Review Article:

Immune Response to the Pathogenesis of COVID-19 Infection: Possible Mechanism of Nutrition (Vitamins, Supplement) and Exercise

Abdullahi Alausa[1], Rofiat Adeyemi[1], Barakat Olaleke[1], Aminat Ismail[2], Faith Sunday Oyelere[1*]

1. Department of Biochemistry, Faculty of Basic Medical Sciences, Ladoke Akintola University of Technology, Ogbomoso, Oyo State Nigeria.
2. Department of Science Laboratory Technology, Faculty of Pure and Applied Sciences, Ladoke Akintola University of Technology, Ogbomoso, Oyo State, Nigeria.

*** Corresponding Author:**
Faith Sunday Oyelere, PhD.
Address: Department of Biochemistry, Faculty of Basic Medical Sciences, Ladoke Akintola University of Technology, Ogbomoso, Oyo State Nigeria.
Phone: +98 (25) 23481478505
E-mail: faithoyelere@gmail.com

Article info:
Received: 10 Jun 2020
Accepted: 04 Aug 2020

Keywords:
COVID-19, Exercise, Immune response, Nutrition, Pathogenesis

ABSTRACT

COVID-19 infection, a ravaging disease attributed to a SARS-CoV-like illness, has brought the world to its knee, causing a pandemic, with human-human transmission as a major source of the spread of this ailment. Alarmingly, this infection based on clinical manifestations is diagnosed as virus-induced pneumonia, with over 5 million cases with a mortality rate of about 7% (based on the recently published global report). However, most deaths have been associated with patients with underlying immune dysfunction or a compromised immune system. As no specific therapeutics and vaccines have been reported, the strengthening of the immune system through nutritional intake and exercise is essential. Also, previous studies have documented the immune-activating capabilities of Vitamin A and D, along with supplementary induction, yielding positive results in combating previous viral challenges. Typically, the gradual upsurge of T-lymphocytes and immune cell activities has been implemented by moderate exercise activities. This review examines the role of nutrition and exercise in immune system enhancement and proposes the possible mechanism of nutrition and exercise in combating COVID-19 infection.

1. Introduction

The reported emergence of pneumonia in the largest city of central China on the eve of 2019 has caused half a million deaths globally at an approximate value of 7%, as well as an increase in intensive-care patients [1]. However, with using molecular tools identifying pneumonia and its link to 2019-nCoV [2], the novel coronavirus infection named COVID-19 on February 11, 2020 [3]. It has been reported to emerge from Bat-SARS coronavirus [4].

Before December 2019, 6 known CoVs cause diseases in humans. Four are classified as low pathogenic CoVs; namely, the HCoV's variants (-229E, -HKU1, -OC43,

Citation Alausa A, Adeyemi R, Olaleke B, Ismail A, Oyelere FS. Immune Response to the Pathogenesis of COVID-19 Infection: Possible Mechanism of Nutrition (Vitamins, Supplement) and Exercise. Pharmaceutical and Biomedical Research. 2020; 6 (Special Issue on COVID-19):81-92.
doi: http://dx.doi.org/10.18502/pbr.v6i(S2).5659

-NL63), guilty for a reprisal rate of 15% common cold [5, 6]. The contagious CoVs activating the health derailing pneumonia, causing aggressive attacks on the lower respiratory tracts, and increasing death tolls are called severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) CoVs [7]. This SARS-CoV-like illness has resulted in a pandemic creating economic and health challenges.

With the majority of COVID-19 infected death attributed to patients with underlying immune dysfunction and or weakened immune system, the fortification of the immune system in triggering an immune response is thus essential as no therapeutics or vaccines has been reported.

The immune response is the coordinated body reaction in response to invading pathogens, including the fatality causing coronavirus with the sole aim of protecting the body's system and maintaining normal body balance [8]. This highly complex reaction is essential in circumventing the viral attack [8], which could invade the oropharyngeal epithelium and cause severe lung infection.

Previous studies have provided a foreground on the protective action of the immune system against invading pathogens by triggering inflammatory responses, clearing dead or non-functional tissues, and continually surveying injurious cells within the host system [9-11].

Nutrition has thus been acclaimed to be a critical determinant of immune responses in fortifying the immune system, preventing viruses and other pathogens [12]. These foods include supplements (zinc, selenium) and vitamins consumed through diet or synthesized naturally via the skin. Moderate levels of exercise can increase in T-lymphocytes functioning, moderate action of neutrophils, timely induction of macrophages, and monocytes activating cascade, which have been shown to influence immune response positively [13].

Generally accepted clinical manifestations for COVID-19 patients include sore muscles, fever, painful cough, increased body stress, labored respiration, decreased HbA1c levels, all of which are shared manifestations by the trite SARS-CoV and MERS-CoV infection [4, 14, 15]. This similarity in clinical manifestation provides the template in understanding the pathogenesis of COVID-19 disease.

This study thus explains the possible mechanism of nutrition (vitamins and supplements) and exercise in boosting and triggering the body's immunity in response to the pathogenesis of COVID-19 infection.

Virology and Symptoms of Coronavirus

Coronavirus (CoV) is an enfolded, positive-sense, highly infectious RNA virus singly stranded. They belong to the viridae clan due to the protruding spikes in their outermost structure surface. This virus looks like a cyclic conformation when viewed under the electron microscope [5, 16]. SARS-CoV-2, identified on January 7, 2020, belongs to the subfamily orthocoronavirinae and the genus betacoronavirus [17].

They are tiny particles ranging between 65 and 125 nm in diameters with an additional length of about 26-32 kb as their nucleic material size (Figure 1). Based on serological and genotypic composition, CoVs can be classified into α, β, γ, and δ-CoVs. However, the present ravaging SARS-CoV2 is believed to emerge from α- and β-CoVs [18, 19].

The mechanism of infection of COVID-19 and SARS-CoV looks alike to that of Bat SARS-CoV. Once in contact with the virus, the human angiotensin-converting enzyme 2 (ACE2), a highly essential protein in maintaining renal homeostasis, is employed. In contrast, a converse receptor dipeptidyl-peptidase 4 (DDP4) is employed by MERS-viral particles [20, 21], causing varying degrees of respiratory illness, which may lead to pulmonary failure and even death [4]. Bat coronavirus, however, employs the ACE2 receptor, displaying a similar infection pattern to SARS-CoV2 [22].

Employing molecular tools, analysis of SARS-CoV2 genomic sequence revealed a dual terminal sequence, the 5' and 3' terminal sequences, a characteristic shared by β-CoVs viruses. These tools further showed 265 nt and 229 nt in the former and later terminal sequence, respectively, with an essential open reading frame at the 5' terminal (1ab-S-envelope(E)-membrane(M)-N-30') [23]. The visualized S, ORF, N, E, and M genes showed ranging degrees of length occurring at different loci of the viral genomic sequence [24]. Although it is noteworthy that MERS-CoV showed a lower degree of fever in infected patients (2%) compared to COVID-19 fever induction [25] (Figure 1).

COVID-19 patients can either be symptomatic or asymptomatic. Symptomatic patients may develop signs within 2-14 days after exposure, as reported on the incubation period of MERS-CoV [26]. Important information, which includes the patient's age at infection, medical history, and the immune status of the patient, is a critical determinant of symptoms, as people aged 70 and above tend to have a fatal outcome compared to the younger people [27].

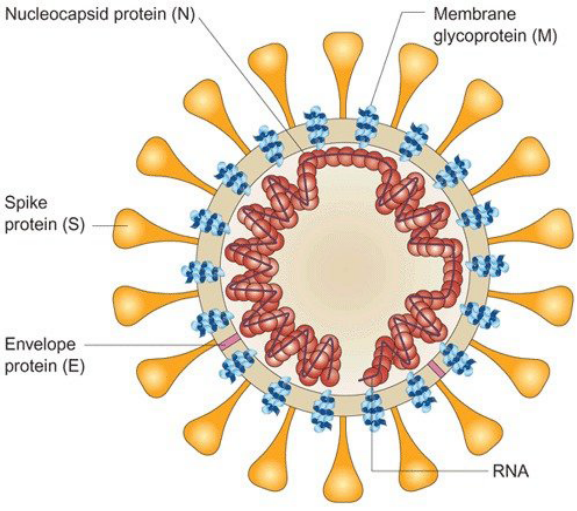

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Figure 1. Visualizing the spikes and surface components of the human coronavirus

Approved symptoms of COVID-19 infection enlisted include sore muscles, painful cough, fever, labored respiration, and decreased HbA1c levels. Besides, emergency warning signs include chest pain, confusion, and inability to arouse [28].

Pathogenesis of COVID-19

To clearly understand the pathogenesis of the novel coronavirus, clear comprehension of the mechanism of SARS-CoV attack and MERS-CoV pathogenesis would be helpful. This process begins with the key interaction of coronavirus and its essential binding protein ACE2 (Figure 2), through which it infiltrates the mucosa of the lungs of infected patients [28, 29].

This interaction occurs when the spherical spikes create a tight association with the receptor. Initially, it was thought to be a simple direct membrane fusion between the viral particle and plasma membrane until studies showed otherwise. It became apparent that the outer spikes must be cleaved by the proteinaceous enzyme called TMPRSS2, which is only effective upon the enzyme activation [30, 31]. This binding is shown in Figure 2.

As a result of the positive interaction between the virus and human ACE2, the oropharyngeal epithelia are infiltrated and attacked. Human ACE2, in addition to its indisputable role as the entry receptor of coronavirus, is involved in the emergence of acute respiratory distress syndrome [33, 34]. As soon as the invasion phase is completed, the ribosomal translating machinery in the cytoplasm becomes activated, triggering the viral replication system [35]. The machinery utilizes multiple enzymes for replication efficiency, containing the numerous copy producing protein polymerase, the unwinding enzyme helicase, the cleavage enzyme protease, the sequence-specific endo- and exo-ribonucleases, ribose-methyl

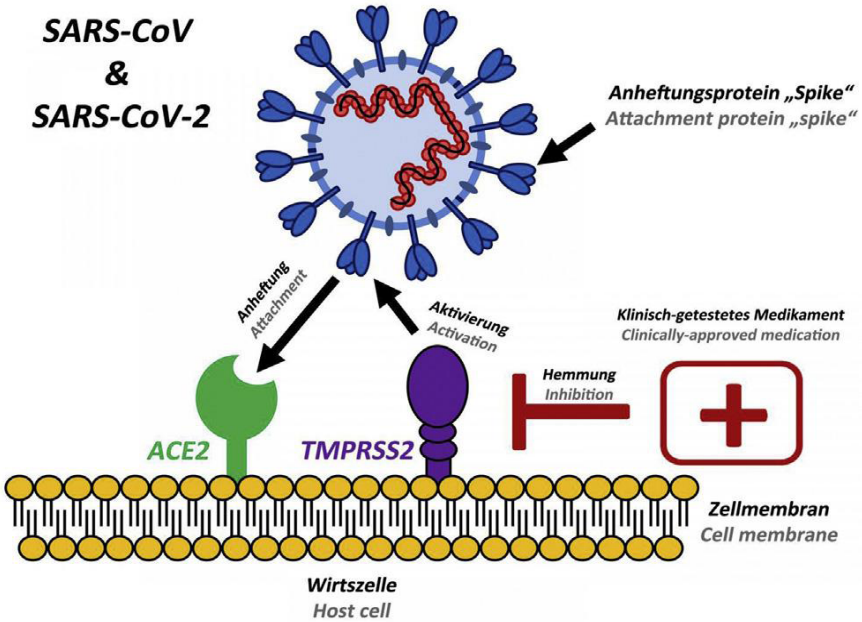

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Figure 2. Illustrating the expressed alveolar cells ACE2 receptor binding upon invasion by a coronavirus

The purple diagram shows that activated TMPRSS2 binds with the surface spikes in the cell membrane. However, to prevent the overexpression of TMPRSS2, it is probable to inhibition [32].

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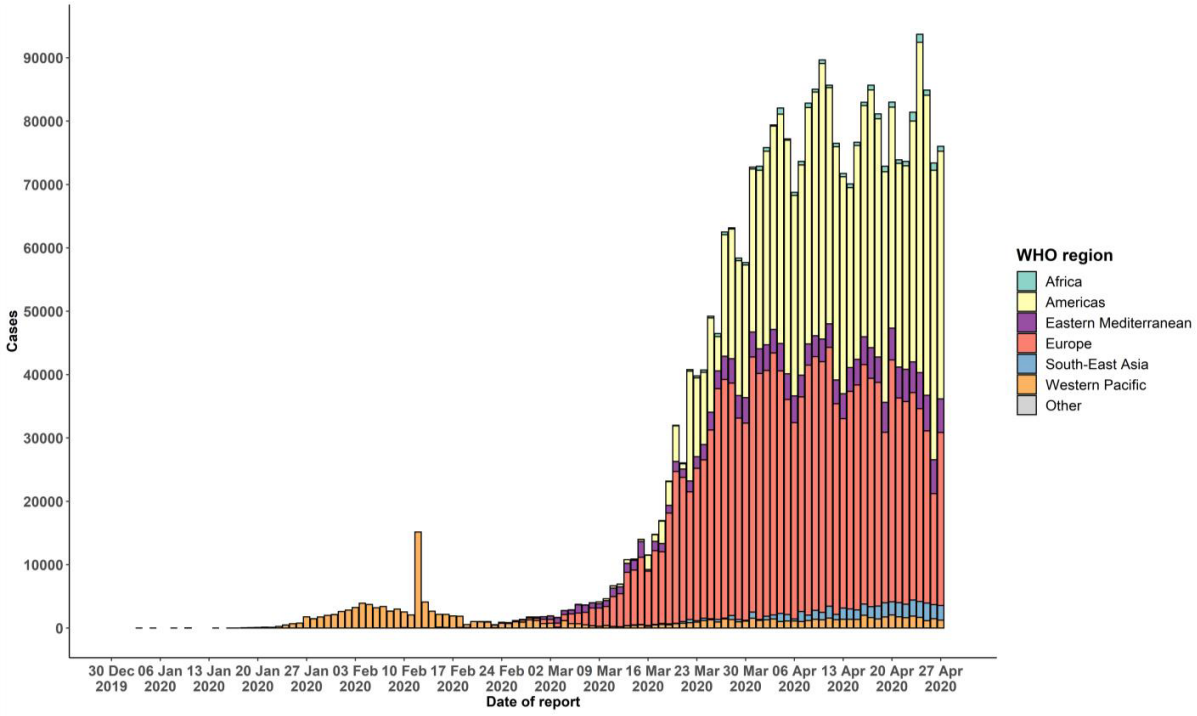

Figure 3. Graphical illustration of the epidemic curve as published in the WHO global report [40]

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transferase, the hydrolase enzyme phosphatase, and finally the phosphodiesterase activities enzyme [36, 37].

The products of translation are glycoproteins, which are two polyproteins and structural proteins. They became enclosed in the endoplasmic reticulum or the Golgi apparatus. As soon as the nucleocapsid protein is encapsidated with genomic RNA, the viral proteinous coat develops. Then, the encapsulated viral proteins grow in the Endoplasmic Reticulum-Golgi Intermediate Compartment (ERGIC) [35]. Finally, the newly replicated viral particles fuse into the plasma membrane, causing its release into the body system and causes health problems [38, 39] (Figure 3).

Immune response to pathogenesis of COVID-19

SARS-CoV2 is a self-limiting virus, with its inability to thrive in a strong immune environment [41]; however, the detailed comprehension of the pathogenesis of COVID-19 infection is mandatory in eliciting the immune response system. SARS-CoV2 elucidates a biphasic immune response: 1. Immune defense-based protective phase; 2. Inflammation-driven-damaging phase [42].

In the early infectious stage, an immune defense-based protective phase is activated against the viral infection by inhibiting the viral replicase system, inducing adaptive immune response while employing the response of interferon (IFN) type I and its downstream cascade to effect [39]. In eliciting an antiviral immune response, the invading coronavirus is often recognized by pathogen-associated molecular patterns (PAMPs) via the endosomal RNA receptors, TLR3 and TLR7, and the cytosolic RNA sensor, RIG-I/MDA5, which starts the downstream signaling cascade (NF-κB [nuclear factor kappa-light-chain-enhancer of activated B cells] and IRF3) [43]. Expression of type I IFN and other proinflammatory cytokines induced by nuclear translocation provides the main line of defense against the viral infection at the entry site [38]. Type I IFN by means of IFNAR, thus, activates the JAK-STAT pathway by kinase phosphorylation of STAT1/2 resulting in STATI/2-IRF9 complex on reacting with IRF9 which translocate into the nucleus initiating the transcription of IFN-stimulated genes (ISGs) regulated by IFN-stimulated response element (ISRE) containing promoters [39]. A slowdown in the release of cytokines, chemokines taking place in respiratory epithelial cells should potentially stifle viral replication and spreading at the early stage of SARS-CoV infection [44] (Figure 4).

Coronavirus is assumed to be a Titan cell. Once bounded to the ACE2 receptor mainly expressed in the lungs, it is recognized via the pathogen-associated molecular pattern (PAMPs), mainly TLR3 and TLR7, and the cytosolic RNA sensor, RIG-I/MDA5. This event results in the actuation of the downstream signaling cascade,

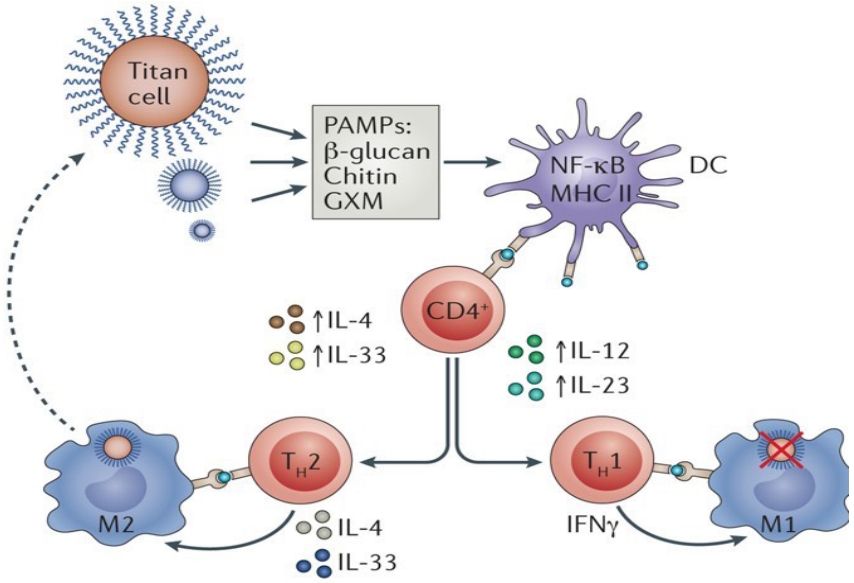

Figure 4. Proposed proinflammatory signaling in response to COVID-19 infection

i.e. NF-κB, which following translocation triggers the release of interferon (IFN) and other proinflammatory cytokines (interleukin [IL]) [45].

In severe stages, in most individuals with a susceptible immune system, the inflammatory-driven damaging phase is activated [42]. In this stage, tricks in preventing the synthesis of type 1-IFN are employed by the virus. In type I IFN induction, the ubiquitination pathway of RNA sensor adaptor molecules MAVS and TRAF3/6 is activated by SARS-CoV, inhibiting nuclear translocation of IRF3 [46]. This induction fortifies the virus by inhibiting STAT1 phosphorylation, thus preventing IFN signaling [38]. A previous study on the mouse model of SARS-CoV infection reveals the dysregulation of type 1 IFN and inflammatory monocyte-macrophages as key players of lethal pneumonia [47]. Excessive production of type 1 IFN, a significant source of proinflammatory cytokines that infiltrate the myeloid cells, results in a severe case of COVID-19 infection. This condition is referred to as a cytokine storm, a significant cause of lung dysfunction [48-50]. With an increased expression of IFN-γ, IL-1β, MCP-1, IP-10 found in COVID-19 infected patients [48], these inflammatory cytokines induce the activation of T-helper type 1 (Th1) cell response [14], an essential inducer of specific immunity [51]. A raised amount of Th2 cell-secreted cytokines (IL-4 and IL-10) restrain the inflammatory response resulting in immunopathological changes in the lungs [52]. A report on COVID-19 resulting pneumonia demonstrated that about 71.2% of the patients depend on mechanical ventilation, with about 67.3% suffering from ARDS [53]. However, a significant fatality rate results in older patients [53].

Role of nutrition in immune response pathway

In combating the fatal coronavirus, a healthy immune system is essential as all therapeutic and vaccines currently undergo clinical trials. Thus, adequate nutritional status (micronutrients and macronutrients) are necessary not only for the proper functioning of the immune system [54] but some (several micronutrients, including vitamins and trace minerals such as vitamin A, C, D, E) are also components of many enzymes. Thus, the physiological functions of the immune system can be altered in individual deficient in both vitamins and trace elements [11]. A previous study has reported the effect of Vitamin A and D in increasing the humoral immunity of pediatric patients following flu immunization [55]. Supplements rich in zinc also reportedly enhance the immune of patients with Torque Teno Virus (TTV) [56]. Likewise, selenium supplementation also shows a favorable response after an influenza vaccination challenge [57].

Possible role of Vitamin D in immunity to COVID-19 infection

Vitamin D, a fat-soluble vitamin from fish oils, fatty fish, animal liver, and egg yolks [58], is beneficial for the proper working of the immune system, acting as the body's primary line of defense against disease and infection [59]. Owing to its anti-inflammatory and immunoregulatory properties, healthy consumption of vitamin D via dietary intake or skin synthesis is critical in activating the immune system against invading pathogens [59].

Metabolism of vitamin D is initiated in the liver by the action of 25-hydroxylase (CYP27A1) to yield prohormone 25-hydroxy vitamin D (25[OH]D), which is subsequently converted in the kidney to calcitriol, a metabolic active form, in an enzyme regulated reaction catalyzed by 1α-hydroxylase (CYP27B1) [60]. NF-κB dimers are bounded at basal levels to specific inhibitory proteins named IκB proteins activated by proinflammatory signals through IκB kinase (IKK)-dependent phosphorylation [61]. Degradation of the inhibitory IκB proteins if translocated to the nucleus activates the transcription of proinflammatory cytokines, chemokines [38]. They are a key player in the regulation of innate immune responses and inflammation as earlier discussed. In severe COVID-19 patients, cytokines are induced in elevated levels in malignant cells [62], leading to a cytokine storm. Calcitriol, the metabolic product of vitamin D, already is known to have a direct modulating effect on basal and cytokine-induced NF-κB activity in numerous cells, including human lymphocytes [63], fibroblasts [64] and peripheral blood monocytes [65]. It blocks NF-κB actuation by promoting the expression of IκB [65, 66], further preventing immunopathological destruction of the lungs.

Vitamin D deficiency is associated with decreased lung function and increased risk of respiratory disease (tuberculosis, asthma, and chronic obstructive pulmonary disease) [67]. Many old individuals who are susceptible to catch severe COVID-19 complications are deficient in vitamin D [68] and could help modulate their vitamin D level. Depending on the blood level, supplementation of about 1000 to 4000 IU vitamin is satisfactory [69]. Optimal vitamin D level ranges between 30 and 60 ng/mL (75-150 nmol/L) [70].

Possible role of vitamin A and B3 in immunity to COVID-19 infection

Vitamin A (retinol) is a significant micronutrient that plays a critical role in maintaining epithelial surfaces, cellular differentiation, immunity, reproduction, growth, and vision. It can be ingested in its preformed state in cod-liver oil, liver, or eggs or as pro-vitamin A in carotenoids carrot, mangoes, papayas, and dark-green verdant vegetables [71]. Vitamin A is found primarily in the body (liver) in the esterified form [72], from where they are released into unique cell targets via an effective specific receptor in combination with retinol-binding protein and transthyretin [73, 74]. In the cytosol, vitamin A undergoes oxidation to retinoic acid [75]. Although several mechanisms of vitamin A action is yet to be elucidated, it is a central player in the inhibition of inflammatory factors [76, 77] and down-regulation of IFN, and up-regulation of IL [78]. Thus the consumption of a healthy amount of vitamin A could enhance the immune defense-based protective phase of COVID19 patients. Ailments such as fever, diarrhea, and respiratory diseases result from Vitamin A deficiency [79, 80]. Also, the preventive action of vitamin B3 (niacin or nicotinamide) in bleomycin-induced lung injury has been reported in animal models [81]. Thus food supplements of vitamin B3 should also be encouraged in COVID-19 patients.

Possible role of Selenium in immunity to COVID-19 infection

Dietary sources of selenium exist in inorganic (selenate and selenite) and organic form (selenocysteine and selenomethionine) [82]. The high impact of selenium found naturally in the spleen, lymph nodes, and liver in enhancing the immune system in response to invading pathogens has been reported [83], although the exact mechanism of action is yet to be elucidated. It is, however, probable that selenium enhanced the immune system via the up-regulation of IL-2 expression on both NK cells and activated lymphocytes [84]. In the development, activation, and functioning of the immune effector cells, IL-2 plays a critical role by transducing signals, maintaining homeostatic regulation of regulatory T (TReg) cells, enhancing the separation of sub-T helper (TH) - TH1, TH2, and TH17 cells and activation of transcription factor 5 (STAT5) [85]. IL-2 also stimulates the production of TH1 by increasing the expression of IL-12 receptor β2 subunit (IL-12Rβ2) and T-bet, resulting in improved production of interferon-γ (IFNγ) [85] whose type I responses and downstream cascade would regulate coronavirus replicase system and induce effective adaptive immunity [43]. The dietary source includes Brazil nuts, seafood, organ meats, muscle meats, cereals, grains, and dairy products [86]. Moreover, annihilating capability of neutrophils [87], T cell counts [84], IL-2R affinity and expression on T cells [88, 89] and differentiation of T cells [90] are eliminated by selenium deficiency.

Possible role of Zinc in immunity to COVID-19 infection

The full capacity of zinc in the immune response is undisputed. It helps cellular growth, survival, and differentiation just as it is essential for the primary development of immunological cells, including neutrophils and natural killer cells. Thus, it improves the host defense system against infection [90-98]. Hence, zinc is critical in both non-specific and specific immunity [90]. Due to its role in influencing T lymphocyte proliferation when induced by IL-1 [99] and IL-2, it is crucial in immune response [100-

103]. Induction of IL-2 is implicated in the development, enactment, and activities of immune effector cells [85], which is useful in response to COVID-19 infection in a likely similar mechanism to selenium. The dietary intake of zinc includes nuts, beans, cereals, whole grains, oysters, red meat, and dairy products [104, 105]. Adhesive creams also contain zinc ranging from 17-34 mg/g [106], although excessive use can result in zinc toxicity.

Possible role of exercise in COVID-19 infection

Depending on its intensity and duration, regular exercise can enhance the immune system [107]. COVID-19 patients display high anxiety and depression [108], concomitantly affecting host mood as implicated in several studies [109-112]. Stress is indicated in immune-based mortality disease [113] by disturbing the homeostasis in immunological cells (for instance, distortion of T-helper cells) via the induction of excess stress hormones (serum corticosteroids and catecholamines hormones) [114] leading to a decrease in the host immunity [115]. Fortunately, moderate aerobic exercise has been reported in inhibiting stress hormones causing moderation between T-helper cells and thus enormously improving the mood and alleviating anxiety [115]. Moreover, moderation in pentraxin levels can enhance the immune system against COVID-19 infection, with too high levels of pentraxin observed in COVID-19 infected patients [116], speeding up the damage to the lungs [117]. Pentraxins, known for their crucial role in inflammatory responses and cytokine induction [118], can be regulated by increasing aerobic exercise, decreasing pentraxin levels, thus preventing lung damage [117, 118]. However, high-intensity exercise should be discouraged in COVID-19 patients with high fever due to the adverse effects on the immune system [119]. Continuous involvement in moderate exercise also triggers hormonal release, including immunoglobulins [120], which are great guardians of the respiratory tracts [121-123].

2. Discussion

Generally, this review explores the virology and pathogenesis of coronavirus while taking into account the rational functions of vitamins, supplements, and exercise in the quest to combat the COVID-19 infection. According to this study, PAMPs via their endosomal receptors play the leading role in eliciting an antiviral immune response, thus actuates necessary signaling cascades (activation of downstream NF-kβ signaling cascades), releasing proinflammatory cytokines. Similarly, the protective capability of vitamins is undisputed; however, optimal intake is strictly advised to ensure proper efficiency. For instance, the cytokine storm is a hallmark of severe COVID-19 patients; however, normal body intake of vitamins modulates appropriate signaling cascades and inflammatory factors as properly elicited earlier. Moderate expression of IL-2 by supplement is also implicated in the enactment of immune effector cells. Furthermore, moderate exercise inhibits stress hormones, decreases pentraxin level, and triggers the release of protective immunoglobin, thus resulting in a stronger immune system. Such a robust immune system is capable of combating not only COVID-19 infection but also similar infections and consequently improving human health.

3. Conclusion

The coronavirus is a leading cause of sickness and mortality worldwide without immunizations or proper treatment soon. So, increasing effort is needed in the present epidemiological, clinical, and trial investigations of compounds that can smother the pathogenicity of COVID-19 while keeping up the cell's integrity. Critical analysis of the roles of supplements, diets, and vitamins, as shown in this review, will enhance the capability of the immune system. Moreover, the role and mechanism of other immune boosters with great potentials, including herbs, in suppressing the pathogenic coronavirus should be given attention because there are no established approved treatment protocols and the WHO risk assessment results are very high.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors' contributions

Conceptualization, supervision, and data collection: Abdullahi Alausa; Writing – original draft: Rofiat Adeyemi, Barakat Olaleke, and Aminat Ismail; Writing – review & editing: Faith Sunday Oyelere; Final approved: All authors.

Conflict of interest

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgments

We appreciate our teachers and lecturers, especially from the Department of Biochemistry, Ladoke Akintola University of Technology, Ogbomoso, Nigeria.

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