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The Crosstalk between Dietary Constituents and Immunity: A Preventive Approach to Fight against Viral Diseases Like COVID-19

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Abstract

As till now there is no specific preventive and curative medicine available to treat against coronavirus disease 2019 (COVID-19), the best weapon to fight against this highly contagious disease is to boost our immune system. There are two paths of the immune system in our body, the innate and adaptive immune axis working 24/7 with their specialized sentinels capable of orchestrating responses against invading agents. These components of the immune system cannot work optimally in a nutrients deficient consortium. Micronutrient deficiency, called the hidden hunger occurs unknowingly when the quality of food people used to consume daily is not meeting the optimum requirement of vitamins and trace elements. In terms of immunity, the importance of crosstalk between the gastrointestinal (GI) tract microbiome with other distant organs, especially the respiratory system is a recent area of understanding. This review highlighted the contribution of macronutrients as well as the potential role of few vitamins, trace elements, and probiotics on preventive and therapeutic applications to strengthen the immune system along with gut homeostasis.

Keywords: COVID-19; Immune system; Micronutrient deficiency; Vitamins; Trace elements; Gastrointestinal tract microbiome; Macronutrients; Gut homeostasis

Introduction

COVID-19, a global pandemic is considered as the most crucial global health calamity of the century. The catastrophic impacts dysregulate every tire of the society specifically among vulnerable population. In a report based on 105 countries, it has shown that this highly contagious disease rapidly spread around the world, losing enormous health, economic, environmental, and social integrity to the entire human population [1]. Data collected from five regions over the world in the period from March to June 2020 illustrate that almost every country (90%) experienced disruption to its health services where low and middle-income countries were worst affected [1]. The first case of COVID-19 was likely occurred from a zoonotic transmission in China, in December 2019 and has now spread with ruthless speed to every continent on earth except Antarctica [2,3]. Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), the cause of COVID-19 was first reported to the World Health Organization (WHO) on December 31, 2019, and WHO declared it a global pandemic on March 11, 2020 [3]. There are seven human coronaviruses HCoV-NL63, HCoV-OC43, HCoV-229E, HCoV-HKU1, SARS-CoV, MERS-CoV, and SARS-CoV-2 [4,5]. Among them HCoV-NL63, HCoV-OC43, HCoV-229E, HCoV-HKU1 typically infect only the upper respiratory tract and cause minor symptoms whereas the other three coronaviruses SARS-CoV, MERS-CoV, and SARS-CoV-2 can replicate in the lower respiratory tract and cause pneumonia [5]. The causative virus SARS-CoV-2 is a positive-sense single stranded RNA-enveloped virus belonging to CoV family of beta coronavirus genus and shares 79% and 98% genetic similarity with SARS-CoV and bat coronavirus RaTG13 respectively [6,7]. In host cells, SARS-CoV-2 begins its life cycle when spike (S) protein (expresses on the surface of the virus particles, giving the characteristic "crown" appearance) binds to the cellular receptor Angiotensin-Converting Enzyme- 2 (ACE2) [8]. After receptor binding, the conformation change in the S protein facilitates viral envelope fusion with the cell membrane through the endosomal pathway. The host polymerase produces a series of subgenomic mRNAs by discontinuous transcription and finally translated them into relevant proteins [9]. The initial overlapping open reading frame ORF1a and ORF1b of the virus genome is translated by the host ribosomes into two large overlapping polyproteins, pp1a and pp1ab which are later cleaved into smaller products by viral proteinases [10]. Viral proteins and genomic RNA are subsequently assembled into virions in the Endoplasmic Reticulum (ER) and Golgi apparatus and

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then transported via vesicles and released out of the cell [11].

The majority of COVID-19 cases (about 80%) are asymptomatic or exhibit mild to moderate symptoms, but approximately 15% progress to severe pneumonia and about 5% eventually develop Acute Respiratory Distress Syndrome (ARDS), septic shock, and/or multiple organ failure [12-14]. Currently, no vaccine and effective drug are available against the COVID-19 [13]. Data shows that the mortality rate of COVID-19 varies dramatically across countries with a higher case fatality ratio has been reported in US (23.54%), India (15.63%), Brazil (15.05%) compared to that of the Spain (1.91%), Italy (1.02%) and UK (1.27%) and Germany (0.92%) [15]. The cause for these disparities is not well understood. Several hypotheses have been proposed, including the emergence and circulation of different strains of the virus with idiosyncrasies in COVID-19 testing strategies and policies across countries, quality, and access to health care and demographic factors such as the prevalence of elderly within a given population, socioeconomic factors and the immunity profile [15-19]. Despite the absence of guideline-supported recommendations, several therapies thought to be effective for COVID-19 are in use around the world where remdesivir and chloroquine/hydroxychloroquine are drug therapies that have received the most attention but later chloroquine/hydroxychloroquine group drugs found to be ineffective [20,21]. The treatment against SARS-CoV-2 is only supportive due to unavailability of specific antiviral drug and vaccine. Recently, Calder *et al.*, has highlighted the importance of optimal nutritional status to protect against viral infections and Wu *et al.*, has provided nutritional advices to reduce damages to the lungs from coronavirus and other lung infections [22,23].

A rapid and well-coordinated immune response represents the first line of defense against any kind of viral infection. The first line of defense is non-specific defense against any invading pathogen involving neutrophils, macrophages, and mast cells. After this step of preliminary elimination, the host organism mobilises the second battle force, the adaptive immune system, which consists of antibodies (Abs) called immunoglobulins (Igs), and B and T cells [24]. These Igs can initiate an immune response that will be able to memorize in the future if the same pathogen invades the body again. A strong immune system can be achieved by a balanced macro-micro nutrients rich diet and healthy way of living which can protect one by creating a barrier that stops those invaders from infecting the body. Recent research on the gut circuits has showed that, far beyond their role as nutrients and food components are the critical players in the operation of the immune system in health and disease [24-27]. Some recent studies have that a strong correlation exists between gut-lung microbiota and beneficial immune response which could be explored to tackle COVID-19 like viral infections [28,29]. Micronutrient deficiencies are highly prevalent even in high-income countries, especially among vulnerable populations such as infants, children, adolescents, during pregnancy and lactation, and the elderly and also who have restricted dietary habits such as food allergies, vegetarians of any subtype, and those having chronic [30-33]. The extent to which a virus can infect a host organism is determined by its virulence or severity and the ability of the hosts' immune response to tackle the intruders. The most protective way to combat this disease is to use our battle force, i.e., fight with components of the immune system.

Methods

A comprehensive search of the literatures with the broad term: "role of carbohydrates, proteins, lipids, vitamins and minerals in gut and lung health related to immunity and COVID-19 infections with its severity, and mortality" was conducted in the following databases; PubMed® (U.S. National Library of Medicine, USA), Web of Science® (Thomson Reuters, USA), and SciVerse Scopus® (Elsevier Properties S.A, USA). The review incorporated number of studied articles published (5th September, 2020) illustrated in English language (Terms of search, language and no. of study material and publication year).

Overview of Immune Response in Human Body

Immunity is the capability of the human body to resist a wide range of foreign organisms or toxins which are tending to damage tissues. It is of two types-innate (non-specific) which developed in a generalised manner and adaptive or acquired (specific) developed against specific foreign materials. All components of both axes of the immune system work synergistically and function in a highly orchestrated manner (Figure 1). The innate immune system, which identifies and attacks foreign threat in a rapid manner whereas the adaptive immunity is activated by exposure to pathogens, and uses an immunological memory to learn about the threat and exhibit the immune response accordingly. The adaptive immune response is much slower to respond to infections than the innate immune response, which is primed and ready to fight at all times.

Immune components

Unlike the innate immune system where a variety of cells carry out the response, the adaptive immune system relies on two types of cells to perform its tasks: B and T lymphocytes or cells. Both cells are derived from multipotent hematopoietic stem cells, in the bone marrow [20]. Both types of lymphocytes are derived originally from the pluripotent hematopoietic stem cells that form common lymphoid progenitor cells in the embryo. Almost all of the lymphocytes undergo some sort of differentiation or "preprocessed" before they end up in the lymphoid tissue. The lymphoid progenitor

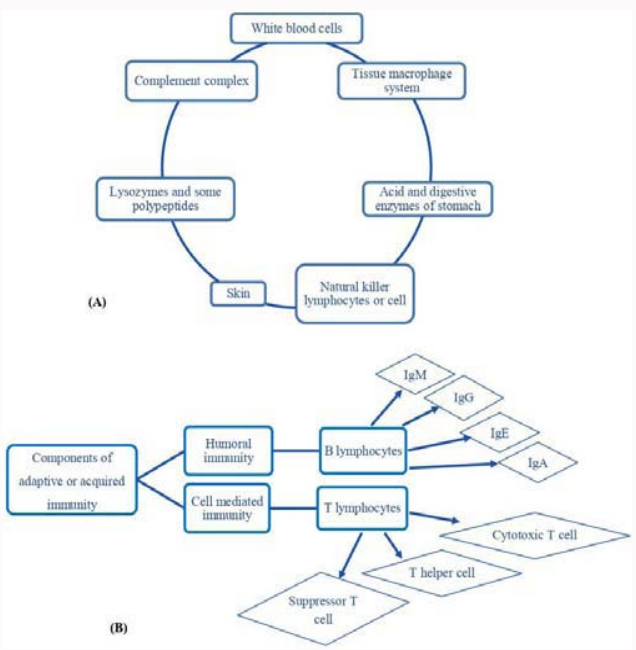

Figure 1: Overview of immunity (A) Crosstalk among various immune components of immune system, (B) Constituents of adaptive immunity. Ig=Immunoglobulin.

cells are designated to form activated T lymphocytes and at first, migrate to and preprocessed in the thymus gland, and thus they are called T lymphocytes. The other population of lymphocytes that was first discovered in birds in a special preprocessing organ called the bursa of Fabricius and so-called the B lymphocytes [20]. They are destined to form Abs and are preprocessed in the liver during mid fetal life and in the bone marrow in late fetal life and after birth. This population of cells is responsible for humoral immunity. After they are made in the bone marrow, they need to be processed and become activated. Each type of cell follows different paths to reach their final mature forms. The lymphocytes are located most extensively in the lymph nodes, but they are also found in special lymphoid tissues such as the spleen, submucosal areas of the GI tract, bone marrow, and thymus [20]. The distribution pattern of lymphoid tissue is such that the body can intercept the invading organisms or toxins before they can spread widely [e.g. the lymphoid tissue of the GI walls is exposed immediately to antigens (Ags) invading from the gut and the Ags that enter through the upper respiratory tract are countered by lymphoid tissue of the throat and pharynx (the tonsils and adenoids)]. Cells of the lymphoid tissue are distinctly divided into two major populations, the T lymphocytes which are responsible for forming the activated lymphocytes and provide "cell-mediated" immunity, and the other population, the B lymphocytes, responsible for forming and secreting Abs that provide humoral immunity (Figure 1). The invading agent first enters the tissue fluids and is carried to the lymph node or other lymphoid tissue by lymph vessels. After entering, the appropriate Ag immediately attaches to the Ab in the cell membrane which leads to the activation process of both the T and B lymphocytes [34].

Antigen-Presenting Cells (APCs)

Although B lymphocytes recognize intact Ags, T lymphocytes respond to Ags only when they are bound to specific molecules called Major Histocompatibility Complex (MHC) proteins on the surface of APCs in the lymphoid tissues (Figure 2). The MHC proteins are encoded by a large group of genes called the MHC. The MHC proteins bind peptide fragments of Ag proteins that are degraded inside APC and then transport them to the cell surface. There are two types of MHC proteins: (1) MHC class I proteins, which present Ags to cytotoxic T (T_c) cells, and (2) MHC class II proteins, which present Ags to T helper (T_H) cells. The three major types of APC are macrophages, B lymphocytes, and dendritic cells [20,34].

Macrophages

Millions of macrophages line the sinusoids of the lymph nodes, spleen, and other lymphoid tissue. Most invading organisms are first phagocytized and partially digested by the macrophages, and the antigenic products are secreted into the macrophage cytosol. The macrophages then pass these Ags directly to the lymphocytes by cell-to-cell contact leading to activation of the specified lymphocytic clones [20,34]. In addition to this, macrophages secrete a special activating substance, interleukin-1 (IL-1) that promotes still further growth and reproduction of the specific lymphocytes.

Dendritic Cells (DCs)

DCs are effective APCs that recognize pathogens and present pathogen-derived Ags to T cells. The interaction of DCs with Pathogen-Associated Molecular Patterns (PAMPs) or Damage-Associated Molecular Patterns (DAMPs) elicits the activation and maturation of DCs [35]. The increased expression of surface MHC molecules and co-stimulatory molecules and the increased production of cytokines occur with the activation of DCs, which allows the effective induction of the T cell response [36-38].

B lymphocytes

When specific Ags come in contact with T and B lymphocytes in the lymphoid tissue-specific T lymphocytes become activated to form active T cells, and certain of the B lymphocytes become activated to synthesise and release Abs or Igs. The Abs react in a highly specific manner against the particular types of Ags that initiated their development. When a naive B cell encounters an Ag that fits its membrane-bound Ab, it quickly divides to become either a memory B cell or an effector B cell, which is also called a plasma cell. Abs can bind to Ags directly though B cells and also express a specialized receptor, called the B Cell Receptor (BCR) [39]. BCRs assist with Ag binding, internalization as well as the processing of the Ag. BCRs also play an important role in signaling pathways. After the Ag is internalized and processed, the B cell can initiate signaling pathways, such as cytokine release for communication with other cells of the immune system. The Abs can inactivate the invading agent either by agglutination or precipitation or by neutralization [20].

T lymphocytes

In the case of the T Cell Receptors (TCRs) are present on the surface of the T cell membrane which are highly specific for one specified activating Ag. T cells are classified into three major groups: (1) T_H cells, (2) T_C cells, and (3) regulatory/suppressor T (T_{reg} or T_{sup}) cells. While in the thymus, the developing T cells start to express TCRs and other receptors called CD4 and CD8 receptors and it

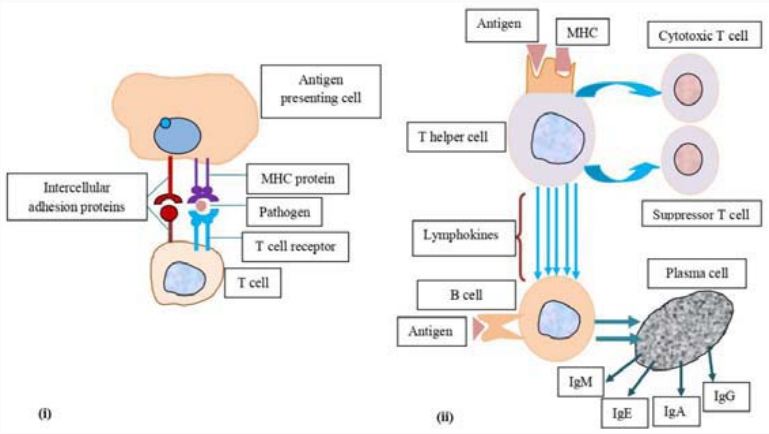

Figure 2: Mechanism of action of adaptive immunity (i) Interaction of Antigen presenting cell and T cell. (ii) Interplay between T helper cell and B lymphocyte.

needs to undergo positive ($CD4^+/CD8^+$) and negative selection. Double-positive cells ($CD4^+/CD8^+$) that interact well with MHC class II molecules and emerge as $CD4^+$ cells, whereas thymocytes that interact well with MHC class I molecules mature into $CD8^+$ cells [38]. T cell down-regulates the expression of its CD8 cell surface receptors becomes a $CD4^+$ [40]. Then positively selected $CD4^+$ cells to interact with MHC class II molecules of the APCs. T cells that interact strongly with the self-Ag, receive an apoptotic signal that leads to cell death and some of them which survive are selected to become T_{reg} or T_{sup}. T_{reg} modulate the immune system and maintain self-tolerance and prevent autoimmune diseases. The remaining T cells exit the thymus and enter in circulation as a mature naive T cell. During the developmental processes in the thymus, about 98% of thymocytes die by failing either positive selection or negative selection and only 2% survive which leaves the thymus to become mature immunocompetent T cells [41]. The thymus contributes fewer cells as a person ages.

Some protein molecules called IL (inter-means communication and leukin-means as many of these proteins are produced by leukocytes and act on leukocytes) are produced by lymphocytes are called lymphokines that mediate the act on other cells of the immune system, as well as on bone marrow cells for immune responses [42]. The T_H cells constituting more than three-quarters of all of T cells serve as the major regulator of virtually all immune functions by forming a series of lymphokines. Among the most important lymphokines secreted by the T_H cells are IL-2, IL-3, IL-4, IL-5, IL-6, Granulocyte-Monocyte Colony-Stimulating Factor (GMCF), and interferon (IFN). The lymphokine IL-2 is designed for causing the growth and proliferation of both T_C and T_{reg}. In the absence of the lymphokines from the T_H cells, the remainder of the immune system is almost paralyzed. Proliferating T_H cells differentiate into two major subtypes of cells known as T_H1 and T_H2 cells (also known as type 1 and type 2 helper T cells, respectively). Some of the T_H cells secrete lymphokines that activate the specified B lymphocytes. Indeed, without the aid of these T_H cells, the quantity of Abs formed by the B lymphocytes is usually slight [20,34].

Age-related immune response

With aging, a variety of changes are observed in the immune system, which translates into less effective innate and adaptive immune responses and increased susceptibility to infections enhancing morbidity and mortality. As a person ages, the thymus shrinks by about 3% a year throughout middle age with a corresponding fall in the thymic production of T cells, leaving peripheral T cell expansion and regeneration to play a greater role in protecting older people [41].

Cytokine storm in COVID

A prompt and well-coordinated immune response represents the first line of defense against any kind of viral infection. But an excessive inflammatory innate response and dysregulated adaptive host immune defense may cause harmful tissue damage both at the site of virus entry and systemic level. Cytokine profile in association with COVID-19 disease severity is characterized by increased IL-2, IL-7, IFN, inducible protein-10, Granulocyte-Colony Stimulating Factor (G-CSF), Macrophage Inflammatory Protein-1 (MIP-1), Monocyte Chemoattractant Protein-1 (MCP-1), and Tumor Necrosis Factor (TNF) and marked decrease in the levels of an absolute number of circulating $CD4^+$ cells, $CD8^+$ cells, B cells and Natural Killer (NK) cells as well as monocytes, eosinophils, and basophils [19-21,43,44]. Serum levels of proinflammatory cytokines like IL-6, IL-1β, IL-2, IL-8, IL-17, G-CSF, GMCSF, IP-10, MCP-1, CCL3, and TNFα were also found to increase in COVID-19 patients [45-47]. The excessive pro-inflammatory host response has been hypothesized to induce an immune pathology resulting in the rapid course of Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS) occurring in SARS-CoV-2 infected victims [48,49]. The massive cytokine and chemokine release, the so-called "cytokine storm", clearly reflects a widespread uncontrolled dysregulation of host immune defense [50]. Thus, given the key role of the immune system in COVID-19, a deeper understanding of the mechanism behind the immune dysregulation, as well as of SARS-CoV-2 immune-escape mechanisms might be a clue for the clinical management of the severe cases and for preventing the transition from mild to severe stages and future investigation concerning the systemic effects of the uncontrolled immune system on other physiological systems, such as the GI tract, neuroendocrine, renal and cardiovascular. A dysregulation in the balance of T_{reg} and T-native favors the naive T cells activity compared with T_{reg} cells which could be highly contributing to hyper inflammation. Huang *et al.*, found that plasma concentrations of IL-1β, IL-1ra, IL-7, IL-8, IL-9, IL-10, basic FGF, G-CSF, GM-CSF, IFN-γ, IP-10, MCP-1, MIP-1α, MIP-1β, PDGF, TNFα, and VEGF were higher in both ICU (Intensive Care Unit) patients and non-ICU patients than in healthy adults [51]. Moreover, when comparing ICU and non-ICU patients, plasma concentrations of IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1α, and TNFα were higher in ICU patients than non-ICU patients, thus indicating that the cytokine storm might be correlated with disease severity [51]. There are some recent report that the disruption of gut microbiome features by the host and environmental factors may predispose healthy individuals to abnormal inflammatory response as observed in COVID-19 [4,52]. In a study Gou et al. constructed a blood proteomic risk score for the prediction of COVID-19 progression to clinically severe phase and observed that core gut microbiota features were significantly correlated with proinflammatory cytokines in a set of 366 individuals, using a machine learning model [53]. Specifically; *Bacteroides genus, Streptococcus genus,* and Clostridiales order have been negatively correlated with most of the tested inflammatory cytokines, whereas the genus of *Ruminococcus, Blautia and Lactobacillus* have been positively associated. Moreover, fecal metabolomics analysis indicated some potential amino acid-related pathways (e.g. biosynthesis pathways of aminoacyl-tRNA, arginine valine, leucine, and isoleucine) that correlate core microbial features with host inflammation among 987 participants. Thus, the core intestinal microbiological characteristics, along with its related metabolites, should be further explored as potential predictors for the individual susceptibility to COVID-19 progression and severity that might represent potential targets for the prevention of susceptible populations, as well as for the development of the therapeutic approach in viral infection. Aging can lead to a weakening of the innate immune system which may play a role in the development of severe COVID-19. Specifically, a weak innate immune response in the elderly can lead to a higher load of SARS-CoV-2 and a consequent over activation of the adaptive immune system, leading to an increased level of cytokine production [54].

Diet in Immune Function

Adequate amount of appropriate nutrition is essential for optimal function of immune components. At the time of infection the energy requirement of the active immune system is enhanced than the basal level. The higher amount of energy demand can be met from diet (exogenous) as well as from body storage (endogenous).

Some dietary components and micronutrients have specific role in development, maintenance and optimum functionality of immune system throughout the life [55-57].

Role of carbohydrates, lipids and proteins

Dietary carbohydrates are quite healthy and 45% to 65% of total daily calorie should be from carbohydrates. However carbohydrates having low glycemic index; GIx are more beneficial than the carbohydrates with high GIx. Potentiality of carbohydrate containing foods to raise the postpandrial blood glucose level is termed as GIx [53-55]. Simple sugars like fructose, glucose and sucrose have a high GIx and complex sugars like polysaccharides have a low GIx. Recent studies found that other than GIx, fibre content of the food servings and glycemic load are two important parameters controlling the blood glucose level after a meal [58]. Metabolites of glucose such as Advanced Glycation End products (AGEs) which accumulate in adipose tissue and fatty liver is considered to be a potent dysregulator of the cytokines production whereas other metabolite flavonoid glycosides is a beneficial one as antioxidant and anti-inflammatory [55,59,60]. It is well established that carbohydrates can restore unfavourable changes in the immune system during a post-workout recovery by maintaining blood sugar levels [61]. Complex carbohydrates can boost up levels of serotonin (5-HT) in the brain and helps to cope stress response which in turn could modify the undesirable mobilisation of immune cells [62]. Some recent studies show that carbohydrate intake can reduce the susceptibility as well as morbidity of respiratory virus challenge by mobilising T lymphocytes [63].

Most foods have a combination of all types of fats and some have higher amounts of healthy fats than others. Dietary fatty acids (FAs) are of two types depending on the absence of double bond (saturated FAs-SFAs) and presence of double bond (unsaturated FAs-UFAs, polyunsaturated FA-PUFA) in their carbon backbone [64]. Studies show that eating foods rich in monounsaturated and polyunsaturated fats are beneficial for health [65]. Some FAs are called essential for mammals (eg. Linoleic acid, C-18:2 and α-Linolenic acid) due to the absence of enzymes within the body which could incorporate double bonds at carbon atoms beyond C-9 in the fatty acid chain cannot [66]. Some FAs such as n-6 PUFAs-linolenic acid (GLA; C18:3) and eicosapentaenoic acid (EPA; C20:5) are called conditionally essential FAs as they are essential for various important physiological functions at every stage of human life and they are synthesized in the body but also should be delivered with foods [67-69]. It is well established that Epithelial Cells (ECs) in the lungs and gut are the first line of protection from potentially harmful factors of the external environment and PUFAs are playing very effective immune modulating role either as pro or anti-inflammatory when act on ECs [70-72]. The enhanced n-3/n-6 PUFAs ratio have anti-inflammatory effect where n-3 PUFAs decrease the secretion of inflammatory cytokines such as IL-6 and/or IL-8 mediated by the nuclear receptor and Peroxisome Proliferator-Activated Receptor-gamma (PPAR) [73,74]. Natural food sources including nuts, dairy products, seeds, avocados and olives are abundant in (monounsaturated fatty acid). Sunflower oil, white olive oil and canola oil contains 85%, 75% and 58% MUFA respectively. Almond, peanut, grape seed, corn, sesame, whole grain wheat and safflower are some good source of MUFA. Foods such as salmon, mackerel, herring and albacore tuna, and trout and oils like walnuts, sunflower seeds and flax seeds or flax oil are with higher amounts of polyunsaturated fats [64]. Hilsa fish (*Tenualosa ilisha*), a highly preferred food among Bengali community is one of the best source of n-3 PUFAs, especially EPA and Docosahexaenoic acid (DHA) [75].

Dietary proteins or amino acids have long been known to boost up immune function and deficiency of these increase the susceptibility to infectious diseases. Protein malnutrition reduces concentrations of most amino acids in amino acid pool of body. Recent findings indicate the role of amino acids regulating immune responses by the activation of T lymphocytes, B lymphocytes, NK cells and macrophages and modulating cellular redox state, gene expression and lymphocyte proliferation [76,77]. The production of Abs, cytokines and other cytotoxic substances are also regulated by dietary proteins [78]. Increasing evidence shows that dietary supplementation of specific amino acids like arginine, glutamine and cysteine precursors to animals and humans with malnutrition and infectious disease enhances the immune status, thereby reducing morbidity and mortality. Arginine was found to be an enhancer of cellular immune mechanisms, in particular T cell function and also essential for the generation of Nitric Oxide (NO) by macrophages [79]. Glutamine is a nonessential amino acid that provides an important energy source for numbers of immune cells including neutrophils, macrophages, and lymphocytes [80]. It also serves as a precursor for nucleotide synthesis, particularly relevant for rapidly dividing cells such as the immune cells during an immune response. During infection, the rate of glutamine consumption by immune cells is equivalent or greater than that for glucose.

Role of vitamins and minerals

An efficient immune system requires adequate supply of micronutrients in terms of vitamins and minerals. It is well established that any deficiency of them can weaken the immune components and a person is predisposed to get infection. Inadequate micronutrients intake suppresses both the innate and adaptive immunity axis by reducing T cell and Ab response respectively [76,81]. Vitamins and minerals are known to play an important role in enhancing immune function, and having a regulatory function in both cellular and humoral immune responses [82]. Antioxidant vitamins and trace elements specific nutrient interventions can further enhance immune function in sub-clinical conditions, and so prevent the onset of infections or chronic inflammatory diseases.

Vitamin A: Among the different form of vitamin A, retinol, retinal, and Retinoic Acid (RA); RA shows the most biological activity [83,84]. RA exists in two significant derivatives: all-trans-RA (ATRA) and 9-cis-RA. Retinol transforms into retinal under the catalytic action of the Alcohol Dehydrogenase (ADH) family followed by catalysis of retinal to form RA by aldehyde dehydrogenase family (RALDH) [85,86]. RA is the ligand of the nuclear RA Receptor (RAR) protein family where the ATRA has the highest affinity to endogenous ligand of RAR [87,88]. The nuclear RAR acts as a ligand-activating transcription factor and regulates gene transcription depending on cell types and tissues [87]. Binding of RA to RAR leads to release of the co-repressor complex and associate with co-activator proteins, followed by altered transcription of downstream target genes and, ultimately changes in cellular function in an autocrine or paracrine manner [88-91]. Vitamin A is involved in the formation of the epithelial and mucous tissues which functions as the "front line" of defense against pathogen invasion [92]. ATRA acts on RAR in the nucleus of neutrophils, inducing neutrophil differentiation and heterogeneity through activation of the mTOR signaling pathway enhancing neutrophil extracellular traps and cytotoxicity [93]. By

down-regulating the expression level of IFN and up-regulating the secretion of IL-5, RA plays a regulatory role in the early differentiation stage of NK cells and T cells [94]. ATRA promotes the anti-inflammatory phenotype characteristic of intestinal DCs, the potent and versatile APCs [95,96]. It was found that the RA can modulate adhesion molecule integrin $\alpha 4\beta 7$ and T cell chemokine receptor, CCR9R which plays a crucial role in controlling T cell migration to the intestine [97,98]. In a signal transduction process receiving a RA signal, RARα binds to the RA response element in the integrin $\alpha 4$ gene and regulates the expression of $\alpha 4\beta 7$ [95,96]. Simultaneously, the heterodimer of RARα-RXR binds to the RAR response element in the promoter region of the CCR9 gene and promotes CCR9R expression [99,100]. RA is an essential regulator for intestinal homing of $CD4^+$ and $CD8^+$ T cells [83,101]. Based on the observations on ATRA induced homing of $CD4^+$ and $CD8^+$ T cells in intestinal lamina propia, ARTA augmentes T cell-based viral vaccines would be promoted for the gut or mucosal to provide increased protection from mucosal viral challenge [101,102]. ATRA inhibit the IL-6-driven induction of proinflammatory T_H-17 cells and promoted anti-inflammatory T_{reg} cell differentiation [103]. ATRA also regulate TGF-β dependent immune responses by interacting with TGF-β and activating the ERK1/2 signaling pathway to enhance histone modification of the Foxp3 promoter region and conserved non-coding DNA region. By this way ARTA helps in Foxp3 gene expression and regulates T_{reg} differentiation and function [103,104]. In addition to this, ATRA has also been reported to maintain both the stability of T_{reg} and their immunoregulatory function [104-107]. Furthermore RA can induce the differentiation of native B cells into B_{reg} which are a class of B cell subsets with immunomodulatory functions and stimulate B_{reg} synthesis to enhance the secretion of IL-10 through RARα [108-112]. Studies show that vitamin A and related retinoids supplementation can reduce the morbidity and mortality in different infectious diseases, such as measles, diarrhoeal disease, measles-related pneumonia, human immunodeficiency virus infection and malaria [83,85]. Vitamin A supplementation to infants has shown the potential to improve Ab response after some vaccines, including influenza virus, measles and anti-rabies vaccination [113]. ATRA could be a promising adjuvant for vaccine preparation especially for elderly peoples in terms of modulation in T_{reg} and B_{reg} of mucosal domain. But till now no data is available on role of RA/ATRA on immunomodulation in COVID-19 and so this area demands more attention.

Vitamin E: A fat-soluble vitamin, is a potent antioxidant and modulator of host immune functions [114]. The direct effects of this vitamin is exerted by alteration of cell membrane integrity which might be a consequence of alterations of signal transduction leading to functional changes in T cells [115]. The stimulatory effect on naive T cell function by vitamin E is associated with key signaling molecules like linker for activation of T cells family member 1 (LAT), tyrosine-protein kinase ZAP70-C (ZAP70), phospholipase and Vav proteins [116]. Vitamin E indirectly suppress inflammatory factors such as pro-inflammatory cytokines and PGE2 production of macrophages by inhibiting enzymatic activity of cyclooxygenase-2 (COX-2), a rate limiting enzyme involved in the conversation of arachidonic acid to prostaglandins [117,118]. In an animal based study the gene expression profile of T cells evidenced that vitamin E influences theT_H1/T_H2 balance [119]. It was reported from animal and human based studies that the immune-regulatory role of vitamin E is associated with reducing risk of respiratory infections, as well as some allergic diseases such as asthma [114,120,121]. Vitamin E might exert its effects on NK cell function by modulating NO levels where NO causes the nitration of $CD16^+$ tyrosine residues on NK cells [73]. However there are reports both in favour and against the effects of vitamin E supplementation which again direct the necessity of further study to evaluate its role on immunomodulation [79,122-124]. The differences in opinion might be due to differential dose of vitamin E supplementation used, magnitude of vitamin E level changes, age of subjects, and application of vaccine during study period and methodology adopted for analysis [125].

Vitamin C: The vitamin is an essential nutrient , cannot be be synthesized by humans due to lose (mutated and non-functional in the biosynthetic pathway) of a key enzyme L-gulonolactone oxidase (GULO), those catalyses the last step in the biosynthesis which is highly mutated and non-functional in the biosynthetic pathway [126,127]. Vitamin C contributes in boosting of immune system by supporting various cellular functions of both the innate and adaptive immune defence [128]. Vitamin C deficiency results in impaired immunity and higher susceptibility to infections. Vitamin C is well known as an essential antioxidant and enzymatic co-factor for many physiological reactions in the body [129,130]. In China promising results have been observed using intravenous vitamin C against COVID-19 [131]. Epidemiological studies have indicated that hypovitaminosis C (plasma vitamin C<23 mol/L) is relatively common in Western populations, and vitamin C deficiency (<11 mol/L) is the fourth leading nutrient deficiency in the United States [132,133]. There are several reasons why vitamin C dietary recommendations are not met, even in countries where food availability and supply would be expected to be sufficient. These include poor dietary habits, life-stages and/or lifestyles either limiting intakes or increasing micronutrient requirements (e.g. smoking and alcohol or drug abuse), various diseases, exposure to pollutants and smoke (both active and passive), and economic reasons (poor socioeconomic status and limited access to nutritious food) [134,135]. Even otherwise 'healthy' individuals in industrialized countries can be at risk due to lifestyle-related factors, such as those on a diet or eating an unbalanced diet, and people facing periods of excessive physical or psychological stresses [134,135]. The role of vitamin C in lymphocytes is less clear, but it has been shown to enhance differentiation and proliferation of B and T cells, likely due to its gene regulating effects [136]. There was a report during SARS coronavirus outbreak in 2003 where vitamin C was suggested to be a potent supportive therapeutic to reduce the susceptibility of respiratory tract infection [137]. Damages through the replication of influenza virus by the production of IFN-α/β at the initial stage of *Influenza A Virus* (H3N2) infections can be effectively prevented when vitamin C concentration is sufficiently high at the initial stage of viral infection [138]. Vitamin C in mega doses administered before or after the appearance of cold and flu symptoms for prevention and relief [139]. Several case studies of efficacy of vitamin C supplementation on viral infections strongly recommended the simultaneous administration of this vitamin along with other drugs for getting better prognosis [128,131,140-143].

Vitamin D: The classical role of vitamin D in human health is on calcium (Ca) and bone homeostasis. Some recent studies recognized the non-classical action of vitamin D upon cell proliferation, differentiation as well as immunologic effects resulting in an ability to maintain tolerance and promote protective immunity [144,145]. There have been multiple cross-sectional studies associating lower levels of vitamin D with increased rate of infection [146-148]. Vitamin

D is obtained from the diet or it is cutaneously produced after exposure to UVB light (290–315) nm [149]. Its synthesis is influenced by latitude, season, time of day, atmospheric components, clothing use of sunblock and skin pigmentation [150-152]. UVB radiation hit cholesterol in the skin cells and photolyzes 7-dehydrocholesterol (7-DHC) in the epidermis to pre-vitamin D_3 which again undergoes thermal isomerization to form vitamin D_3 [149]. This initial inactive vitamin D compound is next hydroxylated in the liver to form 25 OH vitamin D_3 [153]. Vitamin D may act in a paracrine or autocrine manner in an immune environment. Immune components such as APCs (macrophages and DCs), T and B cells have the necessary machinery to synthesize as well as respond to $1,25(OH)_2D_3$/$1,25(OH)_2D$ [154,155]. Vitamin D exerts its immunomodulatory role using three pathways: physical barrier, cellular natural immunity, and adaptive immunity [156]. These comprises of maintaining of cell junctions and gap junctions, increasing innate immunity by secretion of antiviral peptides which improves mucosal defences, decreasing the cytokine storm with influence on IFN and TNF-α and regulating adaptive immunity through inhibiting T_H1 responses and stimulation of T cells induction [157-160]. Vitamin D suppresses T cell proliferation which results a shift from a T_H1 to a T_H2 phenotype and also affects T cell maturation with a skewing away from the inflammatory T_H17 phenotype [160-164]. Furthermore it facilitates the induction of T_{reg} at the level of gene expression *via* Foxp3 which enhance differentiation of $CD25^+$ function of T_{reg} [165-168]. Fork head box-p3; Foxp3 is a negative regulator of immune response of T_{reg} cell lineage [169-171]. These modulations are inversely related to produce inflammatory cytokines (IL-17 and IL-21) and positively related to the production of anti-inflammatory cytokines such as IL-10 [172,173]. Vitamin D also has inhibitory effects on monocytes for the production of pro-inflammatory T_H1 cytokines such as IL-1, IL-6, IL-8, IL-12 and TNFα, and also up-regulates anti-inflammatory cytokines such as IL-10 [174-176]. Differentiation of DCs is also negatively regulated by decreased maturation with preservation of an immature phenotype as evidenced by a decreased expression of MHC class II molecules, co-stimulatory molecules and IL-12 [177,178]. The actions of $1,25(OH)_2D_3$ are mediated by its binding to the Vitamin D Receptor (VDR), which acts as a transcription factor to modulate the expression of genes in a tissue-specific manner [179,180]. Toll like receptors (TLRs) are main innate immunity receptors which are expressed on the cell membrane and intracellular vesicles and recognize several PAMPs and DAMPs to induce immune responses [181,182]. TLR binding leads to increased expression of both the 1-α-hydroxylase and the VDR [183,184]. This results in binding of the 1,25D-VDR-RXR heterodimer to the VDREs of the genes of various antimicrobial peptides such as cathelocidin and β-defensin 4 and subsequent transcription of these proteins [185-188]. These potent antimicrobial peptides exist in neutrophils, monocytes, NK cells and epithelial cells lining of the respiratory tract [189,190].

In recent days numbers of reviews supported the possible role of vitamin D in decreasing the risk of COVID-19 infections and mortality [155,157,191-194]. Vitamin D supplementation is also found to increase gene expression related to anti-oxidation (glutathione reductase modifier subunit) and by doing this, glutathione spares the use of vitamin C, which has potential antimicrobial activities [195-197], and has been suggested to prevent and treat COVID-19 infection [198,199]. The serum response to the given dose is largely varied between the individuals due to differences in demographic and biological variables, such as ethnicity, age, duration of exposure, seasonal variations, Body Mass Index (BMI), intake of certain medications, base-line concentration of vitamin D, genetics and type of vitamin D supplements [153,200,201]. It has been reported that in North America and Europe Influenza epidemics generally reach peaks in the months from December to March when UVB radiation exposure and serum levels of $1,25(OH)_2D$ are lowest among the population [202,203].

Zinc (Zn): Zn is known to be an important micronutrient for the immune system and the second most abundant trace metal in the human body after iron [204]. Even a mild deficiency in Zn has been associated with widespread defects in both the adaptive and innate immune response and its deficiency has been associated with increased susceptibility to infectious diseases, including viral infections [205-208]. A daily intake of up to 15 mg of Zn is needed to maintain a steady-state as there is no specific Zn storage system in the body [204]. It plays a vital role for more than 300 enzymes in the body, and also responsible for protein synthesis, wound healing, DNA synthesis, cell division and is required for proper sense of taste and smell [209-211]. Zn promotes the number of T_H-cells through its anti-apoptotic effects at both the peripheral and thymic levels by conferring cells' resistance to apoptosis inhibiting caspases-3, 6, and 9, and increasing of the Bcl-2/Bax ratio [212]. Furthermore, Zn also helps to maintain robust immune responses by influencing expression of proinflammatory cytokines such as TNF-α, IL-1β, IL-6, IL-8, and MCP (Monocyte Chemoattractant Protein)-1 and down-regulating inflammatory cytokines by decreasing gene expression of IL-1β and TNF-α of activity [213]. Several studies in the past have stated that Zn has a broad-spectrum antiviral activity against a variety of viruses [214-217]. Zn^{2+} inhibits the entry of the virus into the cell may by offering protection or stabilization of the cell membrane [216]. Metallothioneins (MT), a family of low Molecular Weight (MW), cysteine-rich proteins help in storage and transfer of Zn^{2+} and could contribute to the antiviral effects of Zn [217]. Schoggins *et al.*, showed that over expression of multiple members of the MT1 family inhibits the replication of flavi viruses (e.g. yellow fever virus and hepatitis C virus, HCV), as well as the alpha virus (Venezuelan equine encephalitis virus) [216]. Antiviral effects of MT may be either directly with sequestering away from the viral metalloproteins or indirectly by acting as Zn chaperones and facilitating antiviral signaling [217]. Zn inhibits viral replication through interference with the viral genome transcription, protein translation, polyprotein processing, viral attachment, and un-coating [218]. During sepsis, Zn homeostasis is profoundly altered with Zn^{2+} moving from the serum into the liver and may also act synergistically when co-administered with standard antiviral therapy [219,220]. Increased intracellular Zn^{2+} concentrations inhibit RNA-dependent RNA polymerase; RdRp and other proteins essential for the completion of different phases of the virus life cycle [221,222]. It is now choosing to target viral RdRp by Zn^{2+} for novel antiviral drugs since their activity is strictly virus-specific and may be blocked without severely affecting key cellular functions. An inhibitory effect of Zn on the function of viral RdRp was demonstrated in cases of rhinoviruses, HCV, and influenza virus [223,224]. In particular, *in vitro* studies have demonstrated that Zn salts can reduce HCV replication in *Escherichia coli* by 50% (at 100 μM $ZnSO_4$) by inhibiting the HCV RdRp [225]. Zn effectively inhibits the RNA-synthesizing activity of nido viruses which is a large group of positive-strand RNA (+RNA) viruses and includes major pathogens of humans and livestock, such as SARS-CoV and other human coronaviruses, the arteri viruses [e.g. Equine Arteritis Virus

(EAV)], and Porcine Reproductive and Respiratory Syndrome Virus (PRRSV) [226,227]. Another study shows that Zn can alter RdRp activity during the elongation phase of RNA synthesis probably by directly affecting template binding of Zn^{2+} which could be reversed by the addition of a chelator of Zn^{2+} (MgEDTA) [225]. Thus, it may be hypothesized that in the case of coronaviruses, Zn^{2+} may inhibit both the proper proteolytic processing of replicase polyproteins and RdRp activity [225]. RDR and 3CLpro protease of SARS CoV-2 shares over 95% of sequence similarity with those of SARS-CoV instead of the fact that these two viruses demonstrate only 79% sequence homology at the genomic level [228]. In a case study among 103 children (1 month to 5 years) with pneumonia, Murillo A et al., showed that there was a statically significant clinical improvement (duration of illness, respiratory rate, and oxygen saturation) with Zn supplementation. They also demonstrated an increase in the cytokine response in the T_H1 pattern (IL-2 and INF-g) only in the Zn group, with T_H2 cytokines (IL-4 and IL-10) being elevated or remaining high in both groups [229,230]. Another Randomized Control Trial (RCT) on oral supplementation of high-dose Zn (150 mg/day) after stem cell transplantation demonstrated that it enhances thymic þ function and the output of new $CD4^+$ naive T cells, helping to prevent the reactivation of Torque Teno Virus (TTV) [231]. The above observations indicate that Zn could play a promising role by acting synergistically when co-administered with standard antiviral therapy in SARS-CoV-2 as well.

Selenium (Se): Se is essential to human health in trace amounts with a narrow range of dietary deficiency (<40 μg/day) but harmful in excess having toxicity (>400 μg/day) [231,232]. So the dietary intake of Se needs careful control. In nature, Se exists mostly in two forms, namely as selenites with tetravalent (Se^{4+}), and as selenates with hexavalent (Se^{6+}) cations, respectively, from which all other Se species are derived [233,234]. Only one chemical form (sodium selenite, Na_2SeO_3) can offer true protection and the other forms can display toxicity to humans [231]. In a recent study, Nuttal *et al.*, indicated that Se concentration in human serum ranges from 400 to 30000 μg/L, and the levels >1400 μg/L being non-toxic [231]. The mode of antiviral activity of Se is by rendering viral entry into the host cell. It has been established that corona like RNA-viruses start its multiplication by attachment with host cell membrane followed by viral entry into the cell [233,235-237]. The native glycoproteins (gp120) of the viral membrane maintained their structure by intra-molecular disulfide bonds in such a way that they can hide the hydrophobic regions inside their tertiary structure [238]. After attachment with hosts' epithelium these proteins form hydrophobic spikes which are essential for making holes in the host cell membrane for entering into the cell [239,240]. Formation of hydrophobic spikes are catalysed by viral protein disulfide isomerase [PDI-$(SH)_2$]; an enzyme (chaperonic protein) predominantly present in the ER [239]. When one or more thiol groups of [PDI-$(SH)_2$] is oxidised by some reducing agents like Se^{4+}; the sulfhydryl groups (SH_2) in the active site of PDI transformed to inactive disulfide [Se^{4+}+PDI-$(SH)_2$→PDI-SS-PDI+Se^{2+}] [241,242]. The transfer of two electrons reduced Se^{4+} to Se^{2+} and the PDI become oxidized (PDI-SS-PDI) subsequently prevents the formation of reduced hydrophobic gp120 [239,243]. Hydrophobic pockets of gp120 are then unmasked and subsequently in absence of proper chaperones (proteins that assist the conformational folding or unfolding of macromolecules) gp120 react with one another and incorrectly assembled to form large aggregates in viral membrane [244]. Consequently the ability of making hole by hydrophobic viral spikes followed by its entry into host cytoplasm is being prevented [245,246]. Na_2SeO_3 is such a powerful oxidizing agent that oxidizes thiol groups in the viral protein disulfide isomerase and withholds it to penetrate the healthy cell membrane [247,248]. Organic Se compounds are less toxic than inorganic one, but the LD_{50} doses of it vary greatly depending on the duration of exposure, the experimental model, and the blood concentrations achieved (233,249). Se-supplementation may have both beneficial and detrimental effects on cellular immunity and these effects are largely dependent on the form of Se and the supplemental dose. The two important effectors axis of anti-viral immunity, are: Ag-specific T cell proliferation and content of cytotoxic granules are differentially modulated by Se-supplementation [235,250,251]. The importance of using an appropriate Se dose was further highlighted by an analysis of cytolytic enzymes where following supplementation with Se-yeast at 200 μg/day, fewer granzyme+$CD8^+$ cells were noted. However, in the same study dose of 50 μg/day Se-onion increased both granzyme and perforin content of $CD8^+$ cells. So, both the doses and forms of Se used in supplementation can have differential effects which further emphasized the importance of maintaining the form and critical range of dietary Se [250]. Since cytotoxic granule-mediated killing by Cytotoxic T Lymphocyte (CTL) occurs within hours of target cell recognition and perforin up-regulation occurs within hours of activation, it is unlikely that was an immediate consequence of the loss or gain through cytolytic activity [252,253]. It has been found that although plasma Se levels remained relatively unchanged following daily intake of Se-onion in meals, supplementation with Se-onion up-regulated the expression of several selenoprotein genes, including selenoprotein S that is involved in several aspects of immune responses such as enhanced cytokines production (IL-8 and IL-10) which has a wide range of pleiotropic effects, ranging from antioxidant effects to anti-inflammatory properties [254-257]. A recent study by Sies and Parnham *et al.*, demonstrated the therapeutic potential of ebselen, an organoselenium compound, as an inhibitor of the protease of SARS-CoV-2 [235]. A series of study of Beck laboratory in the 1990s showed that host Se deficiency increased the virulence of some RNA viruses such as coxsackie virus B3 and influenza A [258,259]. They also propose that Se-deficient animals could not produce sufficient antioxidant selenoproteins for its protection and the consequence was the mutation of the virus to a virulent form that caused more severe pathology [258,259]. In some review, significant clinical benefits of Se supplementation have also been demonstrated in other viral infections, including human immunodeficiency viruses-1 (HIV-1) where a negative correlation between Se status and mortality has been established [236,237,260,261]. In a recent report by Zhang J *et al.*, showed that the cure rate of COVID-19 inside Hubei province of China, of which Wuhan is the capital, was significantly lower (13.2%) than that in all other provinces combined outside the Hubei (40.6%) (P<0.0001) and the death rate inside Hubei province was significantly higher (3.0%) than the death rate in provinces outside Hubei (0.6%) (P<0.0001) [262,263]. Moreover, the cure rate in Enshi city was much higher (36.4%) than that of other Hubei cities, where the overall cure rate was 13.1% (P< 0.0001) and interestingly Enshi is renowned for its high Se intake and status [mean±SD hair Se: 3.13±1.91 mg/kg for females and 2.21±1.14 mg/kg for males] in comparison with typically low levels in Hubei of 0.55 mg/kg [264,265]. Heilongjiang province in northeast China, a notoriously low Se region in which Keshan (a disease related to an extremely low level of Se in the body) occurred had a much higher death rate (2.4%) due to SARS-CoV-2 than that of other provinces (0.5%; P<0.0001) of China [263]. An RCT

including 725 institutionalized elderly patients, studying delayed-type hypersensitivity skin response, humoral response to influenza vaccine and infectious morbidity and mortality showed that low-dose supplementation of Zn together with Se provides an increase to the humoral response after vaccination in comparison to the control group [264,266]. Se as food supplementation should be carried out in a controlled way, to avoid the opposite effect because Se is one of the most toxic elements in relatively small quantities and at the same time an essential micronutrient with an important biological role. The above observations pointed out the need of a detailed demographic study in aspects of COVID-19 along with food content and geochemical analysis of Se. The Se content of soil is controlled by various parameters like pH and hydration of the soil, rainfall, and occurrence of flood, and differential irrigation pattern [267,268] greatly varies due to its geographical nature.

Magnesium (Mg): Mg plays a vital role in regulating immune function by exerting a marked influence on Ig synthesis, immune cell adherence, Ab-dependent cytolysis, IgM, lymphocyte binding, macrophage response to lymphokines, and TH-B cell adherence [269]. Some *in-vitro* and *in-vivo* studies suggest that Mg is likely to play a role in the immune response against viral infections [270]. A Singapore based cohort study has found that the combination of vitamin D, Mg, and vitamin B_{12} (DMB) could reduce the rate of progression in older patients with COVID-19 in respect to a significant reduction in the proportion of patients with clinical deterioration requiring oxygen support and/or intensive care support [271]. Mg deficiency negatively modulates immune components such as a drop of T cells, increased plasma concentration of inflammatory cytokines, and endothelial dysfunction [272-274]. DMB study also hypothesized that a low Mg status, which is rather common, might instigate the transition from mild to critical clinical manifestations of the COVID-19 [271]. Mg supplementation might be a potential supportive management tool to cope up with the stress triggered by the pandemic as well as the Post-Traumatic Stress Disorder (PTSD) that will plague COVID-19's survivors, health professionals, and common people who have to face important changes of their habits and lifestyle. Correct serum levels of Mg could be an effective and inexpensive preventive countermeasure against the virus and hence fundamental research on an epidemiological and clinical basis is needed to further clarify the potential role of Mg deficiency in COVID-19.

Copper (Cu): Cu plays a crucial role in immunity by participating in the development and differentiation of immune cells [45]. Some *in-vitro* studies have shown that Cu demonstrates antiviral properties such as thujaplicin-Cu chelates inhibit replication of human influenza viruses, while intracellular Cu has been shown to regulate the influenza virus life cycle [275,276]. Turnlund *et al.*, conducted a study to determine the effect of long-term high Cu intake on indices of Cu status, oxidant damage, and immune function [277]. Their results showed that plasma ceruloplasmin activity, benzylamine oxidase, and superoxide dismutase were significantly higher when Cu intake was 7.8 mg/day, in comparison to 1.6 mg/day, indicating an improvement in antioxidant status. However, the higher Cu intake (7.8 mg/day) significantly reduced the percentage of circulating neutrophils, serum IL-2R, and the Ab titer against the Beijing strain of influenza [277]. Both pathogens and the hosts require Cu as an essential micronutrient during viral infection [278]. Cu is involved in the functions of critical T_H cells, B cells, neutrophils, NK cells, and macrophages [278]. Cu-deficient humans show an exceptional susceptibility to infections due to the decreased number and function of these immune components. Moreover, Cu can kill several infectious viruses such as bronchitis virus, poliovirus, HIV-1, other enveloped or non-enveloped, single or double-stranded DNA and RNA viruses [279,280]. In addition to that Cu has the capacity of contact killing of several viruses, including SARS-CoV-2 [281,282]. Based on available data, it can be hypothesized that enrichment of plasma Cu levels would be helpful to boost both the innate and adaptive immunity. Study showed that Cu exposure to human coronavirus 229E destroyed the viral genomes and irreversibly affects virus morphology, including the disintegration of envelope and dispersal of surface spikes [281]. In a cell-based study, Cu^{2+} was found to block papain-like protease-2, a protein that SARS-CoV-1 requires for replication [279,280]. Cu Oxide Nanoparticles (CuONPs) are widely used as catalysts so that the ability of CuONPs to reduce virus application is enhanced [283-286], nanosized Cu(I) iodide particles also show inactivation activity against H1N1 influenza virus (285) and Au/Cu sulfide core-shell nanoparticles (Au/CuS NPs) exhibit variable virucidal efficacy against human norovirus (HuNoV) via inactivation of viral capsid protein [282-286]. The results of the third National Health and Nutrition Examination Survey (NHANES III, 2003) in the USA showed that the mean daily intake of Cu, was (1.54–1.7) mg/day for men and (1.13–1.18) mg/day for women (depending on age) [286]. These results further emphasize that a large portion of the population may have insufficient dietary Cu intake and are suffering from mild Cu deficiency and Cu supplementation may have the protection of people from COVID-19.

Role of Gut-Lung Axis

In recent days numbers of studies demonstrate the existence of a bidirectional relay system in terms of microbiota, their metabolites, immune response as well as alteration of inflammatory patterns between gut and lungs known as gut-lung axis [287-291]. The Gut-Associated Lymphoid Tissue (GALT) is the largest mass of lymphoid tissue in the body which harbors immune cells such as B and T lymphocytes, APCs including macrophages and DCs, and specific epithelial and intraepithelial lymphocytes [292,293]. Natural Ags, such as food proteins and microbiota components, are strong stimuli for the development of the GALT suggesting that luminal Ags and local immune cells influence each other in a circuit of interactions where gut microbiota has a critical role in mediating immune responses in distant sites, including the lungs [294]. However, the cause and effect of this crosstalk is yet to establish and whether the disturbances of gut microflora and alterations of their metabolites are the resultant of lung pathophysiology or vice versa is needed to be explored. The intestine is the largest interface between the body and the external environment and most contacts with foreign antigenic materials occur at the gut mucosa [295]. The gut disturbances in lung diseases including asthma, allergy, chronic obstructive pulmonary disease, cystic fibrosis, and lung cancer were observed by extensive studies [289,296-298]. The role and mechanism underlying the changes in immune responses and reshaping inflammation due to the alteration in intestinal microbiota on respiratory viral infections have been studied in recent years [299-302]. The linear relationship between the reduction in microbes diversity in the GI tract and increased mortality due to respiratory viral infection was also observed [303]. This increase in mortality to respiratory viral infection was associated with an altered immune response characterized by increased lung IFN-g, IL-6, and CCL2, and decreased count of T_{reg}-cells in lung and intestine [304]. Bidirectional virome-microbiome interactions are thought to predispose individuals to bacterial infections [296,305]. The proposed mechanisms underlying this hypothesis include the

aggregation of bacterial pathogens due to disruption of respiratory-epithelium barrier by virus; facilitation of colonisation of specific types of bacterial species which can feed on host-derived nutrients liberated during viral infections; reduction of virus-mediated mucocilliary clearance, and weakening of innate and adaptive immune system of host due to viral pathogenesis [306-312]. One of the best known example of such Viro-Bac interaction was the century old Spanish-flu pandemic in 1918-1919, where after initial infection with *Influenza A*, millions of individuals were succumbed to death due to secondary infection with pneumonia [313]. In a study Groves *et al*., showed that viral lung infections also caused an increase in colonic Muc5ac levels and fecal lipocalin-2, indicating low-grade inflammation in the gut [314]. In another study, the higher population of butyrate-producing bacteria in intestinal microbiota was found to be a contributor to the risk of lower respiratory tract infection following viral infection in patients with allo-HCT [315]. These reports pointed out the role of the appropriate supply of dietary proteins in the formation and maintenance of lymphoid structures such as the gut mucosa. The biologically active form of vitamin A (retinol) is RA which requires two steps conversion in the human body. The first step, from retinol to retinal, is catalyzed by a subfamily of ADH commonly expressed in most cells (including immune cells) but the second step is an irreversible conversion of retinal to RA that is catalyzed by retinal dehydrogenases (RALDH), which are expressed in specific cell types [316]. Only in gut DCs (from laminapropria, mesenteric lymph nodes, and PP) some specific subsets of laminapropria macrophages have the enzyme RALDH to catalyze that irreversible step [317]. In a randomized double-blind study on Malaysian pre-school children aged (2–6) years old, it was shown that *Bifidobacterium longum* BB536, a multifunctional probiotic has relieved the upper respiratory diseases by intestinal microbiota modulating properties [318,319]. The abundance of the genus *Faecalibacterium* associating with anti-inflammation and immuno-modulation was significantly increased by the BB536 (*Bifidobacterium longum*, a multifunctional probiotic) treatment compared to the placebo group. Moreover, *Bifidobacterium infantis*, a recombinant probiotic bacteria, has been proposed as a possible therapeutic agent against lung cancer [289,320]. Vitamin D can also develop a healthy gut microbiota, maintaining the integrity of the gut. Metabolites such as Short-Chain FAs (SCFAs) can reach other organs via the bloodstream to exert immune regulation and anti-inflammatory effect [321]. Recent trends to search for novel therapeutic strategies that target manipulation of the gut microbiome by antibiotics, probiotics, prebiotics, natural products or diets have been tried in various lung diseases [322-325]. Probiotics regulate the functions of systemic and mucosal immune cells and intestinal epithelial cells of the host to regulate immune function, but not all probiotics demonstrate similar health benefits [326,327]. Therefore, probiotic products should be carefully selected depending on the clinical situation, to obtain the relevant beneficial effect. Translational data suggested that an alteration in the metabolic profile of T cells in obese individuals impairs the activation and function of these critical adaptive immune cells [326,328]. The manipulation of the gut microbiota and metabolites as the therapeutic approach showed encouraging results in most of the cases. They can restore the dysbiosis of microbiota and enhance the immune responses. The effects and mechanisms of these therapeutic approaches on the overall host-microbe interactions and progression of lung diseases need to be understood properly by future endeavours.

Physical Activity, Obesity, and Immune Response

The relationship between physical activity, immunity, and susceptibility to URTI has been well investigated [329-331]. Observational and experimental studies have further proposed that the moderately active lifestyles offer greater resistance to pathogens by changing the host defense possibly *via* greater immunosurveillance associated with moderate activity [332]. It is now well-established that obesity in terms of the degree of severity, duration, and differential distribution of the adipose tissue in the body is a pandemic for a generation as well as susceptibility to develop several diseases along with immuncompromisation [333,334]. Obesity is a state of chronic low-grade inflammation having a greater risk of developing infections, particularly those of the respiratory symptoms compared to individuals with a normal BMI (>30 kg/m^2) [335,336]. The study suggested that regular aerobic exercise can prevent, limit, or delay the age-associated decline in immune function referred to as immunosenescence [337-339].

Over the past 30 years, numerous studies have been done on the role of psychological stress on the regulation of immune functions [340]. Stress associated responses are conveyed by sympathetic fibers and descend from the brain into primary (bone marrow and thymus) and secondary (spleen and lymph nodes) lymphoid tissues [341]. A wide range of adrenergic substances released by these fibers can modulate immune responses by binding with adrenergic receptors present in all types of lymphocytes with differential density and expressivity [340-342]. Rosso D *et al*., reported that a reciprocal relationship exists between chronic stress and antitumor immunity since adrenergic signaling has been shown to inhibit immune responses in both autoimmune diseases and infection models [343].

Conclusion

For a viral disease like COVID-19, where no pharmacological strategies for prevention or treatment are presently available and where the exact time of the ending of the alarming situation is unknown, nutritional strategies for enhancing immunity is something to be explored. At the present moment, the therapeutic salute to deal with this disease are only supportive. An optimally functioning immune system is the most powerful safeguard against viral infections at a time when the possibility of having an effective vaccine is months away, if not years. Prevention is always better than cure and we can prevent ourselves from COVID-19 like pandemic by maintaining a good lifestyle in terms of proper diet, physical activities and coping strategies to manage stress in a round manner.

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