Review Article

Potential Dietary Interventions for COVID-19 Infection Based on the Gut-Immune Axis: An Update Review on Bioactive Component of Macronutrients

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Abstract

Recently emerged coronavirus, known as SARS-CoV-2 or Covid-19 is considered as a serious threat for human health. Due to unavailable specific drugs for this virus, there is an urgent need for supportive cares. Epigenetic immune boosting approaches and developing anti-inflammatory agents by gut-associated bioactive macronutrients can be plausible protective cares for COVID-19. Suitable intake of bioactive macronutrients including prebiotics, fatty acids, proteins and branched-chain amino acids may result in anti-viral responses through modulating macrophages and dendritic cells via Toll-like receptors, decreasing viral load, inactivating the enveloped viruses, increasing the anti-inflammatory metabolites and inhibiting the proliferation of microbial organisms. Bioactive macronutrients may help in promotion of immunological responses and recovery acceleration against Covid-19. This review focuses on the mechanisms of bioactive macronutrients and related clinical trials on enveloped viruses with emphasis on gut-microbiome-immune axis. Macronutrients and this axis may be conducive strategies to protect host against the viral infection.

Keywords: *Coronavirus, functional food, immune system, nutrients, prebiotic*

Introduction

An outbreak of pneumonia-causing coronavirus (COVID-19) began in Wuhan, Hubei province in China at the end of 2019. COVID-19 is a global public health issue, which spreads very fast impacting millions of people by increasing morbidity and mortality.[1] By the 21st of March, 2021, the most recent reports indicated that COVID-19 pandemic has caused in 122 536880 confirmed cases and 2703780 deaths worldwide.[2] The male to female sex ratio among the ceferonfirmed cases is 1.03:1, with the average age of 51 (interquartile range: 36-65) years old.[2] Coronaviruses belong to the group of ortho-coronavirinae which is the subfamily of coronaviridae and includes alpha-, beta-, gamma-, and delta-coronavirus.[3] During the past two decades, SARS and MERS (beta-coronaviruses) caused severe acute respiratory and Middle East respiratory syndromes, respectively, and threatened the human life.[4,5] The obtained data of full-genome sequencing and phylogenic analysis demonstrated that COVID-19 belongs to the group of beta-coronaviruses as well. Besides, it has been indicated that the cell receptor of COVID-19 is the same as SARS-CoV which is an angiotensin-converting enzyme II (ACE2).[6] The genomic evidence showed more than 82% identity between SARS-CoV and COVID-19[7,8] also, indicated more similarity to several bat coronaviruses. But it is not obvious yet, that whether bats are the transferring source of COVID-19 or not.[9]

The transmission mechanism of COVID-19 is not clear yet, but the initial relationship between COVID-19 occurrence and seafood markets selling live animals have been observed. Phylogenetic analysis showed that COVID-19 is similar to the coronaviruses observed in Rhinolophus (horseshoe bats), with 98.7% similarity of nucleotides with the RNA-dependent RNA polymerase (RdRp) gene of the bat coronaviruses strain BtCoV/4991 and 87.9% nucleotide similarity with the bat coronaviruses strains bat-SL-CoVZC45 and

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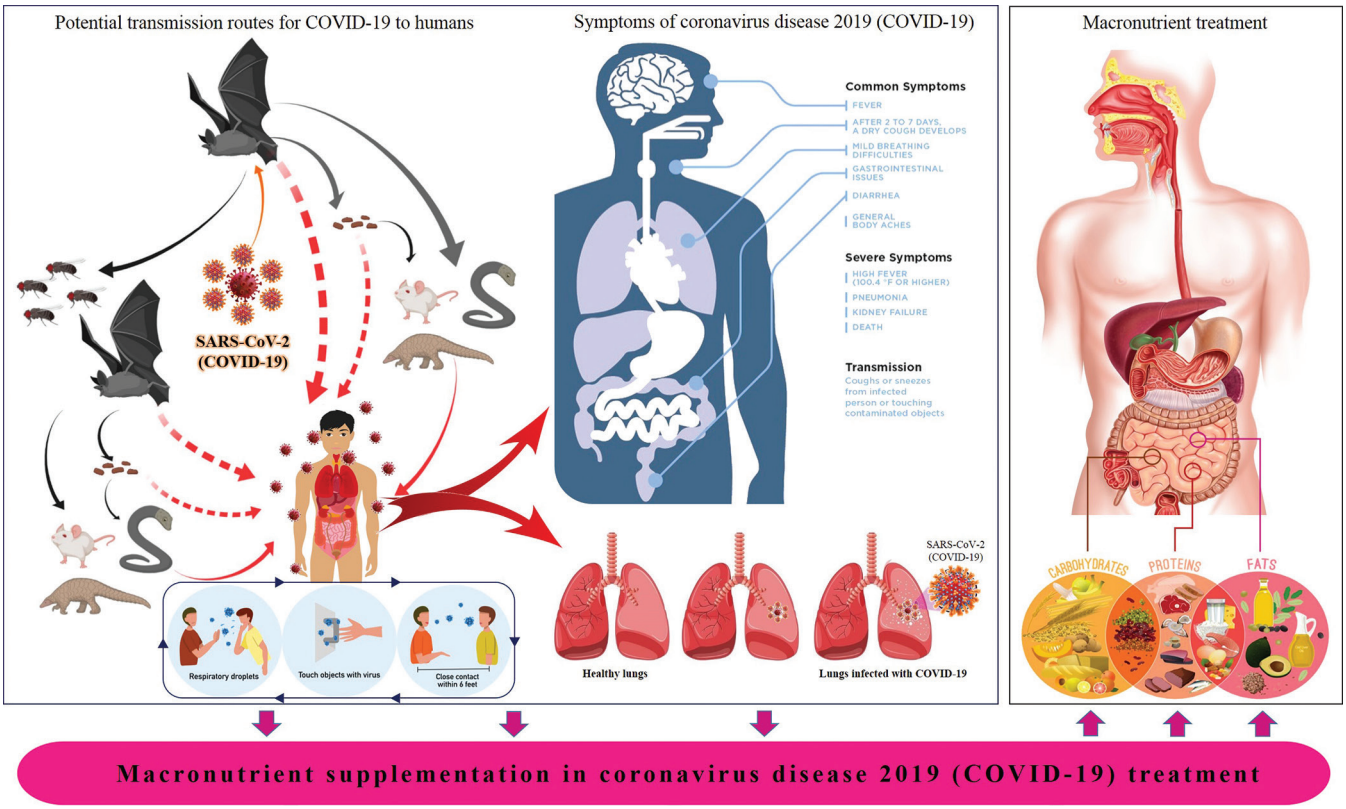

Figure 1: Schematic of macronutrient supplementation in treatment of coronavirus

bat-SL-CoVZXC21.[10] Actually, despite the first origin of this disease, person-to-person transmission is the major reason for virus spreading.[11] Infectious respiratory droplets are known as the major transmission ways of the COVID 19 virus.[12]

It is worth mentioning that there is no exact treatment for COVID-19, till now, and only some antiviral drugs that were developed for other viruses are used for patients. Therefore, it seems that there is an obvious need for using preventive and immune-boosting approaches. Basic preventive measures published by the World Health Organization (WHO) are including health care, maintaining personal hygiene, and social distancing.[1] Novel pathogens, mental stress, lack of sleep, malnutrition, or inappropriate weight are some factors suppressing the immune system function. Immunity, against novel pathogens, can occur both naturally or acquired in a complex mechanism, mostly in collaboration. One of the main influencing factors on natural resistance is appropriate nutrition. According to the literature, balanced nutrition subsidizes the immune system and it has a vital role in making the immune system stronger against infections.[13] The dietary factors leading to the weakness in immunity functions are deficiency in the intake of macronutrients and micronutrients. Moreover, clinical studies have shown that, malnutrition, weight imbalance, frailty, and gut microbiota dysbiosis are the main factors involved in deteriorating the immunity functions of infectious patients. Macronutrients and their bioactive factors play an essential role in balancing weight, reducing weakness, and boosting the immune system. By considering the novelty of COVID-19 and the existence of a significant gap in prevention and therapy points, it seems necessary to notice the potential of nutrition strategies to help to manage this crisis. The current study aims to focus on the role of gut-associated bioactive macronutrients in immune-boosting and managing the coronavirus infections by associating them to other viruses [Figure 1].

Methodology

In the present study, published articles about the effect of macronutrients on different viruses and also their association with COVID-19, were collected for the review. Searches were carried out using keywords of “coronavirus”, “SARS”, “MERS”, and “macronutrient”, “carbohydrate”, “fat”, “protein”, “immune system”, “prebiotic”, “omega 3”, “inflammation”, “respiratory”, “virus” in titles and/or abstracts. Databases, such as Science-Direct, PubMed, Scopus, Cochrane, and ProQuest and Google Scholar for English articles were published from January 1980 to July 2020. Totally, 170 papers were found relevant to viral infection and macronutrients. Then, 134 original articles were chosen using criteria for inclusion and exclusion, describing as follows:

Entry criteria

In this study, accepted original articles on the effect of macronutrients on the reduction or prevention of viral infections were selected. All of the papers included, were in English language.

Exclusion criteria

All of the sources about the effect of macronutrient on bacterial and fungal infections were excluded. Furthermore, studies on effect of micronutrients on viruses were excluded.

Data collection process

All articles were evaluated by two. In some articles, final decision was taken after the study of whole article or a third reviewer suggestion. Selected articles were classified based on the types of macronutrient groups, including, carbohydrates, lipids, and proteins.

Corona Viruses' Family

History of appearance

To date, three identified strains (based on genome sequence and various host cells) of coronaviruses have been reported. In 1960, two HCoV-OC43 and HCoV-229E strains have been emerged by common cold symptoms. SARS is the next life-threatening coronavirus which can lead to lethal pneumonia.[14] The other viral strain which is HCoV-NL63 has been isolated by its genomic sequence from a child (6 months old) and recently, COVID-19 (SARS-CoV-2a) the novel strain of deadly coronaviruses, has raised from China. Infection reports began by the admission of 40 Chinese patients suffering from cough, fever, myalgia, and fatigue on January 2nd, 2020. 30% of patients were transferred to the intensive care unit (ICU), while 15% of patients have died.[15] COVID-19 spread over the world in a short period and led to a global epidemic.

Pathogenesis

Coronaviruses have caused various illnesses, such as gastroenteritis, systemic diseases, bronchitis, hepatitis, and even deaths in, humans, birds, and animals.[16] Earlier, it was believed that coronaviruses only cause moderate and self-limiting respiratory infections in humans, but, SARS and MERS coronaviruses occurrence indicated different points of view.[17] These coronaviruses were responsible for 15–30% of respiratory tract infections in a year after their emergence. These diseases were more likely to occur in old people and persons with previous illnesses. According to reports, COVID-19 has been infected people in all ages, especially "the old people suffering from other problems such as having diabetes, cardiovascular disease, cerebral infarction, chronic bronchitis, hypertension, Parkinson's disease, chronic obstructive pulmonary disease, and cancer".[15,18,19] In general, SARS-CoV involves the lung epithelial cells and also can enter into macrophages and dendritic cells.[20] Infected cells produce pro-inflammatory cytokines such as IL1, IL12, IL18, GCSF, IP10, MCP1, MIP1α, and TNFα, which may cause some immune suppressive and inflammatory diseases.[15]

Pathogenesis mechanism of corona viruses' family

There are few clinical studies on corona viruses, and most of them are related to SARS-CoV infections. Coronaviruses can enter the host cell and cause infection by the interaction between its S proteins with the receptor of the host cell. Some of the virus species such as SARS-CoV use the N-terminus, whereas others bind the C-terminus of the S1 site of the receptor-binding domains.[21] SARS-CoV and HCoV-NL63 use ACE2 receptor, whereas MERS-CoV uses CEACAM1 which is carcinoembryonic antigen-related cell adhesion molecule 1 and DPP4 (dipeptidyl-peptidase 4) as its receptors. Then, proteolytic cleavage at S2′ which is acid-dependent (by enzymes such as serine 2 or cathepsin transmembrane protease), results in the mixture of viral and cellular membranes and thus, the viral genome can release into the cytosol.[22,23] Virus genomic RNA is responsible for gene translation which encodes two huge rep1a and rep1b open reading frames that are responsible for expressing two co-terminal and also nonstructural polyproteins.[24] Furthermore, coronaviruses encode proteases with the ability to cause cleavage in the replicas polyproteins. The nonstructural polyproteins are similar to the replicas-transcriptase complex which creates an appropriate situation for the synthesis of viral RNA.[25]

Overall, sequence assessments of receptor binding motif had shown that the COVID-19 virus binds to the same cell receptor (ACE2) as SARS-CoV.[6] ACE2 has a carboxypeptidase active site in its structure and its function is dependent to zinc existence[26-29] also two lobes are beside the active site of ACE2.[30] Ultimately, literature indicated that binding the SARS-CoV to the N-terminal of the mentioned lobe stimulates the pathogenesis action of the virus.[31] Furthermore, recent researches indicated that the COVID-19 virus binds the human ACE2 receptor with an affinity of 10–20-fold higher than SARS-CoV.[32]

Based on the researchers conducted on coronaviruses, SARS-CoV protein downregulates the ACE2 receptor.[33,34] By downregulation of ACE2, the renin-angiotensin system loses its normal function that leads to an increment in inflammation, vascular permeability, lung edema, and neutrophil accumulation.[35] Some assessments on severe cases of SARS-CoV, reported a huge increase in the levels of transforming growth factor-β *(*TGF-β*)* and prostaglandin E2 (PGE2) that have immunosuppressive characteristics and known as the factors related to prolonged SARS-CoV period in infected cases.[36] Few studies with more concentration on chemokines than cytokines indicated that SARS-CoV infection results in remarkable gene overexpression of chemokines, such as macrophage

inflammatory protein-1α (MIP-1), interleukin-8 (IL-8), interferon gamma-induced protein 10 (IP-10), and monocyte chemoattractant protein-1 (MCP-1)[37-39]; which may lead to acute lung injury.[40]

Furthermore, it is interesting to know that ACE2 is abundant in the epithelia of the intestine and lungs in humans. According to this, the amino acid transport function of ACE2 is linked to the microbial ecology in the gastrointestinal tract. It was reported that in gastrointestinal tract ACE2 mutants cause to a reduction in antimicrobial peptides' expression and to change in gut microbial composition. Also, due to detecting gut dysfunction in patients with COVID-19, it is likely that COVID-19 is related to gut microbial composition.[41] Based on this, it is worthwhile to investigate whether the advantages of ACE2 on pulmonary diseases may be mediated via modulation of lung or/and gut microbiota.

Therapeutic line

According to reports, COVID-19 is spreading in population with dissimilar RNA sequences. For this reason, there is not a specific treatment against different coronavirus variants.[42] The nucleoside inhibitor Gilead's NUC, despite the failure in Ebola treatment, was shown to be effective as a treatment for a 2019-CoV patient in the USA. Similarly, remdesivir (an adenosine analog) was recommended due to its effectiveness against the Ebola virus and other RNA viruses. Another suggested line of treatment for inhibiting COVID-19, is chloroquine and it is approved to have antiviral, anti-malarial, and also immuno-modulatory effects.[43] Preliminary data proved these treatments to be effective in controlling such emerged COVID-19 but due to different RNA sequences, they couldn't be recommended as a certified treatment preference for newly emerged coronavirus. Therefore, this epidemic infection could be a serious challenge for any country by limited therapeutic options and variable treatment outcomes.[44] According to the mentioned context, nutritional intervention can be proposed as an innovative therapeutic approach or at least an adjuvant therapeutic choice for patients with COVID-19. Since gut microbiome health, makes up for 85% of the body's immune system and plays a very important role in immune-promoting of the host, nutritional interventions which aimed to balance the gut microbiota can be one of the main interventions to increase resistance or accelerate the recovery of patients with COVID-19. Due to the lack of studies on nutritional interventions for coronaviruses, studies on viruses with similar pathogenesis mechanisms to coronavirus, have been rendered in this paper.

Carbohydrates

Mechanism of action

Carbohydrates are known as main energy sources that are found in a wide variety of plants and animals and can act as fuel for metabolic requirements.[45] According to their chemical structures, carbohydrates can be categorized into three main groups of simple sugars, oligosaccharides, and polysaccharides or complex carbohydrates. The highest degree of polymerization belongs to complex carbohydrates, which is 10-fold more than simple sugars and oligosaccharides. It was reported that "high sucrose diet weakens the immune-protective action of carbohydrate recognition molecule, surfactant protein-D (SP-D), as molecular and cellular components of the pulmonary innate immune system", and increases susceptibility to airway inflammation.[46] Moreover, beneficial effects of complex carbohydrates such as prebiotic were reported on the pulmonary immune system.[47] Prebiotics are low digestible complex carbohydrates which can have beneficial health effects on the host by affecting the composition and activity of gut microbiome.[48-50] The balanced gut microbiome is necessary for increasing the function of the immune system[51] and positive effects of it on the respiratory and gut tract has been reported which is achieved by improving the immune responses and acting as an amendment for disease defects in the lungs.[52] Recently it is reported that gut–lung axis can identify immune responses and can interfere with the course of respiratory diseases. Gut microbiota can influence the gut and lung immune systems by local and long-reaching interactions, which involve Th17, IL-13, CD8+T cell, IL-25, prostaglandin E2, and/or NF-κB–dependent pathways.[52] Prebiotic carbohydrates are used as the fermentation substrate by the gut microbiome and short-chain fatty acids (acetate, propionate, and butyrate) are produced as a result. Recent clinical studies have reported the beneficial effects of prebiotic products via modulating metabolic endotoxemia, T-helper, CD8, CD4 IL-6, TNF-α, oxidative stress, and/or NF-κB–dependent pathways[53,54] and also effect of balanced microbiome profile on lung health, immune system, inflammatory factors, prostaglandins, and bacterial infection was studied.[55] Furthermore, prebiotics can improve mental health and quality of life via the hypothalamic-pituitary-adrenal axis that is closely associated with immune system function.[56]

As previously mentioned, prebiotics act as immune modulators through affecting the gut microbiome composition. Prebiotics can enhance the gut bifidobacteria population; the bacteria that compete with pathogenic bacteria to stick to the binding sites of the intestinal epithelium. Also, prebiotics have some indirect effects on immune cell activation and among them, decrease in pathogenic bacteria population, producing antibacterial substances (such as bacteriocins) that eliminates pathogens by beneficial bacteria (including Bifidobacterium and Lactobacillus species) and also sticking them to the binding site of the intestinal epithelium are the most important effects.[57] Moreover, short-chain fatty acids produced by fermentation of prebiotics can lead to gut acidification. The acidification of the gut is the key factor for inhibiting the growth of the pathogens[58] such as coliforms and clostridia.[59] Moreover, acidification of gut results in

mucin regeneration that results in a decrease in the pathogenic bacteria population in turn.[60] It has been indicated that the expression of immunity molecules, substantially cytokines are modulated by prebiotics.[61] On the other hand, prebiotics are known as feeding sources of probiotics; thus, other mechanistic routes can be defined based on the probiotic properties.[57] The probiotic related mechanisms are including inhibiting the virus binding to the cell receptor by binding to it, inhibiting the binding of the virus to the epithelial cells by increasing the intestinal mucus production, increasing the CD4+T lymphocytes differentiation to Th1 and Th2 cells and having a virucidal function, and boosting the antiviral activities by producing low-grade nitric oxide.[62] [Figure 2].

Clinical trials

In infants

There are lots of studies on the effect of carbohydrates especially prebiotics on viruses and viral diseases. Luoto *et al.* had investigated prebiotic supplementation (galacto-oligosaccharide and polydextrose mixture, 1:1 at 1 × 600 mg/day (1 to 30 days) and 2 × 600 mg/day (31 to 60 days) in preterm infant older than 32 + 0 weeks and younger than 36 + 6 weeks, and had reported a remarkable decrease in the respiratory tract and rhinovirus infection rates.[63] In another study, the effects of supplementation with 8 g/L galacto-oligosaccharides and fructo-oligosaccharides (mixture 9:1) in 0-6 months infants for 6 weeks, led to a huge decrease in all types of infection including "fever episodes, upper respiratory tract infections, and antibiotic prescriptions".[64] Oligofructose and inulin supplementation (0.2 g/kg body weight/d for 10 weeks) in 8 months old healthy infants which immunized with measles vaccine, was led to an enhancement in post-vaccination total immunoglobulin G (IgG) levels in the blood.[65] Furthermore, supplementation of infants with 9:1 mixture of galacto-oligosaccharides and fructo-oligosaccharides (0.6 g/100 ml formula) for 32 weeks increased the fecal secretory of IgA.[66] Consuming about 0.55 g/d, cereal supplemented with 3.6% w/w oligofructose for six months in 6-12 months old infants from Peru who were immunized with Haemophilus influenzae type B vaccine, did not affect post-vaccination antibody response to H.influenzae type B.[67] Waligora-Dupriet *et al.* mentioned that 2 g/d oligofructose intake for 21 days in infants of 7–19 months old reduces the flatulence, diarrhea, and vomiting occurrence. Also, this supplementation leads to a decrease in the number of infectious diseases requiring antibiotic treatment.[68]

In adults

Lomax *et al*. had reported that the intake of 8 g/d long-chain inulin and oligofructose (50:50 mixture daily) for 8 weeks in healthy adults (45-63 y), improved the antibody response to the H3N2-like strain and an increment in IgG1-specific antibody response level to the vaccine.[69] Inulin intake (4% w/w of a bread) for 5 weeks in male adults (mean age

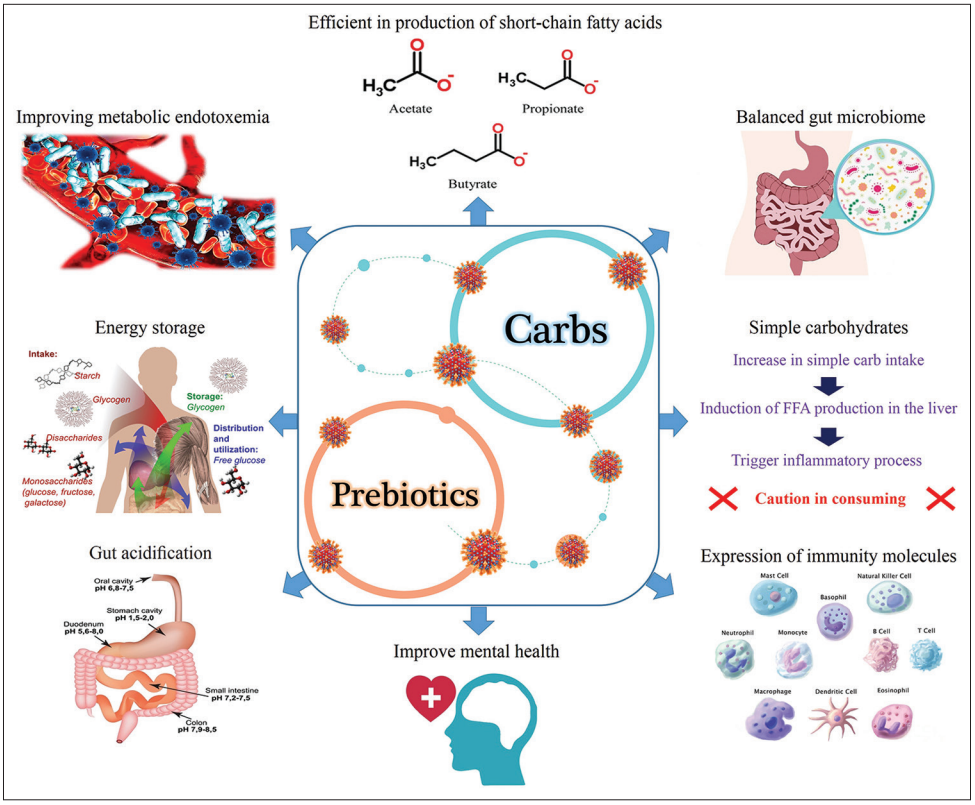

Figure 2: Carbohydrate role associated with coronaviruses

of 27 years) increased CD19 B cells and activated T cells (CD3+ HLA-DR$^+$) and decreased CD3$^+$ NK$^+$ cells and ICAM-1 bearing lymphocytes.[70] Langkamp-Henken *et al*. had expressed that fructo-oligosaccharides' supplementation for 26 weeks (4.95% of the energy intake from the 226.8 g (8oz) formula per day) in adults older than 65 years, has improved response to some vaccine components (15 mg of each of the following hemagglutinin antigens: B/Hong Kong/1434/2002, A/Caledonia/20/99 (H1N1), and A/Panama/2007/99 (H3N2), also has increased the proliferation of the lymphocyte to influenza vaccine components.[71] Furthermore, the other study reported the effect of supplementation with fructo-oligosaccharides (4.95% of the energy intake from 240 ml formula per day for 10 weeks) in adults aged ≥65 years, the results indicated the improved response to some vaccine components, increase in B cells and influenza-activated lymphocytes and decrease in memory cytotoxic T cells, IL-6, IL-10 and fever levels.[72] Vulevic *et al*. indicated that consuming 5.5 g/d prebiotic galacto-oligosaccharides mixture (contain 48% (w:w) galactooligosaccharide) in elderly persons (average range 69) for 10 weeks results in noticeable improvement of phagocytosis and natural killer cells activities. Also, a considerable increment was shown in the anti-inflammatory cytokine interleukin-10 (IL-10) production also a decrement occurred in the proinflammatory cytokines (IL-6, tumor necrosis factor-alpha, and IL-1beta) production.[61] Moreover, oligofructose intake (8 grams per day for 3 weeks) in elderly adults living in a care home (average age of 85 years old) was shown to increase the percent of CD4$^+$, peripheral blood T, and CD8$^+$ and caused a decrease in monocyte and granulocyte phagocytosis of Escherichia coli. Besides, they reported a decrease in IL-6 mRNA expression of peripheral blood mononuclear cells without affecting the total numbers of leucocytes, activated T lymphocytes or natural killer cells in the blood.[73] Bunout *et al*. assessed the effects of the oligofructose and inulin supplementation (raftilose and raftiline mixture) which was 6 grams per day for 28 weeks on free-living adults (≥70 years) that have been immunized with influenza and pneumococcal vaccines at week 2 of the trial; the results indicated an increase in the response of the antibody to *Streptococcus pneumonia* and influenza B virus in both of the control and prebiotic groups.[74]

Generally, carbohydrates are principal structures for immune system identification and general function. However, dietary carbohydrates can affect the host response to COVID-19. According to the results of the mentioned studies, simple carbohydrates may impair the protective action on the pulmonary immune system, and increases susceptibility to airway inflammation, while complex carbohydrates especially prebiotics may heighten the effects on the pulmonary immune system by decreasing metabolic endotoxemia via changing the composition and activity of gut microbiome. So, foods containing prebiotics such as wheat, honey, banana, barley, onion, garlic can be recommended as a preventive or therapeutic supplementation in the people. Although, probiotics may offer health-promoting effects, it was recommended that these compounds should be administrated to immunocompromised individuals with caution. Because probiotics may have potential risks such as systemic infections, and incorrect immune responses in hosts especially in susceptible populations, it also can decrease their capability of transmission of the antibiotic resistance genes to pathogens.[75]

Lipids

Mechanism of action

Lipids are essential components in the diet that have various roles such as energy storage. Also, these compounds are the main membrane ingredient, they can be hormones, and vitamin precursors as well. Lipids are classified into polar (fatty acids, cholesterol, glycerophosphatides, and glycosphingolipids) and non-polar (Triglycerides and cholesteryl esters) groups.[76] Fatty acids are categorized into essential and nonessential fatty acids, based on synthesizing by the human body and saturated (SFA) and unsaturated fatty acids based on their double bond numbers.[77] Essential fatty acids (EFAs), omega 3 and 6, as polyunsaturated fatty acids (PUFA), can just be obtained from the diet and have functional effects on overall human health.[78] Fatty acids affect the T-cells as a section of the immune system by two mechanisms of passive and active. In the passive mechanism, the diffusion of fatty acids occurs through the membrane. While fatty acid transportation and fatty acid-binding proteins or other receptors are involved in the active mechanism of fatty acid uptake.[79] Also, the SFA and PUFA may have an influence on COVID-19 in the host, via modulation inflammatory pathways.

It was reported that binding of COVID-19 to the Toll-Like Receptor (TLR) results in the release of pro-IL-1β and IL-6 that can mediate fibrosis, lung inflammation, and fever.[80] Also, it was shown that viral infection such as H5N1 avian flu, via producing reactive oxygen species (ROS), and production of oxidized phospholipid cytokine by lung macrophages, via TLR4-TRIF, induces acute lung injury.[35] Current observations propose that saturated fatty acids (SFA), were recognized by the CD14-TLR4-MD2 complex. These compounds can be non-microbial TLR4 agonists and can activate its inflammatory responses via modification of gut microbiota and metabolic endotoxemia production. This results in oxidative stress and ox-LDL, that activates the inflammatory pathways of CD14-TLR4-MD2 which are involved in the generation of inflammatory mediators such as chemokines, cytokines, and costimulatory molecules.[81] So, probably, SFA can exacerbate the effects of COVID-19 inflammatory pathways. However, it was reported that supplementation

with omega-3 decreases oxidative stress and inflammatory mediators such as interleukin-1 beta, and tumor necrosis factor-alpha.[82]

EFAs and their metabolites such as docosahexaenoic acid (DHA), dihomo-gamma-linolenic acid (DGLA), gamma-linolenic acid (GLA), eicosapentaenoic acid (EPA), and arachidonic acid (AA) and their products such as prostacyclin, prostaglandin E1, lipoxins, resolvins, and maresins and protectins, can modulate inflammation, can also enhance healing, the phagocytic capacity of macrophages, and microbial clearance and are beneficial for prevention and management of infection conditions and inflammatory responses.[83] It was reported that AA and other unsaturated fatty acids can easily inactivate SARS-CoV-2, SARS, and MERS as enveloped viruses. AA may induce antimicrobial action via inducing leakage and lysis of membranes of microbial cells by disrupting the protein envelopes of the virus, as well as numerous cellular metabolic effects, involving impacts that it can have on transportation of amino acids, also acting as an uncoupler of oxidative phosphorylation. Probably, in the challenge of several microorganisms involving viruses such as SARS-CoV-2, SARS and MERS coronaviruses, by immunocytes such as alveolar macrophages, leukocytes, T and B cells, and NK cells, theses immunocytes release AA into their surrounding milieu that in turn it inactivates the organisms and in this way, it protects lungs also other tissues. So a deficiency in AA may lead to an increased susceptibility to several infections such as SARS, MERS, and SARS-CoV-2.[84]

On the other hand, viral infections have adverse effects on the EFAs organized metabolism and lead to EFAs deficiency. The efficiency of interferon's antiviral effects is associated with EFAs.[85,86] Moreover, EFAs can inhibit cell proliferation and also suppress natural cytotoxicity by decreasing the cytokine (IL-l, IL-2, TNF-α, IFN-y) production.[87] Therefore, EFAs supplementation could lessen problems related to viral diseases. Gutiérrez *et al*. could express the role of EFAs on immune cells via modulating macrophages, natural killer, neutrophils, eosinophils, basophils, dendritic cells, mast cells, and T and B cells, decently.[88]

It is now well approved that anti-inflammatory effects of omega 3 fatty acids are associated with oxygenated metabolites of them through the lipoxygenase and cyclooxygenase pathways. Although, the downstream signaling pathways involved in beneficial effects of omega 3 fatty acids have not been clarified. It seems that a sufficient intake of omega 3 fatty acids could have an effective role in enhancing the phagocytosis and IgM production in response to viral infections.[88] Omega-3 fatty acids intake results in significant changes in gene regulation of macrophages. It was reported that supplementation with DHA (Docosahexaenoic acid) and EPA (Eicosapentaenoic acid) as omega-3 fatty acids, affects the cell cycle gene regulation and immune response gene regulation, respectively.[89]

Literature indicated that EPA, DHA, and other linolenic acid derivatives decrease the gene expression of inflammatory cytokines (MCP1, IL1a, IL1b, and IL6) in macrophages, and omega-3 supplementation can increase the anti-inflammatory cytokine IL-10 levels. Overall, linolenic acid derivatives [13-(S)-HPOTrE and 13-(S)-HOTrE] have anti-inflammatory properties that are mediated by the stimulation of apoptosis also inhibition of autophagy in the lipopolysaccharide challenged macrophages. These anti-inflammatory properties increase in anti-inflammatory cytokines and decrease the pro-inflammatory cytokines/enzymes.[90,91] On the other hand, some studies demonstrated an increase in the phagocytic capacity of macrophages during omega-3 supplementation. The precise mechanism of this route is not assessed yet; but it seems that omega-3 intake modifies the cellular membrane composition and structure which leads to the increased phagocytic capacity of macrophages[92,93] [Figure 3].

Clinical trials

Literature that collected here indicated the effect of different trials on viral infection. Superti *et al*. had examined the impact of several saturated fatty acids (10 to 16 carbon) and some of their derivatives in various concentrations (20 μm, 50 μm, 200 μm) on the SA-11 rotavirus infection in a monkey kidney cell line. Results displayed a substantial dose-dependently increase in rotavirus infected cells.[94] Other study had reported that the intake of fish oil (n-3) PUFA (diet with 25 wt % of fish oil) for 1 month in 6-8 weeks mice did not help immune response in cytomegalovirus (CMV).[95] Fritsche *et al*. reported that linolenic acid-rich diet (10%-by-weight linseed oil) in BALB/c mice for 6-10 weeks; at the end of the trial, led to a huge enhancement in viral-specific cytotoxicity by elevating the immune cells, reducing eicosanoid synthesis and increasing the cell-mediated cytotoxic response to a viral challenge.[96] Fernandes *et al*. had reported that 4 weeks C57BL/6 mice that were fed with 5 or 20% fish oil for 8 weeks, lived longer than the control group when injected with murine retrovirus (LpBM5 MuLV).[97] Besides, other study described that the intake of a diet enriched with 20% fish oil in C57BL/6 female mice for 4 weeks injected with LP-BM5 murine retrovirus decreased the development of murine AIDS by regulating levels of cytokines including TNF-α, IL-β, and IL-2.[98] Experimental investigation on the effect of prostaglandins on virus replication revealed that pretreatment of the cells with 25 μg/ml prostaglandin E_1 for 24 h, attenuates the Mengo, MM, and polioviruses. Probably, prostaglandin inhibits cell division and increases interferon efficiency.[99] In another study, it was observed that *in vitro* incubation (10-60 minutes) of

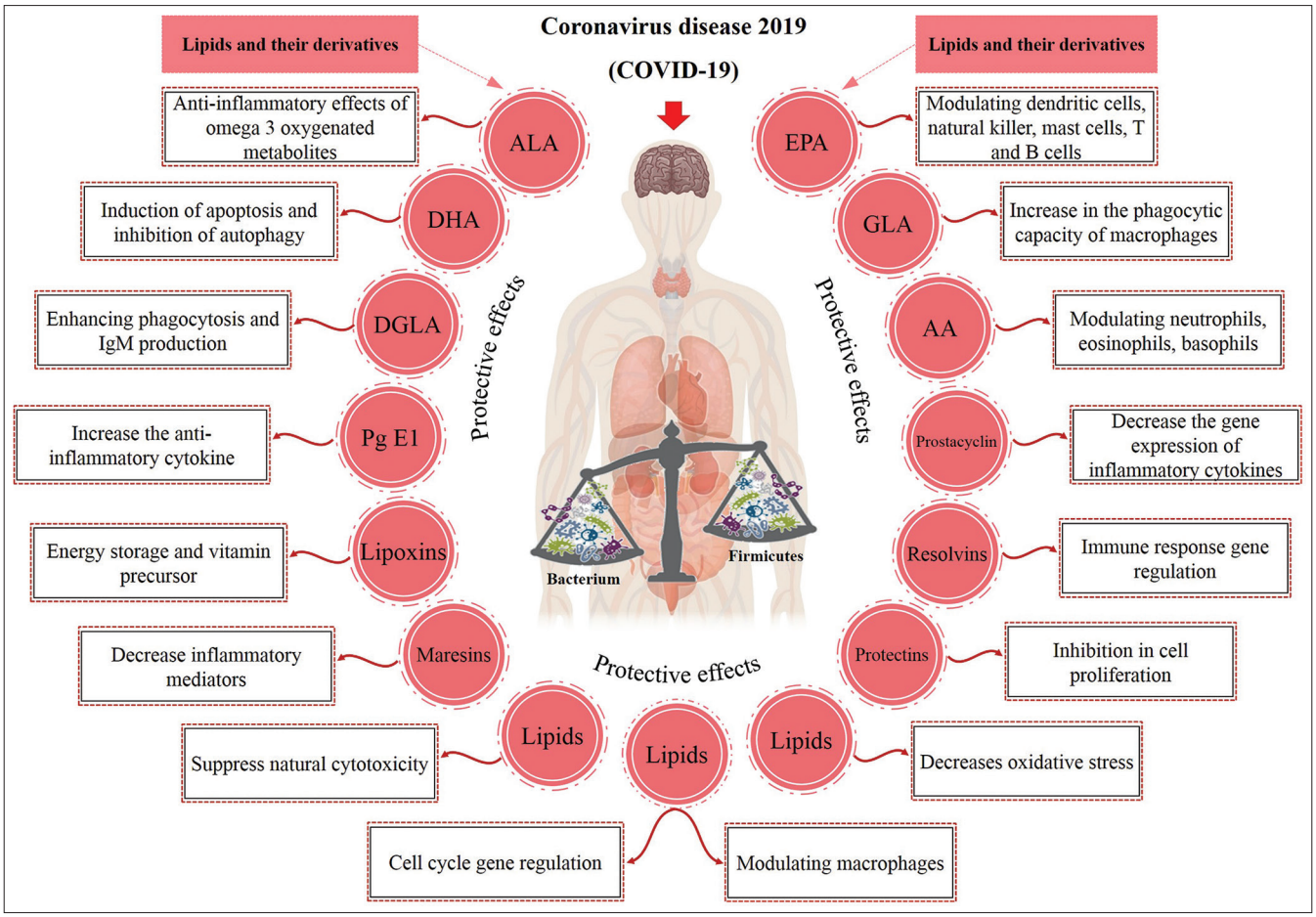

Figure 3: Lipid role associated with coronaviruses

enveloped viruses (Myxovirus, Paramyxovirus, Arbovirus or Herpesvirus) with linoleic acid (C18:2) (10-100 ~μg/ml) decreases the viral infectivity, significantly.[100] The intake of omega-3 series fatty acids may be a beneficial therapeutic approach in AIDS patients. The total plasma lipid levels, especially omega-3 series (C20 and C22) is low in patients with AIDS which can be related to some of the problems associated with the syndrome, thus their supplementation could be effective.[101]

The effect of dietary (omega-3) PUFA intake (17 g fish oil and 3 g sunflower/100 g) for 14 days against influenza A virus (H3N2 strain) was investigated in 6 weeks male BALB/c mice. Results indicated lower Ig G and Ig A titers in serum, virus-specific cytotoxic activity, and IFNɤ rather than the control group. Thus, high (omega-3) PUFA supplementation may impair acquired cell-mediated immunity against the influenza A virus.[102,103] According to Morita *et al*., lipid mediator which is derived from the omega-3 (PUFA) (1 mμ in each infected cell) can inhibit influenza virus replication and rescue the mice with influenza even in cases that antiviral drugs are not efficient.[104]

The effect of peroxidation of 0.1 mM arachidonate for 72 h, on Huh7 cells is shown to be a decrease in the amount of hepatitis C virus (HCV) RNA which inhibits its replication.[105] Probably, PUFAs have anti-hepatitis C virus (HCV) activities by influencing the RNA replicon system. The treatment with arachidonic acid at 4 μM, α-linolenic acid, ɤ-linolenic, and linoleic acid at 100 μM for 24 h on replicon cells containing HCV subgenomic RNA, was shown to decrease HCV RNA levels but saturated fatty acids such as palmitic acid, myristic acid, and stearic acid were not able to inhibit HCV replication.[106] Jones *et al*., also indicated that short term supplementation (3–6 weeks) with omega-3 PUFA (41% kcal) did not affect the recovery time, morbidity, and mortality in poxvirus vaccinated mice (4-6 weeks).[107]

Although, dietary lipids are a good source of energy especially in patients. However, the vital role that dietary lipids have in the management of the immune system responses and alteration in the host natural resistance to viruses is dependent on the kind of fatty acids. According to the results of the mentioned studies, SFAs can exacerbate the effects of the COVID-19 inflammatory pathway by alteration of gut microbiota and metabolic endotoxemia production. But, PUFAs especially omega 3 family modulate different immune parameters including lymphocyte proliferation, phagocytosis, Nk cell activity,

antibody production, CD4, CD8, cytokine production such as IL-6, IL-2, IL-1, and TNF-α and IL-10, oxidative stress and phospholipid profiles. So, it seems that food source and dietary oils containing omega-3 fatty acids consumption to be preventive and therapeutic route in patients with the viral infection. Although animal food sources such as fish are rich with omega-3 fatty acids such as EPA and DHA, plant food sources such as dietary oils containing omega-3 fatty acids and seeds can be recommended options due to their antioxidant ingredients and lack of contaminations such as toxic heavy metals. Also, oral or intravenous use of the unsaturated fatty acids may enhance resistance and accelerate recovery from similar infections such as MERS, SARS-CoV-2, and SARS.

Proteins

Mechanism of action

Proteins are kinds of macromolecules made up of amino acid (AA) units performing various vital functions in the body.[108] They act as antibodies, enzymes, messengers, transporters, and structural components in the body.[3] A wide range of studies indicates that protein supplementation boosts the immune system which specifically improves infectious disease surveillance.[109] Proteins show antiviral activities against both enveloped and naked viruses. They inhibit virus entry to the cell by sticking to cell receptors.[110] Viruses need some enzymes including DNA- or RNA-polymerases, reverse transcriptase, integrase, etc., for viral replication.[111] The investigations indicated that proteins can inhibit the activity of the mentioned enzymes and eventually can prevent virus replication.[112] Therefore, it is obvious that protein deficiency results in loss of immune function.[113] Protein-energy deficiency impairs immune function and also leads to an increase in the viral incidence risk by impairing the T-cell system.[114,115] It is worthy to note that proteins interact with gut microbiota, dependent on their sources.

It was reported that animal-based proteins such as red meat, dairy products, eggs, and fishes are full of choline, lecithin, and carnitine which make them a great source for trimethylamine N-oxide (TMAO). TMAO is the oxidized form of trimethylamine that is produced by gut microbiota flavin-containing monooxygenase-3 (FMO3).[116-118] The investigations have demonstrated that the high level of TMAO leads to NLRP3 (NOD-, LRR- and pyrin domain with protein 3) activation. Then NLRP3 affects pro-caspase-1 to make caspase-1; which results in IL-1ϐ and IL-1β production and promotion of inflammation.[119-121] Moreover, other studies indicated that the high level of TMAO is related to a better expression of pro-inflammatory cytokines, such as TNF-α and IL-1β, and minor expression of the anti-inflammatory cytokine IL-10.[122]

Furthermore, amino acids as protein components play important roles in regulating the immune responses by affecting the natural macrophages, B lymphocytes, T lymphocytes, and killer cells activation. Also, they are involved in synthesizing the cytotoxic substances (antibodies and cytokines) and interacts with gut microbiota. Focusing on AA-microbe interaction is a new insight into immune and antiviral mechanisms. Several mechanisms proposed about dietary AAs (amino acids) also the gut-microbiome-immune axis. Dietary AAs would be metabolized by host intestinal epithelium also by lumen bacteria. These compounds modulate bacterial survival by synthesizing several biologically active molecules that are involved in controlling signal transduction besides nutritional metabolisms.[123] Nutritionally, AAs have an important effect on bacterial activity, composition, and diversity. Also, the investigations had demonstrated that gut microbiota can affect undigested proteins and amino acids to produce SCFAs metabolites.[124] It seems that there is a bidirectional relationship between dietary intake and gut microbiota. Amino acids such as glutamate, glycine, alanine, threonine, lysine, and aspartate are the substrates for acetate production. Alanine and threonine are propionate substrates and butyrate is produced from glutamate and lysine.[125,126] The function of the produced SCFAs in the immune system includes 1) IgA production 2) T-cells promotion and 3) Anti-inflammation properties by inhibiting the growth of colitogenic pathogens[127,128] and 4) Reduction of the luminal PH that inhibits the increase of pathogenic bacteria such as Escherichia and Clostridia.[129] Also, BCAAs adjust immune cells and stimulate the expression of antimicrobial peptides. Met has a downregulating effect on pathogenic genes and adherents to HeLa cells, whereas acyl-homoserine lactones (AHL) may have a regulating effect on the microbe-host axis.[130] It was reported that variations in composition and abundance of AAs can have effect gut microbiome communities also can moderate macrophages and dendritic cells through NOD-like, toll-like, and autoinducer-2 receptors, moreover, they can also control the gut-microbiome-immune axis through serotonin/5-hydroxytryptamine, aryl hydrocarbon receptor, and other signaling pathways, and all of them play vital roles directly or indirectly regulation of the intestinal mucosal immunity and microbiota, which contribute to gut microbiota homeostasis.[131] According to the mentioned context, AAs may influence cellular signaling pathways and can apply immune and barrier defense effects in a physiological concentration. Thus, enough supplementation of nonessential and essential AAs is necessary for maintaining the optimal homeostasis of the host.[132]

Finally, as it is recommended by nutritionists, a planned diet must contain a mixture of animal and plant proteins that provide essential amino acids and nonessential amino acids for host and prevent TMO production as an inflammatory and immune system disorder [Figure 4].

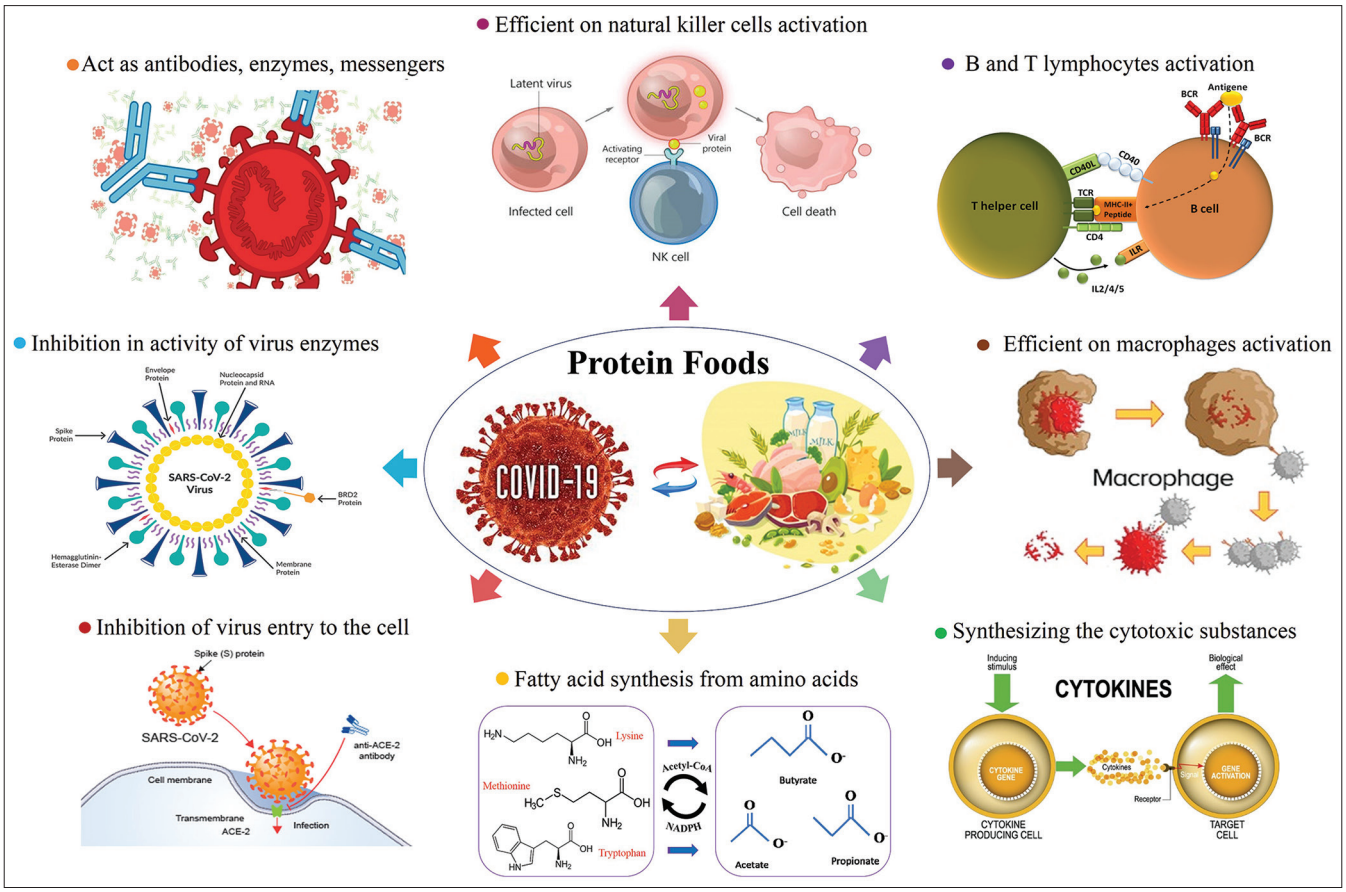

Figure 4: Protein role associated with coronaviruses

Clinical trials

Literature reviews presented the effect of proteins in viral infections. Makino *et al*. had reported that consuming 90 g yogurt per day during eight weeks, with focusing on its protein serve, decreases the infection risk in elderly persons (57-85 years) by increasing the natural killer cell's activity.[133] The effect of long-term yogurt consumption (450 g per day for 4 months) in 20-40 years old persons indicated to be a huge increase in γ-interferon levels produced by isolated T cells.[134] In another study, patients with HIV infection (mean age 42 years) supplemented by 45 g whey protein for two weeks and resulted in improvement in the glutathione deficiency after this short term trial.[135] Furthermore, Sattler *et al*. had indicated that the intake of a 280-kcal high protein supplement with 40 g whey protein (for 12 weeks) in patients with HIV-1 (mean age of 41 years old) leads to an increase in CD4 cell counts.[136] In contrast, high protein and L-lysine intake in cases with HIV indicated an increment in HIV replication and worsened the infection.[137] In the other hand, Ahmed *et al*. had indicated that the intake of 40 g/day polyphenol-enriched protein powder for 17 days prevents virus replication in 19–45 years old athletes and eventually decreases the vesicular stomatitis virus (in the family of Rhabdoviridae) infection incidence.[138]

Pinnock *et al*. had investigated the effect of zero to 11 glasses of milk consuming per day for 10 days in rhinovirus-2 infected patients (adults 18–35 years old). They observed that low dairy intake worsens the infection symptoms like cough and congestion.[139] Moreover, consumption of 600 mg bovine lactoferrin/whey protein immunoglobulin-rich fraction (1:1) per day for 90 days in adults (mean age 32/9 years old) leads to a decrement in the incidence of the common cold and also improvement in its symptoms.[140] Ochoa *et al*. had assessed the effect of 500 mg bovine lactoferrin intake twice per day for six months in norovirus infected children (12-18 months). They found that diarrhea longitudinal prevalence decreased significantly but no differences were seen in noroviral incidence.[141] The whey protein supplementation (oral gavage 80% protein/once daily) in rotavirus infected 9-17 days mice led to a reduction in the viral load and also promotion in the immune response. Increasing neutrophil or natural killer cell activity resulted in a decline in disease severity and duration.[142] In another similar study, Low *et al*. had reported that the whey protein concentrate consumption (24% w/w/12 weeks) in 6-7 weeks mice leads to immune-boosting effects by promotion in antibody response to antigens (Vaccine antigens including influenza vaccine, diphtheria, and tetanus toxoids, poliomyelitis vaccine, ovalbumin, and cholera toxin sub-unit).[143] Wahl

Table 1: Summary of recent studies on the effect of macronutrients on different viruses

Macronutrient	Intervention	Dose-time	Virus	Participant	Age mean	Health effect	Ref
Carbohydrate	Galacto-oligosaccharide and polydextrose mixture	1×600 mg/d; 1-30 d 2×600 mg/d; 31-60 d	Rhinovirus	Preterm infants	≥32 + 0 and ≤36 + 6 wk	Decreased respiratory tract and rhinovirus infection rates	(63)
	Galactooligosaccharide and fructo-oligosaccharide	8 g/L/6 wk	_	Term infants	0-6 mo	A decrease in all types of infection, upper respiratory tract infections, fever episodes, and antibiotic prescriptions	(64)
	Oligofructose and inulin supplementation	0·2 g/kg bw/d/10 wk	Measles	Healthy infants	8 mo	Increased post-vaccination IgG of blood	(65)
	Galacto-oligosaccharides and fructo-oligosaccharides	0·6 g/100 ml formula/32 wk	_	Newborn infants	0-32 wk	Increased fecal secretory of IgA	(66)
	oligofructose	0·55 g/d/six mo	Haemophilus influenzae type B	Peruvian infants	6-12 mo	No effect on post-vaccination antibody response	(67)
	Oligofructose	2 g/d/21 d	_	Infants	7-19 mo	Decreased flatulence, diarrhea, vomiting, occurrence number of infectious diseases requiring antibiotic treatment	(68)
	Long-chain inulin and oligofructose	8 g/d/8 wk	Influenza	Adults	45-63 y	Increased antibody response to the H3N2-like strain of vaccine, IgG1	(69)
	Inulin	9 g inulin/d/5 wk	_	Smokers/ non-smokers males	Mean age 27 y	Increased CD19 (B) cells, $CD3^+$ HLA-DR^+ (activated T cells); decreased ICAM-1 bearing lymphocytes, $CD3^+$ NK^+ cells	(70)
	Fructo-oligosaccharides	4·95% of the energy intake of the 226·8 g (8oz) formula/d/26 wk	Influenza	Adults	≥ 65 y	Improved response to some vaccine components; increased lymphocyte proliferation to influenza vaccine components	(71)
	Fructo-oligosaccharides	4·95% of the energy intake of the 240 ml formula/d/10 wk	Influenza	Frail adults	≥ 65 y	Improved response to some vaccine components, Increased B cells and influenza-activated lymphocytes; decreased memory cytotoxic T cells, IL-6, IL-10 and fever level	(72)
	Galacto-oligosaccharides	5.5 g/d/10 wk	_	Elderly adults	Mean age 69 y	Improved phagocytosis and NK cells activities; increased anti-inflammatory cytokine IL-10; decreased proinflammatory cytokines (IL-6, IL-1beta, and TNF-α)	(61)
	Oligofructose	8 g/d/3 wk	_	Elderly adults	Mean age 85 y	Increased T, $CD4^+$, and $CD8^+$; decreased monocyte and granulocyte phagocytosis of Escherichia coli; decreased IL-6 mRNA expression without effect on the total number of leucocytes, activated T lymphocytes or NK cells in the blood	(73)
	Oligofructose and inulin	6 g/d/28 wk	Influenza and pneumococcal	Elderly adults	≥ 70 years	Increased antibody response in both prebiotic and control groups	(74)
Lipids	Saturated fatty acids from 10 to 16 carbon and some derivatives	Various concentration 20 µm, 50 µm, 200 µm	Rotavirus	Monkey kidney cell line	_	Increased rotavirus infected cells with a dose-dependent relationship	(94)
	Fish oil (n-3) PUFA	(diet with 25 wt % of fish oil)/1 mo	Cytomegalovirus (CMV)	Mice	6-8 wk	Not help immune response	(95)

Contd...

Table 1: Contd...

Macronutrient	Intervention	Dose-time	Virus	Participant	Age mean	Health effect	Ref
	Linolenic acid	(10% of BW linseed oil)/6-10 wk		Mice	_	Increased viral-specific cytotoxicity; reduced eicosanoid synthesis and increased cytotoxic response	(96)
	Fish oil	5 or 20% fish oil/8 wk	Murine retrovirus	Mice	4 wk	Longer lifespan	(97)
	Fish oil	A diet enriched with 20% fish oil/4 wk	Murine retrovirus	Mice	_	Decreased the progression of murine AIDS by modulating levels of cytokines including TNF-α, IL-β, and IL-2	(98)
	Prostaglandin E1	25 µg/ml prostaglandin E1/24 h	Mengovirus, MM and polioviruses	_	_	Attenuated the Mengo, MM, and polioviruses; inhibited the cell division; increased the interferon efficiency	(99)
	In vitro incubation of enveloped viruses with linoleic acid (C18:2)	10-100 ~µg/ml/10-60 min	Myxovirus, Paramyxovirus, Arbovirus or Herpesvirus	_	_	decreased viral infectivity	(100)
	Fish oil	17 g fish oil and 3 g sunflower/100 g/14 d	Influenza	Mice	6 wk	lower Ig G and Ig A titers in serum, virus-specific cytotoxic activity, and IFNɤ; suppression of virus-specific lung T cell cytotoxicity and increased virus-specific proliferative responses; impaired acquired cellular immunity, but not innate immunity	(102)
	Fish oil	3 g/100 g of sunflower oil with either 17 g/100 g of fish oil/14 d	Influenza	Mice	6 wk	Impaired production of IFNɤ, serum Ig G and lung Ig A-specific antibodies	(103)
	Lipid mediator derived from the omega-3 (PUFA)	1 mµ in each infected cell	Influenza	Mice	_	Inhibited influenza virus replication; improved survival	(104)
	Arachidonate	0.1 mM arachidonate to Huh7 cells/72 h	Hepatitis C	_	_	Decreased HCV RNA amount; inhibited its replication	(105)
	Arachidonic acid, α-linolenic acid, ɤ-linolenic, and linoleic acid	Arachidonic acid at 4 µM, α-linolenic acid, ɤ-linolenic, and linoleic acid at 100 µM/24 h in replicon cells containing HCV subgenomic RNA	Hepatitis C	_	_	Decreased HCV RNA levels	(106)
	A diet enriched in omega-3 polyunsaturated fatty acids	A high fat (41% kcal) diet rich in n-3 PUFAs/3-6 wk	Poxvirus Vaccinia	Mice	4-6 wk	Not affect recovery time, morbidity and mortality	(107)
Proteins	Yogurt	90 g/day/8 wk	Influenza virus	Elderly adults	57-85 y	Decreased infection risk; increased NK cell activity	(133)
	Yogurt	450 g/day/4 mo	_	Persons	20-40 y	Increased γ-interferon levels	(134)
	Whey protein	45 g whey protein/2 wk	HIV	Persons	Mean age 42 y	Improved the glutathione deficiency	(135)
	Whey protein	40 g whey protein twice/d/12 wk	HIV	Persons	Mean age 41 y	Increased CD4 cell counts	(136)

Contd...

Table 1: Contd...

Macronutrient	Intervention	Dose-time	Virus	Participant	Age mean	Health effect	Ref
	High protein and L-lysine	–	HIV	Persons	–	Increased HIV replication; worsen the infection	(137)
	Polyphenol-enriched protein powder	40 g/d/17 d	Stomatitis	Athletes	19-45 y	Prevents virus replication; decreases the vesicular stomatitis virus infection incidence	(138
	Milk	0-11 glasses/d/10 d	Rhinovirus-2	Persons	18 to 35 y	Worsen infection symptoms like cough and congestion symptoms	(139)
	Bovine lactoferrin/whey protein immunoglobulin-rich fraction; 1:1	600 mg/d/90 days	Rhinovirus or influenza virus	Persons	Mean age 32/9 y	Decreased incidence of cold; improved symptoms	(140)
	Bovine lactoferrin intake	500 mg twice/d/six mo	Norovirus	Children	12-18 mo	Decreased diarrhea longitudinal prevalence; no difference in noroviral incidence	(141)
	Whey protein	Oral gavage 80% protein/d	Rotavirus	Mice	9-17 d	Reduced viral load; increased immune response, neutrophil or NK cell activity; decreased disease severity and duration	(142)
	Whey protein concentrate	24% w/w/12 wk	Influenza, poliomyelitis	Mice	6-7-wk	Increased antibody response to antigens	(143)
	Human breast milk	–	HIV	Mice	–	Inhibition of oral HIV transmission	(144)
	Bovine lactoferrin	1.5% soluble in drinking water/10 d	HSV-1	Mice	6 or 7 wk	Prevents body-weight loss; increased cytokine responses	(145)

et al. had examined human breast milk's effect on the transmission of oral HIV in humanized mice. They found that human breast milk inhibits the transmission of oral HIV significantly.[144] The findings demonstrated that bovine lactoferrin supplementation (1.5% soluble in drinking water) for 10 days, inhibits body-weight loss and promotes cytokine responses in HSV-1 (herpes simplex virus type 1) infected 6-7 weeks mice.[145] Related clinical trials are summarized in Table 1.

Conclusions

According to the mentioned context nutritional interventions especially gut-associated ones can be proposed as new therapeutic approaches or at least adjuvant therapeutic choices for patients with COVID-19. Preliminary data of SARS-CoV and MERS-CoV nutritional interventions are showed to be effective in controlling such emerged COVID-19, but due to the different RNA sequences, they could not be suggested as a certified adjuvant therapeutic option for this newly emerged strain of coronaviruses. Dietary macronutrients especially bioactive ingredients of macronutrients can be one of the main interventions to increase resistance to COVID-19 or accelerate the recovery of infected patients with COVID-19, based on the preceding treatments for SARS-CoV and MERS-CoV and other viruses. We have found that the appropriate health diet containing prebiotics, PUFAs (especially omega 3 sources), and proteins via providing required energy and nutrients of host and balanced gut microbiota can improve the host immune response to viral infection. Thus, the nutritional status of the host can be considered as a contributing factor to the emergence or prevention of viral infectious diseases. The review on literature in the present study revealed that oral or intravenous utilization of AA, EPA, DHA, and other unsaturated fatty acids, prebiotics and animal-plant mix diet especially consuming proteins or solutions containing glycine, alanine, threonine, glutamate, lysine, and aspartate, alanine, threonine, glutamate, lysine, and BCAAs may improve resistance to COVID-19 and accelerate recovery from it according to the dietary recommendations of SARS-CoV and MERS-CoV. The knowledge regarding how macronutrients and their metabolisms could affect the immune system and regulate the gut-microbiome-immune axis is conducive for developing new strategies with the aim of an improved immune system of the host against viral infections.

Ethics statements

Our research did not include any human subjects and animal experiments.

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Conflicts of interest

There are no conflicts of interest.

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