15–30 mg [41]. Even though Zn is not a vitamin, its antiviral and immunomodulatory properties, along with its capability for regulating the inflammatory response and maintain the redox system, have been credited as plausible explanations for its importance in the treatment of COVID-19 disorders.

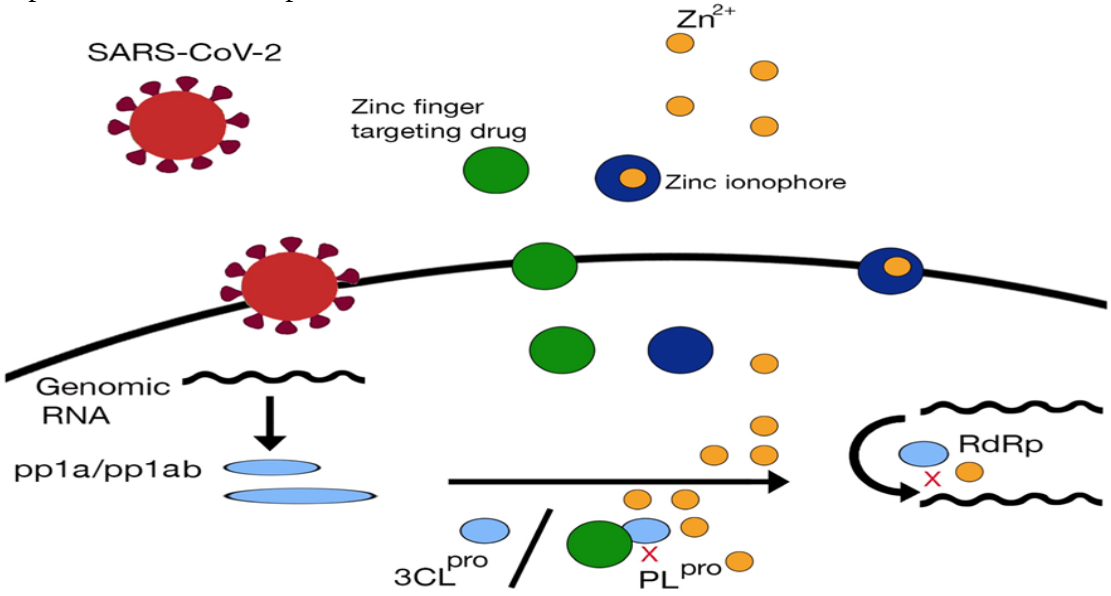

Figure (5): The possible mechanism of action of the drugs targeting Zn Metallo-enzymes in coronavirus 2019 [42].

Zn in papain like protease (PLpro) (or another important enzyme of SARS-CoV2) might be bound by a medication targeting Zn fingers in Zn metalloenzymes. Such a medication might destabilize the enzyme by removing Zn from it, resulting in an increase in intracellular zinc concentration. Increased intracellular Zn could be achieved by combining Zn with its ionophore. The virus's RNA- dependent RNA polymerase (RdRp) would be inhibited by intracellular Zn [42].

4. Other Supplements with Immune-Boosting Potential

Aside from the items listed above, several supplements could be helpful in improving the immune responses, such as:

Vitamin B

Vitamin B serves as a vital cofactor in a variety of cellular reactions, including the creation of basic antibody structure units, amino acids, and cytokines. Also, they play a key role in lymphocyte maturation and generation, both of which are essential components of the initial immune response. The numerous types of vitamin B, like (B3, B2, B12, and B6), are water - soluble and primarily function as coenzymes in the body's different important activities. Each one of the B vitamins has a specific purpose and is necessary for infection prevention. Vitamin B2, commonly referred to as riboflavin, is involved in cellular energy-generating metabolic processes. Based on the silico research, vitamin B12 appears to reduce the SARS-CoV-2 virus's RNA-dependent RNA polymerase activity, the major enzyme involved in viral replication. Vitamins B12, B6, and B9 (folic acid) boost the function of natural killer cells, which help to fight viruses. Those results suggest that B vitamins may help to prevent COVID-19 infection complications [43].

Vitamin E

Vitamin E can be defined as one of the lipid-soluble compounds with antioxidant capabilities that are found in high concentrations in immune cells. It interacts with a variety of enzymes, changing their capability for attaching to the plasma membrane and altering a variety of cell signaling pathway. Vitamin E regulates enzymes such as protein phosphatases, protein kinases, enzymes, and lipid kinases, involved in cAMP (cyclic adenosine monophosphate) metabolism. A lot of such enzymes are involved in key immune system processes and inflammatory events, such as the phospholipase A2, cyclooxygenase-2 (COX2), protein tyrosine kinases, and protein kinase C [44]. A few of the proposed pathways included in vitamin E's effects include: i) the reduction of PGE2 development through inhibiting COX2 activity which is induced through the reduction of the nitric oxide production, ii) the increase of effective immune synapse formation in naive T cells and initiating T cell activation signals, iii) the regulation of Th1/Th2 equilibrium. Vitamin E caused a decrease in IL-12 production and an increase in NK cell activity [45].

Vitamin E also inhibiting the production of pro-inflammatory cytokines like IL-6, IL-1, TNF, and chemokine IL8 by macrophages and monocytes. Vitamin E has the capacity to activate the type-I interferon system within the cell, which has antiviral effects [44]. Several researches have shown that the supplementation of vitamin E might harm the immune system, particularly in CVD and cancer, and there is no definitive proof of vitamin E's role in the treatment of COVID-19. However, vitamin E protecting cell membrane integrity from free radical damage and can impact adaptive and innate immunity [46].

N-Acetyl Cysteine (NAC)

NAC can be defined as one of the natural antioxidants generated from allium-based plants which facilitating glutathione (GSH) synthesis and are directly ROS scavenged through the thiol group. Since it is utilized for restoring the depletion of GSH in a variety of circumstances, NAC was suggested as a nutraceutical which might aid in controlling RNA viruses like coronavirus and influenza. Recently, it was postulated that NAC might be employed in both COVID-19 therapy and prevention, depending on its protective function in animal models of influenza and other viruses. NAC was demonstrated for protecting against some COVID-19-associated illnesses, such as CVD, in recent studies. In severe COVID-19 disease, NAC treatment was suggested as one of the feasible options for maintaining endothelial function and reducing micro thrombosis [47].

Conclusion

Vitamin and element supplementation tactics for increasing immunity are something to consider for a viral condition such as COVID-19, in which no effective pharmacological treatment alternatives are accessible and the precise time of the difficult situation's troubling is unknown. Because of the high demand for such nutrients in the event of virus interaction and the start of the inflammatory process, appropriate Zn and vitamin D and C intake could be a useful pharmaceutical strategy. As a result, nutritional supplemental therapy may be included inpatient care to help patients survive this life-threatening condition (COVID-19) and recover faster. Most notably, preventing malnutrition and offering adequate nutritional supplementation is essential for the immune system's normal functioning in the human body. This procedure is low-cost, simple, and risk-free. Even though high dosages of micronutrients might be required to rectify deficiencies, for long-term micronutrient intake, it is better to stay to the prescribed upper acceptable intake amounts.

Conflict of interest

The authors declare that they have no conflicts of interest.

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