SCIENCEFORECAST
A digital science library

Review Article
Published: 17 Dec, 2020

Journal of Nutrition and Food Science Forecast

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

Basu BR*

Faculty, Surendranath College, University of Calcutta, Kolkata, India

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

OPEN ACCESS

Correspondence:
Basu BR, Department of Physiology, Surendranath College, University of Calcutta, Kolkata, West-Bengal, India.
E-mail: *braybasu@gmail.com*

Received Date: *22 Oct 2020*
Accepted Date: *11 Dec 2020*
Published Date: *17 Dec 2020*

Citation: *Basu BR. The Crosstalk between Dietary Constituents and Immunity: A Preventive Approach to Fight against Viral Diseases Like COVID-19. J Nutri Food Sci Forecast. 2020; 3(1): 1015.*

ISSN 2643-8186

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

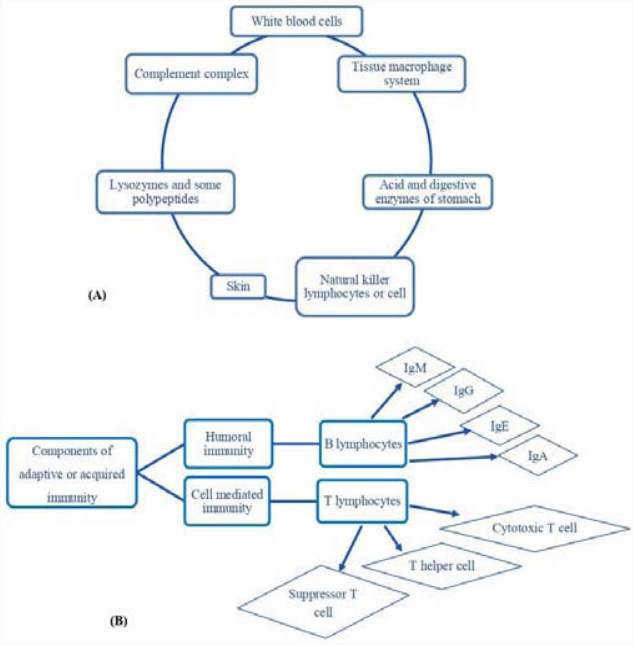

Figure 1: Overview of immunity (A) Crosstalk among various immune components of immune system, (B) Constituents of adaptive immunity. Ig=Immunoglobulin.

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

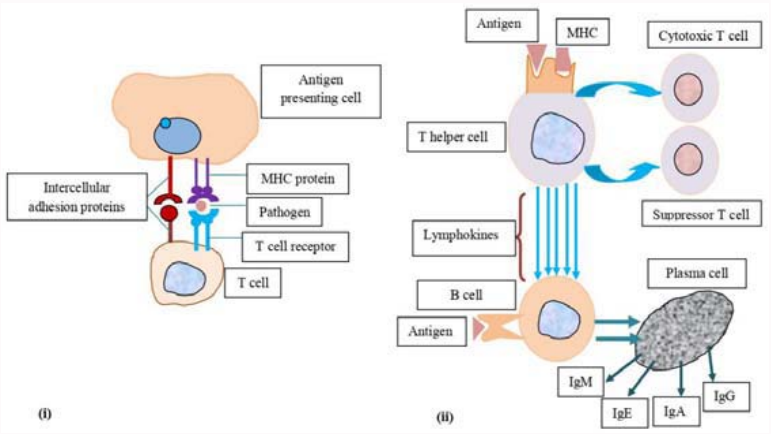

Figure 2: Mechanism of action of adaptive immunity (i) Interaction of Antigen presenting cell and T cell. (ii) Interplay between T helper cell and B lymphocyte.

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.

References

1. World Health Organization. In WHO global pulse survey, 90% of countries report disruptions to essential health services since COVID-19 pandemic. 2020.
2. Mackenzie JS, Smith DW. COVID-19: a novel zoonotic disease caused by a coronavirus from China: what we know and what we don't. Microbiol Aust. 2020.
3. World Health Organization. Situation report-198. 2020.
4. Catanzaro M, Racchi M, Govoni S, Lanni C, Fagiani F, Corsini E. Immune response in COVID-19: addressing a pharmacological challenge by targeting pathways triggered by SARS-CoV-2. Signal Transduct Target Ther. 2020; 5: 1-10.
5. Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. Nat Rev Microbiol. 2019; 17: 181-192.
6. Corman VM, Muth D, Niemeyer D, Drosten C. Hosts and sources of endemic human coronaviruses. Advin Virus Res. 2018; 100: 163-188.
7. Lu R, Zhao X, Niu P, Wang W, Huang B, Ma Xuejun, et al. Genomic

characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020; 395: 565-574.

8. Zheng J. SARS-CoV-2: an emerging coronavirus that causes a global threat. Int J Biol Sci. 2020; 16: 1678-1685.
9. Sariol A, Perlman S. Lessons for COVID-19 immunity from other coronavirus infections. Immunity. 2020; 53: 248-263.
10. Nakagawa K, Lokugamage KG, Makino S. Viral and cellular mRNA translation in coronavirus-infected cells. Adv Virus Res. 2016; 96: 165-192.
11. Hoffmann M, Weber HK, Schroeder S, Drosten C, Kruger N, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020; 181: 271-280.
12. Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. Methods Mol Biol. 2015; 1282: 1-23.
13. Chowdhury MA, Hossain N, Kashem MA, Shahid A, Alam A. Immune response in COVID-19: a review. Journal of Infection and Public Health. 2020; 13: 1619-1629.
14. Mason RJ. Pathogenesis of COVID-19 from a cell biology perspective. Eur Respir J. 2020; 55: 2000607.
15. COVID-19Coronavirus/Cases. Worldometer. 2020.
16. Tang X, Wu C, Li X, Song Y, Yao X, Wu X, et al. On the origin and continuing evolution of SARS-CoV-2. Natl Sci Rev. 2020; 7: 1012-1023.
17. Yao H, Lu X, Chen Q, Xu Kaijin, Chen Y, Cheng L, et al. Patient-derived mutations impact pathogenicity of SARS-CoV-2. BMJ Yale medRxiv. 2020.
18. Coronavirus has mutated into 30 strains and ones in US are less deadlier than those in Europe, finds study. News Break. 2020.
19. Dowd JB, Andriano L, Brazel DM, Rotondi V, Block P, Ding X, et al. Demographic science aids in understanding the spread and fatality rates of COVID-19. Proc Natl Acad Sci USA. 2020; 117: 9696-9698.
20. Hall JE. Guyton and Hall Textbook of Medical Physiology. Elsevier. 2016.
21. Faria AMC, Santos ACG, Goncalves JL, Moreira TG, Medetos SR, Dourado LPA, et al. Food components and the immune system: from tonic agents to allergens. Front Immunol. 2013; 4: 1-16.
22. Calder PC, Cazz AC, Gombart AF, Eggersdorfer M. Optimal nutritional status for a well-functioning immune system is an important factor to protect against viral infections. Nutrients. 2020; 12: 1-9.
23. Wu J, Zha P. Treatment strategies for reducing damages to lungs in patients with coronavirus and other infections. Preprints. 2020.
24. Lee YK, Mazmanian SK. Has the microbiota played a critical role in the evolution of the adaptive immune system? Science. 2010; 330: 1768-1773.
25. Maslowski KM, Mackay CR. Diet, gut microbiota and immune responses. Nat Immunol. 2011; 12: 5-9.
26. Chang CS, Kao CY. Current understanding of the gut microbiota shaping mechanisms. J Biomed Sci. 2019; 26: 1-11.
27. Amedei A, Boem F. I've gut a feeling: microbiota impacting the conceptual and experimental perspectives of personalized medicine. Int J Mol Sci. 2018; 19: 3756.
28. Zhang D, Zhang Z, Li S, Wang N, Tan HY, Zhang Z, et al. The cross-talk between gut microbiota and lungs in common lung diseases. Front Microbiol. 2020; 11; 301.
29. Man WH, Piters WAADS, Bogaert D. The microbiota of the respiratory tract: gatekeeper to respiratory health. Nat Rev Microbiol. 2017; 15: 259-270.
30. European Centre for Disease Prevention and Control. Rapid risk assessment: coronavirus disease 2019 (Covid-19) in the Eu/Eea and the UK-eighth update. 2020.
31. World Health Organization. Report of the WHO-China joint mission on coronavirus disease 2019 (COVID-19). 2020.
32. Huang C, Zhang L, Yu T, Jiaan X, Wei Y, Wu W, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395: 497-506.
33. Chen N, Dong X, Wei Y, Xia J, Yu T, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020; 395: 507-513.
34. Molnar C, Gair J. Concepts of Biology. 2019.
35. Land WG. The role of damage- associated molecular patterns in human diseases part I- promoting inflammation and immunity. Sultan Qaboos Univ Med J. 2015; 15: e9-e21.
36. Magee CN, Boenisch O, Najafian N. The role of co-stimulatory molecules in directing the functional differentiation of allo-reactive T helper cells. Am J Transplant. 2012; 12: 2588-2600.
37. Hwang YH, Kim SJ, Yee ST. Physcion-matured dendritic cells induce the differentiation of Th1 cells. Int J Mol Sci. 2020; 21: 1753.
38. Obregon C, Kumar R, Pascual MA, Golshayan D, Vassalli G. Update on dendritic cell-induced immunological and clinical tolerance. Front Immunol. 2017; 8: 1514.
39. Adler LN, Jiang W, Macaubas C, Hung SC, Mellins ED, Bhamidipati K. The other function: class II-restricted antigen presentation by B cells. Front Immunol. 2017; 8: 1-14.
40. Zerrahn J, Held W, Raulet DH. The MHC reactivity of the T cell repertoire prior to positive and negative selection. Cell. 1997; 88: 627-636.
41. Hayaes BF, Markert ML, Sempowski GD, Patel DD, Hale LP. The role of the thymus in immune reconstruction in aging, bone marrow transplantation, and HIV-1 infection. Annu Rev Immunol. 2000; 18: 529-560.
42. Giovine FSD, Duff GW. Interleukin 1: the first interleukin. Immunol Today. 1990; 11: 13-20.
43. Coperchinia F, Chiovato L, Croce L, Magri F, Rotondi M. The cytokine storm in COVID-19: an overview of the involvement of the chemokine/chemokine-receptor system. Cytokine Growth Factor Rev. 2020; 53: 25-32.
44. Li D, Liu H, Jia Y, Li F, Wang W, Wu J, et al. Immune dysfunction leads to mortality and organ injury in patients with COVID-19 in China: insights from ERS- COVID-19 study. Signal Transduct Target Ther. 2020; 5: 62.
45. Ruiz VJC, Motes RI, Puerta JMP, Ruiz C. SARS-Cov-2 infection: The role of cytokines in COVID-19 disease. Cytokine Growth Factor Rev. 2020; 54: 62-75.
46. Qin C, Zhou L, Hu Z, Yang S, Shang K, Wang W, et al. Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis. 2020; 71:762-768.
47. Zhang B, Zhou Z, Zhu C, Qiu FFY, Feng J, Jia Q, et al. Immune phenotyping based on neutrophil-to-lymphocyte ratio and IgG predicts disease severity and outcome for patients with COVID-19. Front Mol Biosci. 2020; 7: 157.
48. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020; 395: 1033-1034.
49. Xu Z, Shi L, Zhang J, Huang L, Zhang C, Zhao P, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020; 8: 420-422.
50. Bhatia M, Zemans RL, Jeyaseelan S. Role of chemokines in the pathogenesis of acute lung injury. Am J Respir Cell Mol Biol. 2012; 46: 566-572.

51. Catanzaro M, Fagiani F, Racchi M, Corsini E, Govoni S, Lanni C. Immune response in COVID-19: addressing a pharmacological challenge by targeting pathways triggered by SARS-CoV-2. Signal Transduct Target Ther. 2020; 5: 84.

52. Chi Y, Ge Y, Wu B, Zhang W, Wu T, Wen T, et al. Serum cytokine and chemokine profile in relation to the severity of coronavirus disease 2019 in China. J Infect Dis. 2020; 222: 746-754.

53. Dhar D, Mohanty A. Gut microbiota and Covid-19- possible link and implications. Virus Res. 2020; 285: 198018.

54. Gou W, Fu Y, Yue L, Chen GD, Cai M, Shuai M, et al. Gut microbiota may underlie the predisposition of healthy individuals to COVID-19. MedRxiv. 2020.

55. Zugich JN, Bhattacharya D, Fain MJ, Knox KS, Natt B, Rios CT. SARS-CoV-2 and COVID-19 in older adults: what we may expect regarding pathogenesis, immune responses, and outcomes. Geroscience. 2020; 42: 505-514.

56. Simpson RJ, Lowder TW, Spielmann G, Bigley AB, LaVoy EC, Kunz H. Exercise and the aging immune system. Ageing Res Rev. 2012; 11: 404-420.

57. Maijo M, Clements SJ, Ivory K, Nicoletti C, Carding SR. Nutrition, diet and immunosenescence. Mech Ageing Dev. 2014; 136-137: 116-128.

58. Smith RE. Medicinal chemistry-fusion of traditional and Western medicine. Bentham Science Publishers. 2013.

59. Esser N, Poels SL, Piette J, Scheen AJ, Paquot N. Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. Diabetes Res Clin Pract. 2014; 105: 141-150.

60. Myles IA. Fast food fever: reviewing the impacts of the Western diet on immunity. Nutr J. 2014; 13: 1-17.

61. Smith RE, Tran K, Richards KM, Luo R. Dietary carbohydrates that modulate the immune system. Clinical Immunology, Endocrine and Metabolic Drugs. 2015; 2: 35-42.

62. Hollman PCH, Arts ICW. Flavonols, flavones and flavanols –nature, occurrence and dietary burden. Journal of the Science of Food and Agriculture. 2000; 80:1081-1093.

63. Souich PD, García AG, Vergés J, Montell E. Immunomodulatory and anti-inflammatory effects of chondroitin sulphate. J Cell Mol Med. 2009; 13: 1451-1463.

64. Peake JM, Neubauer O, Walsh NP, Simpson RJ. Recovery of the immune system after exercise. J Appl Physiol. 2016; 122: 1077-1087.

65. Singh K. Nutrient and stress management. Journal of Nutrition and Food Sciences. 2016; 6: 1-6.

66. Orsavova J, Misurcova L, Ambrozova JV, Vicha R, Micek J. Fatty acids composition of vegetable oil and contribution to dietary energy intake and dependence of cardiovascular mortality on dietary intake of fatty acids. Int J Mol Sci. 2015; 16: 12871-12890.

67. Diet and Health. Implications for Reducing Chronic Disease Risk. National Research Council (US) Commettee on Diet and Health. National Academy Press. 1989.

68. Brown HA, Marnett LJ. Introduction to lipid biochemistry, metabolism, and signaling. Chem Rev. 2011; 111: 5817-5820.

69. Radzikowska U, Rinaldi AO, Sozener ZC, Akdis M, Akdis CA, Sokolowska M, et al. The influence of dietary fatty acids on immune responses. Nutrients. 2019; 11: 2990.

70. Bustillos LA, Dao DT, Fell GL, Baker MA, Gura MA, Bistrian BR, et al. Redefining essential fatty acids in the era of novel intravenous lipid emulsions. Clin Nutr. 2018; 37: 784-789.

71. Le HD, Meisel JA, Meijer VED, Gura KM, Puder M. The essentiality of arachidonic acid and docosahexaenoic acid. Prostaglandins Leukot Essent Fatty Acids. 2009; 81: 165-170.

72. Hishikawa D, Valentine WJ, Hishikawa, YI, Shindou, H, Shimizu T. Metabolism and functions of docosahexaenoic acid-containing membrane glycerophospholipids. FEBS Lett. 2017; 591: 2730-2744.

73. Schleimer RP, Kato A, Kern R, Kuperman, D, Avila PC. Epithelium: at the interface of innate and adaptive immune responses. J Allergy Clin Immunol. 2007; 120: 1279-1284.

74. Salim SY, Soderholm JD. Importance of disrupted intestinal barrier in inflammatory bowel diseases. Inflamm Bowel Dis. 2010; 17: 362-381.

75. Peterson LW, Artis D. Intestinal epithelial cells: regulators of barrier function and immune homeostasis. Nat Rev Immunol. 2014; 14: 141-153.

76. Venter C, Meyer RW, Nwaru BI, Roduit C, Untersmayr E, Patient, KA, et al. EAACI position paper: influence of dietary fatty acids on asthma, foodallergy, and atopic dermatitis. Allergy. 2019; 74: 1429-1444.

77. Venter C, Greenhawt M, Meyer RW, Agostoni C, Reese I, Toit GD, et al. EAACI position paper on diet diversity in pregnancy, infancy and childhood: novel concepts and implications for studies in allergy and asthma. Allergy. 2020; 75: 497-523.

78. Begam M, Khan S, Bhowmik S, Lisa SA, Juliana FM, Hossain MS. Fatty acid composition of hilsa (Tenualosa ilisha) fish muscle from different locations in Bangladesh. Thai Journal of Agricultural Science. 2019; 52: 172-179.

79. Davison G, Kehaya C, Jones AW. Nutritional and physical activity interventions to improve immunity. Am J Lifestyle Med. 2014; 10: 152-169.

80. Daly JM, Reynolds J, Sigal RK, Shou J, Liberman MD. Effect of dietary protein and amino acids on immune function. Crit Care Med.1990; 18: S86-S93.

81. Benson KF, Carter SG, Patterson KM, Patel D, Jensen GS. A novel extract from bovine colostrum whey supports anti-bacterial and anti-viral innate immune functions in vitro and in vivo: I. Enhanced immune activity in vitro translates to improved microbial clearance in animal infection models. Prev Med. 2012; 54: S116-S123.

82. Cruzat V, Keane KN, Newsholme P, Rogero MM, Curi R. Glutamine: metabolism and immune function, supplementation and clinical translation. Nutrients. 2018; 10: 1-31.

83. Childs CE, Calder PC, Miles EA. Diet and Immune Function. Nutrients. 2019; 11: 1933.

84. Calder PC, Kew S. The immune system: a target for functional foods? Br J Nutr. 2002; 88: S165-S177.

85. Huang Z, Liu Y, Qi G, Brand D, Zheng SG. Role of vitamin A in the immune system. J Clin Med. 2018; 7: 1-16.

86. Lagos PK, Guo Y, Noelle RJ. Retinoic acid: a key player in immunity. Biofactors. 2010; 36: 430-436.

87. Mora JR, Iwata M, Andrian UHV. Vitamin effects on the immune system: vitamins A and D take centre stage. Nat Rev Immunol. 2008; 8: 685-698.

88. Lera ARD, Bourguet W, Altucci L, Gronemeyer H. Design of selective nuclear receptor modulators: RAR and RXR as a case study. Nature Rev Drug Discov. 2007; 6: 811-820.

89. Egly CR, Germain P. Dynamic and combinatorial control of gene expression by nuclear retinoic acid receptors (RARs). Nucl Recept Signal. 2009; 7: 1-18.

90. Repa JJ, Hanson KK, Dame MC. All-trans-retinol is a ligand for the retinoic acid receptors. Proc Natl Acad Sci USA. 1993; 90: 7293-7297.

91. Taimi M, Helvig, C, Wisniewski J, Ramshaw H, White J, Amad M, et al. A novel human cytochrome P450, CYP26C1, involved in metabolism of

9-cis and all-trans isomers of retinoic acid. Biol Chem. 2004; 279: 77-85.

92. Abed SSA, Beckett BR, Chiba H, Chithalen JV, Jones G, Metzger D, et al. Mouse P450RAI (CYP26) expression and retinoic acid-inducible retinoic acid metabolism in F9 cells are regulated by retinoic acid receptor gamma and retinoid X receptor alpha. J Biol Chem. 1998; 273: 2409-2415.

93. Ribes V, Schuhbaur B, Dolle P, Otto DME, Schmidt K, Tickle C, et al. Rescue of cytochrome P450 oxidoreductase (Por) mouse mutants reveals functions in vasculogenesis, brain and limb patterning linked to retinoic acid homeostasis. Dev Biol. 2007; 303: 66-81.

94. Mccullough FS, Clewes CAN, Thurnham DI. The effect of vitamin A on epithelial integrity. Proc Nutr Soc.1999; 58: 289-293.

95. Shrestha S, Kim SY, Yun YJ, Song DK, Kim JK, Lee JM, et al. Retinoic acid induces hypersegmentation and enhances cytotoxicity of neutrophils against cancer cells. Immunol Lett. 2017; 182: 24-29.

96. Chang HK, Hou WS. Retinoic acid modulates interferon- gamma production by hepatic natural killer T cells via phosphatase 2A and the extracellular signal-regulated kinase pathway. J Interferon Cytokine Res. 2015; 35: 200-212.

97. Sun CM, Hall JA, Blank RB, Bouladoux N, Belkaid Y, Oukka M, et al. Small intestine lamina propria dendritic cells promote de novo generation of Foxp3 T reg cells via retinoic acid. J Exp Med. 2007; 204: 1775-1785.

98. Coombes JL, Siddiqui KR, Carcamo CVA, Hall J, Sun CM, Belkaid Y, et al. A functionally specialized population of mucosal CD103+DCs induces Foxp3+ regulatory T cells via a TGF-beta and retinoic acid–dependent mechanism. J Exp Med. 2007; 204: 1757-1764.

99. Mora JR, Andrian UHV. T-cell homing specificity and plasticity: new concepts and future challenges. Trends Immunol. 2006; 27: 235-243.

100. Hosoe N, Miura S, Watanabe C, Tsuzuki Y, Hokari R, Oyama T, et al. Demonstration of functional role of TECK/CCL25 in T lymphocyte-endothelium interaction in inflamed and uninflamed intestinal mucosa. Am J Physiol Gastrointest Liver Physiol. 2004; 286: G458-G466.

101. Ohoka Y, Yokota A, Takeuchi H, Maeda N, Iwata M. Retinoic acid-induced CCR9 expression requires transient TCR stimulation and cooperativity between NFATc2 and the retinoic acid receptor/retinoid X receptor complex. J Immunol. 2011; 186: 733-744.

102. Kang SG, Park J, Cho JY, Ulrich B, Kim CH. Complementary roles of retinoic acid and TGF-beta1-in coordinated expression of mucosal integrins by T cells. Mucosal Immunol. 2011; 4: 66-82.

103. Lampen A, Meyer S, Arnhold T, Nau H. Metabolism of vitamin A and its active metabolite all-trans-retinoic acid in small intestinal enterocytes. J Pharmacol Exp Ther. 2000; 295: 979-985.

104. Allie SR, Zhang W, Tsai CY, Noelle RJ, Usherwood EJ. Critical role for all-trans retinoic acid for optimal effector and effector memory CD8 T cell differentiation. J Immunol. 2013; 190: 2178-2187.

105. Tan X, Sande JL, Pufnock JS, Blattman JN, Greenberg PD. Retinoic acid as a vaccine adjuvant enhances CD8+ T cell response and mucosal protection from viral challenge. J Virol. 2011; 85: 8316-8327.

106. Mucida D, Park Y, Kim G, Turovskaya O, Scott I, Kronenberg M, et al. Reciprocal TH17 and regulatory T cell differentiation mediated by retinoic acid. Science. 2007; 317: 256-260.

107. Zhou X, Kong N, Wang J, Fan H, Zou H, Horwitz D, et al. Cutting edge:all-trans retinoic acid sustains the stability and function of natural regulatory T cells in an inflammatory milieu. J Immunol. 2010; 185: 2675-2679.

108. Liu ZM, Zheng SG, Wang KP, Ma J. The role of all-trans retinoic acid in the biology ofFoxp3+ regulatory T cells. Cell Mol Immunol. 2015; 12: 553-557.

109. Scott CL, Aumeunier AM, Mowat AM. Intestinal CD103+ dendritic cells: master regulators of tolerance? Trends Immunol. 2011; 32: 412-419.

110. Kwok SK, Park MK, Cho ML, Oh HJ, Park EM, Lee DG, et al. Retinoic acid attenuates rheumatoid inflammation in mice. J Immunol. 2012; 189: 1062-1071.

111. Iwata Y, Matsushita T, Horikawa M, Dilillo DJ, Yanaba K, Venturi GM, et al. Characterization of a rare IL-10-competent B-cell subset in humans that parallels mouse regulatory B10 cells. Blood. 2011; 117: 530-541.

112. Fillatreau S, Sweenie CH, McGeachy MJ, Gray D, Anderton SM. B cells regulate autoimmunity by provision of IL-10. Nat Immunol. 2002; 3: 944-950.

113. Villamor E, Fawzi WW. Effects of vitamin A supplementation on immune responses and correlation with clinical outcomes. Clin Microbiol Rev. 2005; 18: 446-464.

114. Lewis ED, Meydani SN, Wu D. Regulatory role of vitamin E in the immune system and inflammation. IUBMB Life. 2019; 71: 487-494.

115. Wang X, Quinn PJ. Vitamin E and its function in membranes. Prog Lipid Res. 1999; 38: 309-336.

116. Marko MG, Ahmed T, Bunnell SC, Wu D, Chung H, Huber BT, et al. Age-associated decline in effective immune synapse formation of cd4(+) T cells is reversed by vitamin E supplementation. J Immunol. 2007; 178: 1443-1449.

117. Hayek MG, Mura C, Wu D, Beharka AA, Han SN, Paulson KE, et al. Enhanced expression of inducible cyclooxygenase with age in murine macrophages. J Immunol. 1997; 159: 2445-2451.

118. Wu D, Mura C, Beharka AA, Han SN, Paulson KE, Hwang D, et al. Age-associated increase in PGE2 synthesis and COX activity in murine macrophages is reversed by vitamin E. Am J Physiol. 1998; 275: C661-C668.

119. Han SN, Wu D, Ha WK, Beharka A, Smith DE, Bender BS, et al. Vitamin E supplementation increases T helper 1 cytokine production in old mice infected with influenza virus. Immunology. 2000; 100: 487-493.

120. Gavazzi G, Krause KH. Ageing and infection. Lancet Infect Dis. 2002; 2: 659-666.

121. Hemila H, Kaprio J. Vitamin E supplementation and pneumonia risk in males who initiated smoking at an early age: effect modification by body weight and dietary vitamin C. Nutr J. 2008; 7: 1-9.

122. Meydani SN, Leka LS, Fine BC, Dallal GE, Keusch GT, Singh MF, et al. Vitamin E and respiratory tract infections in elderly nursing home residents: a randomized controlled trial. JAMA. 2004; 292: 828-836.

123. Andreone P, Fiorino S, Cursaro C, Graenzi A, Margotti M, Giammarino LD, et al. Vitamin E as treatment for chronic hepatitis B: results of a randomized controlled pilot trial. Antiviral Res. 2001; 49: 75-81.

124. Jayawardena R, Sooriyaarachchi P, Chourdakis M, Jeewandara C, Ranasinghe P. Enhancing immunity in viral infections, with special emphasis on COVID-19: a review. Diabetes Metab Syndr. 2020; 14: 367-382.

125. Shakoor H, Dhaheri ASA, Ali H, Platat C, Stojanovska L, Feehan J, et al. Immune-boosting role of vitamins D, C, E, zinc, selenium, and omega-3 fatty acids: could they help against COVID-19? Maturitas. 2020; 143: 1-9.

126. Nishikimi M, Yagi K. Molecular basis for the deficiency in humans of gulonolactone oxidase, a key enzyme for ascorbic acid biosynthesis. Am J Clin Nutr. 1991; 54: 1203S -1208S.

127. Drouin G, Godin JR, Page B. The genetics of vitamin C loss in vertebrates. Curr Genomics. 2011; 12: 371-378.

128. Carr AC, Maggini S. Vitamin C and immune function. Nutrients. 2017; 9: 1-25.

129. Padayatty SJ. Vitamin C physiology: the known and the unknown and Goldilocks. Oral Dis. 2016; 22: 463-493.

130. Traber MG, Stevens JF. Vitamins C and E: beneficial effects from a mechanistic perspective. Free Radic Biol Med. 2011; 51: 1000-1013.

131. Boretti A, Banik BK. Intravenous vitamin C for reduction of cytokines storm in acute respiratory distress syndrome. Pharma Nutrition. 2020; 12: 1-8.

132. Schleicher RL, Carroll MD, Ford ES, Lacher DA. Serum vitamin C and the prevalence of vitamin C deficiency in the United States: 2003–2004 national health and nutrition examination survey (NHANES). Am J Clin Nutr. 2009; 90: 1252-1263.

133. Pfeiffer CM, Stenberg MR, Schleicher RL, Haynes BMH, Rybak ME, Pirkel JL. The CDC's second national report on biochemical indicators of diet and nutrition in the U.S. population is a valuable tool for researchers and policy makers. J Nutr. 2013; 143: 938S-947S.

134. Maggini S, Beveridge S, Sorbara J, Senatore G. Feeding the immune system: the role of micronutrients in restoring resistance to infections. CAB Rev. 2008; 3: 1-21.

135. Huskisson E, Maggini S, Ruf M. The role of vitamins and minerals in energy metabolism and well-being. J Int Med Res. 2007; 35: 277-289.

136. Anderson R, Oosthuizen R, Maritz R, Theron A, Rensburg AJ. The effects of increasing weekly doses of ascorbate on certain cellular and humoral immune functions in normal volunteers. Am J Clin Nutr.1980; 33: 71-76.

137. Hemila H. Vitamin C and SARS coronavirus. J Antimicrob Chemother. 2003; 52: 1049-1050.

138. Kim Y, Kim H, Bae S, Choi J, Lim SY, Lee N, et al. Vitamin C is an essential factor on the anti-viral immune responses through the production of interferon-alpha/beta at the initial stage of influenza A virus (H3N2) infection. Immune Netw. 2013; 13: 70-74.

139. Johnston CS, Barkyoumb GM, Schumacher SS. Vitamin C supplementation slightly improves physical activity levels and reduces cold incidence in men with marginal vitamin C status: a randomized controlled trial. Nutrients. 2014; 6: 2572-2583.

140. Klein M. The mechanism of the virucidal action of ascorbic acid. Science. 1945; 101: 587-589.

141. Pauling L. The significance of the evidence about ascorbic acid and the common cold. Proc Natl Acad Sci USA. 1971; 68: 2678-2681.

142. While LA, Freeman CY, Forrester BD, Chappell WA. In vitro effect of ascorbic acid on infectivity of herpesviruses and paramyxoviruses. J Clin Microbiol. 1986; 24: 527-531.

143. Gonzalez MJ, Berdiel MJ, Duconge J, Levy TE, Alfaro IM, Borges RM, et al. High dose intravenous vitamin C and influenza: a case report. Journal of Orthomolecular Medicine. 2018; 33: 1-3.

144. Hewison M. Vitamin D and immune function: an overview. Proc Nutr Soc. 2012; 71: 50-61.

145. Adams JS, Hewison M. Unexpected actions of vitamin D: new perspectives on the regulation of innate and adaptive immunity. Nat Clin Pract Endocrinol Metab. 2008; 4: 80-90.

146. Youssef DA, Miller CW, Abbassi AME, Cutchins DC, Cutchins C, Grant WB, et al. Antimicrobial implications of vitamin D. Dermatoendocrinol. 2011; 3: 220-229.

147. Aranow C. Vitamin D and the immune system. J Investig Med. 2011; 59: 881-886.

148. Zdrenghea MT, Bagacean C, Stanciu LA, Makrinioti H, Johnston SL, Bush A, et al. Vitamin D modulation of innate immune responses to respiratory viral infections. Rev Med Virol. 2017.

149. Holick MF, MacLaughlin JA, Clark MB, Holick SA, Potts JT, Anderson RR, et al. Photosynthesis of previtamin D3 in human skin and the physiological consequences. Science. 1980; 210: 203-205.

150. Holick MF. Vitamin D (Physiology, Molecular Biology, and Clinical Applications). Springer. 1999.

151. Bener P. The Biologic Effects of Ultraviolet Radiation. Pergamon Press. 1969.

152. Webb AR, Kline L, Holick MF. Influence of season and latitude on the cutaneous synthesis of vitamin D3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D3 synthesis in human skin. J Clin Endocrinol Metab. 1988; 67: 373-378.

153. Ross AC, Taylor CL, Yaktine AL, Valle HBD. Dietary Reference Intake for Calcium and Vitamin D. National Accademic Press. 2011.

154. Dankers W, Lubberts E, Hamburg JPV, Colin EM. Vitamin D in autoimmunity: molecular mechanisms and therapeutic potential. Front Immunol. 2017; 7: 1-26.

155. Razdan K, Singh K, Singh D. Vitamin D levels and COVID-19 susceptibility: is there any correlation? Med Drug Discov. 2020; 7: 1-3.

156. Rondanelli M, Miccono A, Lamburghini S, Avanzato I, Faliva MA, Peroni G, et al. Self-care for common colds: the pivotal role of vitamin D, vitamin C, zinc, and Echinacea in three main immune interactive clusters (physical barriers, innate and adaptive immunity) involved during an episode of common colds-practical advice on dosages and on the time to take these nutrients/botanicals in order to prevent or treat common colds. Evid Based Complement Alternate Med. 2018; 2018: 5813095.

157. Ali N. Role of vitamin D in preventing of COVID-19 infection, progression and severity. Journal of Infection and Public Health. 2020; 13: 1373-1380.

158. Gombart AF, Borregaard N, Koeffler HP. Human cathelicidin antimicrobial peptide (CAMP) gene is a direct target of the vitamin D receptor and is strongly up-regulated in myeloid cells by 1,25-dihydroxyvitamin D3. FASEB J. 2005; 19: 1067-1077.

159. Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, et al. Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. Nutrients. 2020; 12: 1-19.

160. Cantorna MT, Snyder L, Lin YD, Yang L. Vitamin D and 1, 25 (OH) 2D regulation of T cells. Nutrients. 2015; 7: 3011-3021.

161. Mattner F, Smiroldo S, Galbiati F, Muller M, Lucia PD, Poliani PL, et al. Inhibition of Th1 development and treatment of chronic-relapsing experimental allergic encephalomyelitis by a non-hypercalcemic analogue of 1,25-dihydroxyvitamin D(3). Eur J Immunol. 2000; 30: 498-508.

162. Boonstra A, Barrat FJ, Crain C, Heath VL, Savelkoul HF, Garra AO. 1alpha,25-dihydroxyvitamin d3 has a direct effect on naive CD4(+) T cells to enhance the development of Th2 cells. J Immunol. 2001; 167: 4974-4980.

163. Tang J, Zhou R, Luger D, Zhu W, Silver PB, Grajewski RS, et al. Calcitriol suppresses antiretinal autoimmunity through inhibitory effects on the Th17 effector response. J Immunol. 2009; 182: 4624-4632.

164. Daniel C, Sartory NA, Zahn N, Radeke HH, Stein JM. Immune modulatory treatment of trinitrobenzene sulfonic acid colitis with calcitriol is associated with a change of a T helper (Th) 1/Th17 to a Th2 and regulatory T cell profile. J Pharmacol Exp Ther. 2008; 324: 23-33.

165. Penna G, Roncari A, Amuchastegui S, Daniel KC, Berti E, Colonna M, et al. Expression of the inhibitory receptor ILT3 on dendritic cells is dispensable for induction of CD4+Foxp3+ regulatory T cells by 1,25-dihydroxyvitamin D3. Blood. 2005; 106: 3490-3497.

166. Gregori S, Casorati M, Amuchastegui S, Smiroldo S, Davalli AM, Adorini L. Regulatory T cells induced by 1 alpha, 25-dihydroxyvitamin D3 and mycophenolate mofetil treatment mediate transplantation tolerance. J Immunol. 2001; 167: 1945-1953.

167. Barrat FJ, Cua DJ, Boonstra A, Richads D, Crain C, Savelkoul HF, et al. In vitro generation of interleukin 10-producing regulatory CD4(+) T cells is induced by immunosuppressive drugs and inhibited by T helper type 1 (Th1)- and Th2-inducing cytokines. J Exp Med. 2002; 195: 603-616.

168. Cantorna MT. Mechanisms underlying the effect of vitamin D on the immune system. Proc Nutr Soc. 2010; 69: 286-289.

169. Rudensky AY. Regulatory T cells and Foxp3. Immunol Rev. 2011; 241: 260-268.

170. Bennett CL, Christie J, Ramsdell F, Brunkow ME, Ferguson PJ, Whitesell L, et al. The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. Nat Genet. 2001; 27: 20-21.

171. Hori S, Nomura T, Sakaguchi S. Control of regulatory T cell development by the transcription factor Foxp3. Science. 2003; 299: 1057-1061.

172. Hori S. Lineage stability and phenotypic plasticity of Foxp3+ regulatory T cells. Immunol Rev. 2014; 259: 159-172.

173. Colamatteo A, Galgani M, Fusco C, Carbone F, Rosa VD, Bruzzaniti S, et al. Molecular mechanisms controlling Foxp3 expression in health and autoimmunity: from epigenetic to post-translational regulation. Front Immunol. 2020; 10: 1-20.

174. Sharifi A, Vahedi H, Nedjat S, Rafiei H, Attar MJH. Effect of single-dose injection of vitamin D on immune cytokines in ulcerative colitis patients: a randomized placebo-controlled trial. APMIS. 2019; 127: 681-687.

175. Almerighi C, Sinistro A, Cavazza A, Ciaprini C, Rocchi G, Bergamini A. 1Alpha,25-dihydroxyvitamin D3 inhibits CD40L-induced pro-inflammatory and immunomodulatory activity in human monocytes. Cytokine. 2009; 45: 190-197.

176. Liu W, Zhang L, Xu HJ, Li Y, Sun MY, Hu CM, et al. The anti-inflammatory effects of vitamin D in tumorigenesis. Int J Mol Sci. 2018; 19: 2736.

177. Piemonti L, Monti P, Sironi M, Fraticelli P, Leone BE, Cin ED, et al. Vitamin D3 affects differentiation, maturation, and function of human monocyte-derived dendritic cells. J Immunol. 2000; 164: 4443-4451.

178. Pike JW, Meyer MB. The vitamin D receptor: new paradigms for the regulation of gene expression by 1,25-dihydroxyvitamin D(3). Endocrinol Metab Clin North Am. 2010; 39: 255-269.

179. Feldman D, Pike JW, Glorieux F. Vitamin D. Elsevier. 2004.

180. Bikle DD. Vitamin D metabolism, mechanism of action, and clinical applications. Chem Biol. 2014; 21: 319-329.

181. Liu PT, Stenger S, Li H, Wenzel L, Tan BH, Krutzit SR, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science. 2006; 311: 1770-1773.

182. Kawasaki T, Kawai T. Toll-like receptor signaling pathways. Front Immunol. 2014; 5: 1-8.

183. Wang TT, Nestel FP, Bourdeau V, Nagai Y, Wang Q, Liao J, et al. Cutting edge: 1,25-dihydroxyvitamin D3 is a direct inducer of antimicrobial peptide gene expression. J Immunol. 2004; 173: 2909-2912.

184. Nie L, Cai SY, Chen J, Shao JZ. Toll-like receptors, associated biological roles, and signalling networks in non-mammals. Front. Immunol. 2018; 9: 1-19.

185. Mangelsdorf DJ, Evans RM. The RXR heterodimers and orphan receptors. Cell. 1995; 83: 841-850.

186. Gombart AF. The vitamin D-antimicrobial peptide pathway and its role in protection against infection. Future Microbiol. 2009; 4: 1151-1165.

187. Akira S, Takeda K, Kaisho T. Toll-like receptors: critical proteins linking innate and acquired immunity. Nat Immunol. 2001; 2: 675-680.

188. Gallo RL, Murakami M, Ohtake T, Zaiou M. Biology and clinical relevance of naturally occurring antimicrobial peptides. J Allergy Clin Immunol. 2002; 110: 823-831.

189. Bartley J. Vitamin D: emerging roles in infection and immunity. Expert Rev Anti Infect Ther. 2010; 8:1359-1369.

190. Ginde AA, Mansbach JM, Camargo CA. Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the third national health and nutrition examination survey. Arch Intern Med. 2009; 169: 384-390.

191. McCartney DM, Byrne DG. Optimisation of vitamin D status for enhanced immuno-protection against Covid-19. Ir Med J. 2020; 113: 1-4.

192. Lau FH, Majumder R, Torabi R, Saeg F, Hoffman R, Cirillo JD, Greiffenstein P. Vitamin D insufficiency is prevalent in severe COVID-19. MedRxiv. 2020.

193. Alipio M. Vitamin D supplementation could possibly improve clinical outcomes of patients infected with coronavirus-2019 (COVID-19). SSRN Electronic Journal.2020.

194. Lei GS, Zhang C, Cheng BH, Lee CH. Mechanisms of action of vitamin D as supplemental therapy for pneumocystis pneumonia. Antimicrob Agents Chemother. 2017; 61: e01226-e01217.

195. Raharusun P, Priambada S, Budiarti C, Agung E, Budi C. Patterns of COVID-19 mortality and vitamin D: an indonesian study. JEN REYES. 2020.

196. Mousavi S, Bereswill S, Heimesaat MM. Immunomodulatory and antimicrobial effects of vitamin C. Eur J Microbiol Immunol. 2019; 9: 73-79.

197. Biancatelli RMLC, Berrill M, Marik PE. The antiviral properties of vitamin C. Expert Rev Anti Infect Ther. 2020; 18: 99-101.

198. Watkins J. Preventing a covid-19 pandemic. BMJ. 2020; 368: 1-2.

199. Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, et al. Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. Nutrients. 2020; 12: 988.

200. Mazahery H, Hurst PRV. Factors affecting 25-hydroxyvitamin D concentration in response to vitamin D supplementation. Nutrients. 2015; 7: 5111-5142.

201. Fabbri A, Infante M, Ricordi C. Editorial-vitamin D status: a key modulator of innate immunity and natural defense from acute viral respiratory infections. Eur Rev Med Pharmacol Sci. 2020; 24: 4038-4052.

202. Juzeniene A, Ma LW, Kwitniewski M, Polev GA, Lagunova Z, Dahlback A, et al. The seasonality of pandemic and non-pandemic influenzas: the roles of solar radiation and vitamin D. Int J Infect Dis. 2010; 14: e1099-e1105.

203. Cannell JJ, Vieth R, Umhau JC, Holick MF, Grant WB, Madronich S, et al. Epidemic influenza and Vitamin D. Epidemiol Infect. 2006; 134: 1129-1140.

204. Soumitra Das. Zinc can play pertinent role in mitigating COVID-19. The Economic Times. 2020.

205. Overbeck S, Rink L, Haase H. Modulating the immune response by oral zinc supplementation: a single approach for multiple diseases. Arch Immunol Ther Exp. 2008; 56: 15-30.

206. Gammoh NZ, Rink L. Zinc in infection and inflammation. Nutrients. 2017; 9: 1-25.

207. Hasegawa H, Suzuki K, Suzuki Ko, Nakaji S, Sugawara K. Effects of zinc on the reactive oxygen species generating capacity of human neutrophils and on the serum opsonic activity in vitro. Luminescence. 2000; 15: 321-327.

208. Singh M, Das RR. Zinc for the common cold. Cochrane Database Syst Rev. 2013.

209. Kubala J. Zinc: everything you need to know. Healthline. 2018.

210. Zastrow ML, Pecoraro VL. Designing hydrolytic zinc metalloenzymes. Biochemistry. 2014; 53: 957-978.

211. Lyckholm L, Heddinger SP, Parker GP, Coyne PJ, Ramakrishnan V, Smith TJ, et al. A randomized, placebo controlled trial of oral zinc

forchemotherapy-related taste and smell disorders. J Pain Palliat Care Pharmacother. 2012; 26: 111-114.

212. Perry DK, Smyth MJ, Stennicke HR, Salvesen GS, Duriez P, Hannun YA. Zinc is a potent inhibitor of the apoptotic protease, caspase-3. A novel target for zinc in the inhibition of apoptosis. J Biol Chem .1997; 272: 18530-18533.

213. Jarosz M, Olbert M, Wyszogrodzka G, Młyniec K, Librowski T. Antioxidant and anti-inflammatory effects of zinc. Zinc-dependent NF-kappa B signaling. Inflammopharmacology. 2017; 25: 11-24.

214. Prasad AS, Bao B, Beck FWJ, Kucuk O, Sarkar FH. Antioxidant effect of zinc in humans. Free Radic Biol Med. 2004; 37: 1182-1190.

215. Lanke K, Krenn BM, Melchers WJG, Seipelt J, Kuppeveld FJM. PDTC inhibits picornavirus polyprotein processing and RNA replication by transporting zinc ions into cells. J Gen Virol. 2007; 88: 1206-1217.

216. Pasternak CA. A novel form of host defence: membrane protection by Ca2+ and Zn2+. Biosci Rep. 1987; 7: 81-91.

217. Kumar A, Chernov M, Kasuya H, Kubota Y. Potential role of zinc supplementation in prophylaxis and treatment of COVID-19. Med Hypotheses. 2020; 144: 109848.

218. Schoggins JW, Panis M, Murphy MY, Jones CT, Rice CM, Wilson SJ, et al. A diverse array of gene products are effectors of the type I interferon antiviral response. Nature. 2011; 472: 481-485.

219. Gaudernak E, Seipelt J, Triendl A, Grassauer A, Kuechler E. Antiviral effects of pyrrolidine dithiocarbamate on human rhinoviruses. J Virol. 2002; 76: 6004-6015.

220. Alker W, Haase H. Zinc and sepsis. Nutrients. 2018; 10: 1-17.

221. Velthuis AJWT, Worm SHEVD, Snijder EJ, Hemert MJV. Zn2+ inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. PLoS Pathog. 2010; 6: 1-10.

222. Kar M, Khan NA, Panwar A, Medigeshi GR, Bais SS, Basak S, et al. Zinc chelation specifically inhibits early stages of dengue virus replication by activation of NF-kappaB and induction of antiviral response in epithelial cells. Front Immunol. 2019; 10: 1-15.

223. Ferrari E, Minogue JW, Fang JWS, Baroudy BM, Lau JYN, Hong Z. Characterization of soluble hepatitis C virus RNA-dependent RNA polymerase expressed in *Escherichia coli*. J Virol. 1999; 73: 1649-1654.

224. Hung M, Gibbs CS, Tsiang M. Biochemical characterization of rhinovirus RNA-dependent RNA polymerase. Antiviral Res. 2002; 56: 99-114.

225. Kar M, Khan NA, Panwar A, Medigeshi GR, Bais SS, Basak S, et al. Zinc chelation specifically inhibits early stages of dengue virus replication by activation of NF-kappa B and induction of antiviral response in epithelial cells. Front Immunol. 2019; 10: 1-15.

226. Gorbalenya AE, Enjuanes L, Ziebuhr J, Snijder EJ. Nidovirales: evolving the largest RNA virus genome. Virus Res. 2006; 117: 17-37.

227. Perlman S, Netland J. Coronaviruses post-SARS: update on replication and pathogenesis. Nat Rev Microbiol. 2009; 7: 439-450.

228. Denison MR, Graham RL, Donaldson EF, Eckerle LD, Baric RS. Coronaviruses. RNA Biol. 2011; 8: 270-279.

229. Murillo JAA, Leon MLG, Cordova JLS, Rodriguez APG, Chew RMW, Reyes VF. Zinc supplementation promotes a Th1 response and improves clinical symptoms in fewer hours in children with pneumonia younger than 5 years old. A randomized controlled clinical trial. Front Pediatr. 2019; 7: 1-11.

230. Nuttall KL. Evaluating selenium poisoning. Ann Clin Lab Sci. 2006; 36: 409-420.

231. Iovino L, Mazziotta F, Carulli G, Guerrini F, Orciuolo E, Buda G, et al. High-dose zinc oral supplementation after stem cell transplantation causes an increase of TRECs and CD4+ naive lymphocytes and prevents TTV reactivation. Leuk Res. 2018; 70: 20-24.

232. Kieliszek M, Błazejak S. Current knowledge on the importance of selenium in food for living organisms: a review. Molecules. 2016; 21: 1-16.

233. Kieliszeka M, Lipinski B. Selenium supplementation in the prevention of coronavirus infections (COVID-19). Med Hypotheses. 2020; 143: 109878.

234. Dhillon K, Dhillon K. Distribution and management of seleniferous soils. Advances in Agronomy. 2003; 79: 119-184.

235. Vavougios GD. Temporal removal: selenium-associated gene signatures within the SARS-CoV-2-host genomic interaction interface. Free Radic Biol Med. 2020.

236. Taylor EW, Ruzicka JA, Premadasa L, Zhao L. Cellular selenoprotein mRNA tethering via antisense interactions with Ebola and HIV-1 mRNAs may impact host selenium biochemistry. Curr Top Med Chem. 2016; 16:1530-1535.

237. Steinbrenner H, Quraishy SA, Dkhil MA, Wunderlich F, Sies H. Dietary selenium in adjuvant therapy of viral and bacterial infections. Adv Nutr. 2015; 6: 73-82.

238. Anfinsen CB. Principles that govern the folding of protein chains. Science. 1973; 181: 223-230.

239. Lipinski B. Can selenite be an ultimate inhibitor of Ebola and other viral infections? Journal of Advances in Medicine and Medical Research. 2015; 6: 319-324.

240. Zhou Y, Simmons G. Development of novel entry inhibitors targeting emerging viruses. Expert Rev Anti Infect Ther. 2012; 10: 1129-138.

241. Kieliszek M. Selenium- fascinating microelement, properties and sources in food. Molecules. 2019; 24: 1298.

242. Diwaker D, Mishra KP, Ganju L. Potential role of protein disulfide isomerase in viral infections. Acta Virol. 2013; 57: 293-304.

243. Markovic I, Stantchev TS, Fields KH, Tiffany LJ, Tomic M, Weiss CD, et al. Thiol/disulfide exchange is a prerequisite for CXCR4-tropic HIV-1 envelope-mediated T-cell fusion during viral entry. Blood. 2004; 103: 1586-1594.

244. Lipinski B, Egyud LG. Thiol-induced crosslinking of human blood proteins: implications for tumor immunity. Bioorganic and Medical Chemistry Letters. 1992; 2: 919-924.

245. Eckert DM, Kim PS. Mechanisms of viral membrane fusion and its inhibition. Annu Rev Biochem. 2001; 70: 777-810.

246. Winkler HH, Kaup F, Pohlann S. Host cell factors in filovirus entry: novel players, new insights. Viruses. 2012; 4: 3336-3362.

247. Guillin OM, Vindry C, Ohlmann T, Chavatte L. Selenium, selenoproteins and viral infection. Nutrients. 2019; 11: 2101.

248. Zhao L, Cox AG, Ruzicka JA, Bhat AA, Zhang W, Taylor EW. Molecular modeling and in vitro activity of an HIV-1-encoded glutathione peroxidase. Proc Natl Acad Sci USA. 2000; 97: 6356-6361.

249. Schomburg L. A large-bolus injection, but not continuous infusion of sodium selenite improves outcome in peritonitis. Shock. 2010; 33: 554-555.

250. Ivory K, Prieto E, Spinks C, Armah CN, Goldson AJ, Dainty JR, et al. Selenium supplementation has beneficial and detrimental effects on immunity to influenza vaccine in older adults. Clin Nutr. 2017; 36: 407-415.

251. Gill H, Walker G. Selenium, immune function and resistance to viral infections. Nutrition and Dietetics. 2008; 65: S41-S47.

252. Sanderson CJ. The mechanism of T cell mediated cytotoxicity: I. The release of different cell components. Procedings of the Royal Society B: Biological Science. 1976.

253. Hersperger AR, Makedonas G, Betts MR. Flow cytometric detection of perforin upregulation in human CD8 T cells. Cytometry A. 2008; 73: 1050-1057.

254. Hurst R, Armah CN, Dainty JR, Hart DJ, Teucher B, Goldson AJ, et al. Establishing optimal selenium status: results of a randomized, double-blind, placebo-controlled trial. Am J Clin Nutr. 2010; 91: 923-931.

255. Goldson AJ, Armah CN, Dainty JR, Furniss C, Hart DJ, Teucher B, et al. Effects of selenium supplementation on selenoprotein gene expression and response to influenza vaccine challenge: a randomized controlled trial. PLoS One. 2011; 6: e14771.

256. Stoedter M, Renko K, Hog A, Schomburg L. Selenium controls the sex-specific immune response and selenoprotein expression during the acute-phase response in mice. Biochem J. 2010; 429: 43-51.

257. Rayman MP. Selenium and human health. Lancet. 2012; 379: 1256-1268.

258. Hoffmann PR, Berry MJ. The influence of selenium on immune responses. Mol Nutr Food Res. 2008; 52: 1273-1280.

259. Beck MA, Handy J, Levander OA. Host nutritional status: the neglected virulence factor. Trends Microbiol. 2004; 12: 417-423.

260. Alburaki M, Smith KD, Adamczyk J, Karim S. Interplay between selenium, selenoprotein genes, and oxidative stress in honey bee Apis mellifera L. Journal of Insect Physiology. 2019; 117: 103891.

261. Baum MK, Posner GS, Lai S, Zhang G, Lai H, Fletcher MA, et al. High risk of HIV-related mortality is associated with selenium deficiency. J Acquir Immune Defic Syndr Hum Retrovirol. 1997; 15: 370-374.

262. Zhang J, Taylor EW, Bennett K, Saad R, Rayman MP. Association between regional selenium status and reported outcome of COVID-19 cases in China. Am J Clin Nutr. 2020.

263. Zhang J, Taylor EW, Bennett K, Saad R, Rayman MP. Association between regional selenium status and reported outcome of COVID-19 cases in China. Am J Clin Nutr. 2020.

264. Huang Y, Wang Q, Gao J, Lin Z, Banuelos GS, Yuan L, et al. Daily dietary selenium intake in a high selenium area of Enshi, China. Nutrients. 2013; 5: 700-710.

265. Li S, Banuelos GS, Wu L, Shi W. The changing selenium nutritional status of Chinese residents. Nutrients. 2014; 6: 1103-1114.

266. Lee GY, Han SN. The role of vitamin E in immunity. Nutrients. 2018; 10: 1614.

267. Rosenfeld I. Selenium: geobotany, biochemistry, toxicity, and nutrition. Academic Press. 1964.

268. Yadav SK, Singh I, Singh D, Han SD. Selenium status in soils of northern districts of India. Journal of Environmental Management. 2005; 75: 129-132.

269. Liang RY, Wu W, Huang J, Jiang SP, Lin JG. Magnesium affects the cytokine secretion of CD4+ T lymphocytes in acute asthma. J Asthma. 2012; 49:1012-1015.

270. Delalande BC, Li FY, Connor GMO, Lukacs MJ, Jiang P, Zheng L, et al. Mg2+ regulates cytotoxic functions of NK and CD8 T cells in chronic EBV infection through NKG2D. Science. 2013; 341: 186-1891.

271. Tan CW, Ho LP, Kalimuddin S, Cherng BPZ, Thien SY, Wong HM, et al. A cohort study to evaluate the effect of combination Vitamin D, Magnesium and Vitamin B12 (DMB) on progression to severe outcome in older COVID-19 patients. MedRxiv. 2020.

272. Mazur A, Rock E, Gueux E, Maier J, Nowacki W, Rayssiguier Y, et al. Magnesium and the inflammatory response: potential physiopathological implications. Arch Biochem Biophys. 2007; 458: 48-56.

273. Castiglioni S, Cazzaniga A, Locatelli L, Maier JAM. Burning magnesium, a sparkle in acute inflammation: gleams from experimental models. John Libbey Eurotext. 2017; 30: 1-15.

274. HuT, Xu H, Wang C, Qin H, An Z. Magnesium enhances the chondrogenic differentiation of mesenchymal stem cells by inhibiting activated macrophage-induced inflammation. Scientific Reports. 2018; 8: 3406.

275. Miyamoto D, Kusagaya Y, Endo N, Sometani A, Takeo S, Suzuki T, et al. Thujaplicin-copper chelates inhibit replication of human influenza viruses. Antivir Res. 1998; 39: 89-100.

276. Rupp JC, Locatelli M, Grieser A, Ramos A, Campbell PJ, Yi H, et al. Host cell copper transporters CTR1 and ATP7A are important for influenza A virus replication. Virol J. 2017; 14: 11.

277. Turnlund JR, Jacob RA, Keen CL, Strain JJ, Kelley DS, Domek JM, et al. Long-term high copper intake: effects on indexes of copper status, antioxidant status, and immune function in young men. Am J Clin Nutr. 2004; 79: 1037-1044.

278. Raha S, Mallick R, Basak S, Duttaroy AK. Is copper beneficial for COVID-19 patients? Med Hypotheses. 2020; 142: 109814.

279. Percival SS. Copper and immunity. Am J Clin Nutr. 1998; 67: 1064S-1068S.

280. Koller LD, Mulhern SA, Frankel NC, Steven MG, Williams JR. Immune dysfunction in rats fed a diet deficient in copper. Am J Clin Nutr. 1987; 45: 997-1006.

281. Santos YMS, John SES, Mesecar AD. The SARS-coronavirus papain-like protease: structure, function and inhibition by designed antiviral compounds. Antiviral Res. 2015; 115: 21-38.

282. Han YS, Chang GG, Juo CG, Lee HJ, Yeh SH, Hsu JT, et al. Papain-like protease 2 (PLP2) from severe acute respiratory syndrome coronavirus (SARS-CoV): expression, purification, characterization, and inhibition. Biochemistry. 2005; 44: 10349-1059.

283. Warnes SL, Little ZR, Keevil CW. Human coronavirus 229E remains infectious on common touch surface materials. mBio. 2015; 6: e01697-e01715.

284. Ishida T. Antiviral activities of Cu2+ ions in viral prevention replication, RNA degradation, and for antiviral efficacies of lytic virus, ROS-mediated virus, copper chelation. World Scientific News. 2018; 99: 148-168.

285. Ren G, Hu D, Cheng EWC, Reus MAV, Reip P, Allaker RP. Characterisation of copper oxide nanoparticles for antimicrobial applications. Int J Antimicrob Agents. 2009; 33: 587-590.

286. Mohammadyari A, Razavipour ST, Mohammadbeigi M, Negahdary M, Ajdary M. Exploring vivo toxicity assessment of copper oxide nanoparticle in Wister rats. J Biol Today's World. 2014; 3: 124-128.

287. Fujimori Y, Sato T, Hayata T, Nagao T, Nakayama M, Nakayama T, et al. Novel antiviral characteristics of nanosized copper(I) iodide particles showing inactivation activity against 2009 Pandemic H1N1 influenza virus. Appl Environ Microbiol. 2012; 78: 951-955.

288. Reiser S, Smith JC, Mertz W, Holbrook JT, Scholfield DJ, Powell AS, et al. Indices of copper status in humans consuming a typical American diet containing either fructose or starch. Am J Clin Nutr. 1985; 42: 242-251.

289. Barcik W, Boutin RCT, Sokolowska M, Finlay BB. The role of lung and gut microbiota in the pathology of asthma. Immunity. 2020; 52: 241-255.

290. Chang CS, Kao CY. Current understanding of the gut microbiota shaping mechanisms. J Biomed Sci. 2019; 26: 59.

291. Ye ZW, Yuan S, Yuan KS, Fung SY, Chan CP, Jin DY. Zoonotic origins of human coronaviruses. Int J Biol Sci. 2020; 16: 1686-1697.

292. Josef N. Gastroenterology and Nutrition: Neonatology Questions and Controversies. Elsevier. 2018.

293. Khuroo MS. Chloroquine and hydroxychloroquine in coronavirus disease 2019 (COVID-19). Facts, fiction and the hype: a critical appraisal.

Int J Antimicrob Agents. 2020; 56: 106101.

294. Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. Cell. 2014; 157: 121-141.

295. Mayer L. Mucosalimmunity. Immunol Rev. 2005.

296. Dwyer DNO, Dickson RP, Moore BB. The lung microbiome, immunity and the pathogenesis of chronic lung disease. J Immunol. 2016; 196: 4839-4847.

297. Marsland BJ, Trompette A, Gollwitzer ES. The gut-lung axis in respiratory disease. Ann Am Thorac Soc. 2015; 12: S150-S156.

298. Dickson RP. The microbiome and critical illness. Lancet Respir Med. 2016; 4: 59-72.

299. Budden KF, Gellatly SL, Hansbro PM, Wood DL, Cooper MA, Morrison M, et al. Emerging pathogenic links between microbiota and the gut-lung axis. Nat Rev Microbiol. 2017; 15: 55-63.

300. Berger AK, Mainou BA. Interactions between enteric bacteria and eukaryotic viruses impact the outcome of infection. Viruses. 2018; 10: 19.

301. Hanada S, Pirzadeh M, Carver KY, Deng JC. Respiratory viral infection-induced microbiome alterations and secondary bacterial pneumonia. Front Immunol. 2018; 9: 2640.

302. Li N, Ma WT, Pang M, Fan QL, Hua, JL. The commensal microbiota and viral infection: a comprehensive review. Front Immunol. 2019; 10: 1551.

303. Frieman M, Heise M, Baric R. SARS coronavirus and innate immunity. Virus Res. 2008; 133: 101-112.

304. Grayson MH, Camarda LE, Zemple SJ, Hunter DA, Santoro JL, Rohlfing M, et al. Intestinal microbiota disruption reduces regulatory T cells and increases respiratory viral infection mortality through increased IFNgamma production. Front Immunol. 2018; 9: 1587.

305. Short K, Vissers M, Kleijn SD, Zomer AL, Kedzierska K, Grant E, et al. Bacterial lipopolysaccharide inhibits influenza virus infection of human macrophages and the consequent induction of CD8+ T cell immunity. J Innate Immun. 2014; 6: 129-139.

306. Avadhanula V, Rodriguez CA, Devincenzo JP, Wang Y, Webby RJ, Ulett GC, et al. Respiratory viruses augment the adhesion of bacterial pathogens to respiratory epithelium in a viral species- and cell type-dependent manner. J Virol. 2006; 80: 1629-1636.

307. Ramphal R, Small PM, Shands JW, Fischlschweiger JW, Small PAJ. Adherence of Pseudomonas aeruginosa to tracheal cells injured by influenza infection or by endotracheal intubation. Infect Immun. 1980; 27: 614-619.

308. Siegel SJ, Roche AM, Weiser JN. Influenza promotes pneumococcal growth during coinfection by providing host sialylated substrates as a nutrient source. Cell Host Microbe. 2014; 16: 55-67.

309. Pittet LA, Stoodley LH, Rutkowski MR, Harmsen AG. Influenza virus infection decreases tracheal mucociliary velocity and clearance of Streptococcus pneumoniae. Am J Respir Cell Mol Biol. 2010; 42: 450-460.

310. Didierlaurent A, Goulding J, Patel S, Snegrove R, Low L, Bebien M, et al. Sustained desensitization to bacterial Toll-like receptor ligands after resolution of respiratory influenza infection. J Exp Med. 2008; 205: 323-329.

311. Sun K, Metzger DW. Inhibition of pulmonary antibacterial defense by interferon gamma during recovery from influenza infection. Nat Med. 2008; 14: 558-564.

312. Robinson KM, McHugh KJ, Mandalapu S, Clay ME, Lee B, Scheller EV, et al. Influenza A virus exacerbates Staphylococcus aureus pneumonia in mice by attenuating antimicrobial peptide production. J Infect Dis. 2014; 209: 865-875.

313. Taubenberger JK, Reid AH, Fanning TG. The 1918 influenza virus: a killer comes into view. Virology. 2000; 274: 241-245.

314. Groves HT, Tregoning JS, Cuthbertson L, James P, Moffatt MF, Cox MJ. Respiratory disease following viral lung infection alters the murine gut microbiota. Front Immunol. 2018; 9: 182.

315. Haak BW, Littmann ER, Morjaria SM, Taur Y, Fontana E, Gyaltshen Y, et al. Impact of gut colonization with butyrate-producing microbiota on respiratory viral infection following allo-HCT. Blood. 2018; 13: 2978-2986.

316. Iwata M, Hirakiyama A, Eshima Y, Kagechika H, Kato C, Song SY. Retinoic acid imprints gut-homing specificity on Tcells. Immunity. 2004; 21: 527-538.

317. Manicassamy S, Pulendran B. Retinoic acid-dependent regulation of immune responses by dendritic cells and macrophages. Semin Immunol. 2009; 21: 22-27.

318. Lau ASY, Hor YY, Lew LC, Chuah LO, Choi SB, Liong MT, et al. Bifidobacterium longum BB536 alleviated upper respiratory illnesses and modulated gut microbiota profiles in Malaysian pre-school children. Benef Microbes. 2018; 9: 61-70.

319. Sugahara H, Odamaki T, Abe F, Kato T, Fukuda S, Ohno H, et al. Probiotic Bifidobacterium longum alters gut luminal metabolism through modification of the gut microbial community. Sci Rep. 2015; 5: 13548.

320. Wong CB, Odamaki T, Xiao JZ. Beneficial effects of Bifidobacterium longum subsp. longum BB536 on human health: Modulation of gut microbiome as the principal action. Journal of Functional Foods. 2019; 54: 506-519.

321. Besten GD, Eunen KV, Groen AK, Venema K, Reijngoud DJ, Bakker BM. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. J Lipid Res. 2013; 54: 2325-2340.

322. Vieira AT, Fukumori C, Ferreira CM. New insights into therapeutic strategies for gut microbiota modulation in inflammatory diseases. Clin Transl Immunol. 2016; 5: e87.

323. Turnbaugh PJ, Ley RE, Hamady M, Liggett CMF, Knight R, Gordon JI, et al. The human microbiome project. Nature. 2007; 449: 804-810.

324. Preidis GA, Versalovic J. Targeting the human microbiome with antibiotics, probiotics, and prebiotics: gastroenterology enters the metagenomics era. Gastroenterology. 2009; 136: 2015-2031.

325. Pennisi E. Massive microbial sequence project proposed. Science. 2007; 315: 1781.

326. Yan F, Polk DB. Probiotics and immune health. Curr Opin Gastroenterol. 2011; 27: 496-501.

327. Kechagia M, Konstantopoulou S, Dimitriadi D, Gyftopoulou K, Skarmoutsou N, Fakiri EM, et al. Health benefits of probiotics: a review. ISRN Nutr. 2013; 2013: 481651.

328. Green WD, Beck MA. Obesity altered T cell metabolism and the response to infection. Curr Opin Immunol. 2017; 46: 1-7.

329. Committee on Military Nutrition Research Food and Nutrition Board Institute of Medicine. Military Strategies for Sustainment of Nutrition and Immune Function in the Field. National Academies Press. 1999.

330. Nieman DC, Wentz LM. The compelling link between physical activity and the body's defense system. J Sport Health Sci. 2019; 8: 201-217.

331. Romeo J, Warnberg J, Marcos TPA. Role of physical activity on immune function Physical activity, immunity and infection. Proc Nutr Soc. 2010; 69: 390-399.

332. Jones AW, Davison G. Exercise, immunity, and illness. Muscle and Exercise Physiology. 2019.

333. Kyrou I, Feingold KR, Randeva HS, Anawalt B, Tsigos C, Boyce A, et al. Clinical problems caused by obesity. Endotext. 2018.

334. Francisco V, Pino J, Cabaleiro VC, Fernández CR, Gualillo O, Mera A, et al. Obesity, fat mass and immune system: role for leptin. Front Physiol. 2018; 9: 640.

335. Gibson GJ. Obesity, respiratory function and breathlessness. Thorax. 2000; 55: S41-S44.

336. Gamal HE, Khayat A, Shikora S, Unterborn JN. Relationship of dyspnoea to respiratory drive and pulmonary function tests in obese patients before and after weight loss. Chest. 2005; 128: 3870-3874.

337. Simpson RJ, Guy K. Coupling aging immunity with a sedentary lifestyle: has the damage already been done? -- a mini-review. Gerontology. 2009; 56: 449-458.

338. Turner JE. Is immunosenescence influenced by our lifetime "dose" of exercise? Biogerontology. 2016; 17: 581-602.

339. Simpson RJ. Aging, persistent viral infections, and immunosenescence: can exercise "make space"? Exer Sport Sci Rev. 2011; 39: 23-33.

340. Segerstrom SC, Miller GE. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. Psychol Bull. 2004; 130: 601-630.

341. Felten SY, Felten DL. Neural-immune interactions. Prog Brain Res. 1994; 100: 157-162.

342. Bae YS, Shin EC, Bae YS, Eden WV. Editorial: stress and immunity. Front Immunol. 2019; 10: 245.

343. Rosso MED, Sterle HA, Cremaschi GA, Genaro AM. Beneficial effect of fluoxetine and sertraline on chronic stress-induced tumor growth and cell dissemination in a mouse model of lymphoma: crucial role of antitumor immunity. Front Immunol. 2018; 9: 1341.