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Review Article

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Omega 3 Fatty Acids and COVID-19: A Comprehensive Review

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ABSTRACT

The rapid international spread of severe acute respiratory syndrome coronavirus 2 responsible for coronavirus disease 2019 (COVID-19) has posed a global health emergency in 2020. It has affected over 52 million people and led to over 1.29 million deaths worldwide, as of November 13th, 2020. Patients diagnosed with COVID-19 present with symptoms ranging from none to severe and include fever, shortness of breath, dry cough, anosmia, and gastrointestinal abnormalities. Severe complications are largely due to overdrive of the host immune system leading to "cytokine storm". This results in disseminated intravascular coagulation, acute respiratory distress syndrome, multiple organ dysfunction syndrome, and death. Due to its highly infectious nature and concerning mortality rate, every effort has been focused on prevention and creating new medications or repurposing old treatment options to ameliorate the suffering of COVID-19 patients including the immune dysregulation. Omega-3 fatty acids are known to be incorporated throughout the body into the bi-phospholipid layer of the cell membrane leading to the production of less pro-inflammatory mediators compared to other fatty acids that are more prevalent in the Western diet. In this article, the benefits of omega-3 fatty acids, especially eicosapentaenoic acid and docosahexaenoic acid, including their anti-inflammatory, immunomodulating, and possible antiviral effects have been discussed.

Keywords: SARS-CoV-2; Omega-3 fatty acids; Eicosapentaenoic acid; Docosahexaenoic acid; COVID-19

INTRODUCTION

The coronavirus disease 2019 (COVID-19), now known the world over, is an emerging respiratory disease that was first identified in December 2019, in Wuhan, the capital of China's Hubei province. It has since spread globally, resulting in the ongoing COVID-19 pandemic [1, 2]. In December 2019, this world-changing phenomenon began with an outbreak of pneumonia due to an unknown cause in Wuhan, with an epidemiological link to the Huanan Seafood Wholesale Market Place. The World Health Organization (WHO) was notified on December 31, 2019, by the Chinese Health Authorities [1]. The Chinese Center for Disease Control and Prevention identified a novel coronavirus on January 7, 2020, from the throat swab of a patient, which the WHO subsequently named 2019-nCoV [3]. This

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respiratory disease rapidly spread beyond the borders of China and by February 15, 2020, 26 countries were affected by this disease [4]. Considering this, the WHO declared it a public health emergency of international concern on January 30, 2020 and called for collaborative efforts of all countries to prevent the rapid spread of the virus [5]. Despite these efforts, the virus continued to spread, and the WHO declared it a pandemic on March 11, 2020 [2]. From its first outbreak in Wuhan, through November 13th, 2020, a total of over 52 million laboratory-confirmed cases of COVID-19 along with over 1.29 million associated deaths, have been reported globally [6]. In the United States (US), the total confirmed cases of COVID-19 have surpassed 10 million with over 240,000 deaths as of November 13th, 2020 [6].

The novel COVID-19 infection in humans may cause a wide range of symptoms, while some patients may remain asymptomatic even if they test positive for the virus. Possible clinical presentations may include fever, fatigue, sore throat, dry cough, shortness of breath, body aches, nasal congestion, anosmia, abdominal pain, and diarrhea, but other less common presentations have been reported as well. The minority of patients may however develop severe symptoms and serious complications such as interstitial pneumonia, septic shock, adult respiratory distress syndrome (ARDS), stroke, disseminated intravascular coagulation (DIC), and multi-organ failure (MODS). Strikingly, even asymptomatic patients are believed to be able to spread the disease [7].

Omega-3 fatty acids (FAs) are polyunsaturated fatty acids (PUFAs) that are abundantly available in nature. Omega-3 FAs belong to a category of supplements known as GRAS (generally recognized as safe). The Omega-3 Index Test serves as a measure of the amount of Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA) in the blood, especially in the red blood cell membranes. This index shows the ratio of omega-3 FAs to all other fatty acids. A recent study showed that more than 90% of American people consumed less than the recommended optimal value for omega-3 FAs in the diet (0.17 g/day) [8]. The metabolites of both omega-3 and omega-6 play an important role in the synthesis of different inflammatory mediators such as prostaglandins (PG), leukotrienes (LT), thromboxanes (TX), protectins, and resolvins. Omega-3 FA (fatty acid) plays a role in the host cellular membrane which regulates membrane fluidity and intricate lipid raft assembling in the cell membrane. A study conducted by Gutierrez and colleagues showed that omega-3 FA is incorporated throughout the body into the bi-phospholipid layer of the cell membrane of neutrophils and produces different mediators such as prostaglandins, leukotrienes, and maresins [9]. For that reason, if the injury occurs the byproducts of those cell membranes may produce less inflammatory provoking mediators compared to omega-6, which is more prevalent in the American diet [10]. Omega-3 FAs improve the function of the macrophages by secreting cytokines and chemokines, promoting the ability of phagocytosis, and activating macrophages by polarization [11]. Omega-3 FAs are also known to down-regulate Nuclear Factor-κ Beta (NF-κB). NF-κB is considered to be a transcription factor involved in cell signaling to initiate an inflammatory response by the innate immune system. The study shows that fish oil enhances antiviral response by inducing interferon (IFN) which inhibits viral replication [11]. Omega-3 FAs weaken the antiviral response of CD_8 T cells and thereby could potentially be used to modulate cytokine responses to viral invaders [12].

A lack of omega-3 FAs in the diet can change the composition of the cell membrane. Every cell needs a healthy, functioning lipid bilayer to facilitate physiological responses and to maintain fluidity. However, the American diet contains high levels of omega-6 FAs as opposed to omega-3. One of the major causes of death in patients infected with severe acute

respiratory syndrome coronavirus-2 (SARS-CoV-2) is multiorgan failure, which is a result of immune system overdrive causing cytokine storms. The omega-3 FA is known to produce less pro-inflammatory cytokines, therefore increasing omega-3 FA intake in the diet or supplementation could decrease viral entry, promote better immune function, and decrease severity among those who have been diagnosed with COVID-19. As we are still searching for definitive treatment, omega-3 FAs might be a safe and relatively inexpensive prophylactic and treatment approach for those who are at high risk and those who have the disease. This review aims at describing the health benefits of consuming a diet rich in omega-3 FAs in addition to the possible role in COVID-19.

CORONAVIRUS IN HUMANS

Coronaviruses are a family of spherical viruses, and their surfaces are covered with 'crown-like' spikes. These viruses are enveloped with single-stranded linear positive-sense RNA genomes. They are classified under the order Nidovirales, family Coronaviridae, and subfamily Orthocoronavirinae [13]. They have the largest genome for RNA viruses and based on genetic and antigenic criteria, they have been divided into four genera: alpha, beta, gamma, and delta Coronaviruses [14]. They have been widely distributed in nature and can affect other species like birds, bats, cats, rodents, pigs, and other mammals [15]. The seven coronaviruses that infect humans are SARS-CoV-2, alphacoronavirus 229E and NL63, and betacoronavirus HKU1, OC43, coronavirus associated with the SARS-CoV and coronavirus associated with respiratory syndrome in the Middle East (MERS -CoV) [16].

A wide range of similarities exists between SARS-CoV and SARS-CoV-2, as shown in **Table 1**. Both of them belong to the family Coronaviridae [17]. Studies show that there is a 76.47%

Table 1. Brief comparison of SARS-CoV, MERS-CoV, and SARS-CoV-2 [77-83]

	SARS-CoV (2003)	MERS-CoV (2012)	SARS-CoV-2 (2019)
Family	Coronaviridae	Coronaviridae	Coronaviridae
Illness caused	Severe Acute Respiratory Syndrome	Middle East Respiratory Syndrome	COVID-19
1st outbreak	Shunde, Guangdong, China	Saudi Arabia	Wuhan City, China
Spike protein on 3' end	21493 aa	1270 aa	1273 aa
Amino acid differences	Presence of 8a accessory protein	N/A	8b is 37 amino acids longer than SARS-CoV, 3b is shorter by 132 than SARS-CoV.
Major reservoir	Bats	Dromedary camels	Bats
Primary host	Human	Human	Human
Transmission	Human to human (respiratory droplets, close personal contact)	Non-human to human, Human to human (respiratory droplets, aerosols, direct contact)	Human to human (respiratory droplets, aerosols, direct contact)
Incubation Period	5 days	5 days	2 - 14 days
Receptors on the human body for attachment	ACE-2	DPP4, CD26 in respiratory epithelial cells and pneumocytes	ACE-2
Common symptoms	Cough, fever with rigors, malaise, myalgias, headache, shortness of breath, diarrhea	Cough, fever, shortness of breath, diarrhea, pneumonia, acute respiratory distress syndrome	Cough, fever, shortness of breath, fatigue
Chest X-ray findings	Ground-glass opacities	Bilateral multifocal ground-glass opacities	Ground-glass opacities
Prevention	Respiratory hygiene, social distancing, and hand hygiene.	Hand washing after touching animals, avoid eating raw/unprocessed meat, avoid drinking raw camel milk	Respiratory hygiene, social distancing, and hand hygiene.
Treatment	Supportive	Supportive	Mainly supportive
Case Fatality Rate	9.6%	34.3%	1.38 - 3.4%

SARS-CoV, severe acute respiratory syndrome coronavirus; MERS-CoV, Middle East respiratory syndrome coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; N/A, not applicable; ACE-2, angiotensin-converting enzyme 2; DPP4, dipeptidyl peptidase 4; CD26, cluster of differentiation 26.

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similarity in amino acid sequences in both of them [18]. Comparison of RNA sequence and protein modeling showed that the domain on the spike protein which is responsible for attaching SARS-CoV-2 to the receptors on the host cell is similar to SARS-CoV [19]. Both use angiotensin-converting enzyme 2 (ACE-2) receptors for entry in the human respiratory epithelium cells [5, 17]. They are transmitted by respiratory droplets and contact with infected people [20, 21] and responsible for causing symptoms like fever, cough, shortness of breath, and fatigue [22]. They cause the appearance of ground-glass opacities on the Chest X-ray. The simple way to prevent them is by hand hygiene, social distancing, and respiratory hygiene [21]. MERS-CoV uses Dipeptidyl peptidase-4 (DPP4), CD26 receptors to attach to the respiratory epithelial cells, and pneumocytes [17].

The basic reproduction number (R_0) of COVID-19 is between 1.4 to 2.5 according to the statement based on January 23rd, 2020. R_0 is much higher for COVID-19 compared to that of SARS (1.7 – 1.0) and that of MERS (<1). COVID-19 has been a clinical mystery, as of now, with unique epidemiology, pathogenesis, and clinical outcomes [23]. This type of attachment enhances viral fusion to the human cells and atypical severe clinical outcomes in the host. ACE-2 receptors are present in the heart, lungs, gastrointestinal tract, and blood vessels. ACE-2 receptors are the receptors that mediate the viral entry of SARS-CoV-2, causing vasoconstriction, inflammation, and thrombosis [17, 24].

The diameter of the virus is 125 nm. The 3-D structure shows that nucleocapsid protein and nucleic acid are found beneath lipid bilayer [25]. It contains 14 functional open reading frames (ORFs), out of which two ORFs make replicase genes responsible for encoding proteins needed for the synthesis of viral RNA. The other 12 ORFs are responsible for making eight accessory proteins and four structural proteins: membrane, spike, envelope, and nucleocapsid [26, 27]. One of the main virulence factors of coronavirus is N protein, which is highly infectious [28]. The structure of the coronavirus spike is very complex, with three main segments. These three segments consist of a short intracellular tail, single-pass transmembrane anchor, and a large ectodomain. The ectodomain contains a receptor-binding subunit S1 and a membrane-fusion subunit S2. The coronavirus spike on electron microscopy is a clover-shaped trimer with three S1 sections and a trimer. When the coronavirus infects a host cell, it loosely binds to the receptor via the S1 subunit and the S2 subunit connects the ACE-2 receptors on the host cell with the coronavirus cell membrane. This allows for the integration of the coronavirus genome with the host cell genome [19, 29, 30]. ACE2 receptors are present in the nose, lungs, blood vessels, intestines, and certain areas of the brain [31]. It uses Transmembrane protease serine 2 (TMPRSS2) serine protease to prime S protein [32].

Accumulating evidence suggests that SARS-CoV-2 is most likely a zoonotic source from the wet market in Wuhan. A vast number of people were exposed to this animal marketplace. This proposes the idea of the animal to human transmission at some point likely being the primary source of spread [33]. According to Rothan and Byrareddy, SARS-CoV-2 is primarily transmitted via person-to-person direct contact through respiratory droplets by cough and sneezing [33]. Numerous case studies have also indicated the presence of SARS-CoV-2 live viral RNA in feces. This is suggestive that there is a high probability of fecal-oral transmission with SARS-CoV-2 as another possible route of transmission [34]. The novel Coronavirus is a developing situation where through data analysis and time we will be able to understand more possible routes of transmission. According to Qu and colleagues, strong evidence suggests that the coronavirus can thrive for extended lengths of time outside of its host cell.

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It is also believed that the COVID-19 virus can survive for many hours on a large number of surfaces including sterile sponges, aluminum, or latex materials. This increases the virus' opportunity for transmission from the external environment into the host cell through contact with the eyes, mouth, and nose [35]. A study by van Doremalen and team analyzed surface integrity and aerosol of SARS-CoV-2 compared to SARS-CoV. This study utilized Bayesian regression to measure the decay rates of both viruses in aerosol and surfaces. COVID-19 showed viability in aerosol for up to 3 hours, with a decay rate of $10^{3.5}$ to $10^{2.7}$ Median Tissue Culture Infectious Dose $(TCID)_{50}$/L . This decay rate was very similar to the decay rate seen in SARS-CoV, which was $10^{4.3}$ to $10^{3.5}$ $TCID_{50}$/mL suggesting that aerosols can remain infectious for several hours and surfaces can remain infectious for up to one day [36].

Every person is at risk to be infected with SARS-CoV-2 if exposed; however, not everyone develops severe, life-threatening infections [37]. Patients who are more susceptible to develop severe infections include patients with comorbidities like diabetes mellitus, chronic obstructive pulmonary disease, interstitial lung disease, chronic heart failure, coronary artery diseases, cardiomyopathies, metabolic syndrome, and hypertension [37]. The older age group (especially above 85 years of age) and with underlying medical conditions like chronic kidney disease, sickle cell disease, cystic fibrosis, cerebrovascular diseases, liver diseases, smoking, thalassemia, neurologic diseases like dementia and immunocompromised state due to transplantation of solid organ, obesity (body mass index 20 or greater), use of steroids/other immunomodulatory drugs, human immunodeficiency virus, blood or bone marrow transplant are also at increased risk [6, 37, 38]. The SARS-CoV-2 life cycle into host cell is shown in **Figure 1**.

OMEGA-3 FATTY ACIDS

Omega-3 FAs might be a safe and relatively inexpensive prophylactic approach for those who are at high risk. For a problem that has arisen from nature, we may return to nature for the cure.

Omega-3 FAs have been investigated repeatedly since 1994 when the tremendous health benefits were first established. They were found to lower the risk of thrombosis in cardiovascular disease and it may impact positively on inflammatory diseases, brain function, and mental health, among a multitude of other benefits [39]. The term omega-3 comes from the structural descriptor for a family of PUFAs. Within the omega-3 FA family, we can find and linolenic acid (LNA) and its derivatives, including α-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). All of which are crucial elements for the functions of various cells and organs such as the brain, eyes, cardiovascular system, immune system, and general human growth [40]. In that sense, it has been shown that neural membranes of our neurons contain high concentrations of PUFAs. The omega-3 FAs belong to the essential fatty acid group within the PUFAs family and previous studies have demonstrated that our bodies cannot synthesize them. Therefore, they must be obtained from the diet [41].

Extensive evidence has been published about levels of omega-3 PUFAs that can mediate anti-inflammatory effects [9, 40-43]. For example, omega-3 FAs play a role in mediating inflammatory processes and immunomodulation for both innate and acquired immune systems [9]. Also, a study done by Chanda and team concluded that omega-3 FAs could be a potential antimicrobial drug with little potential for drug resistance [44]. However, the use

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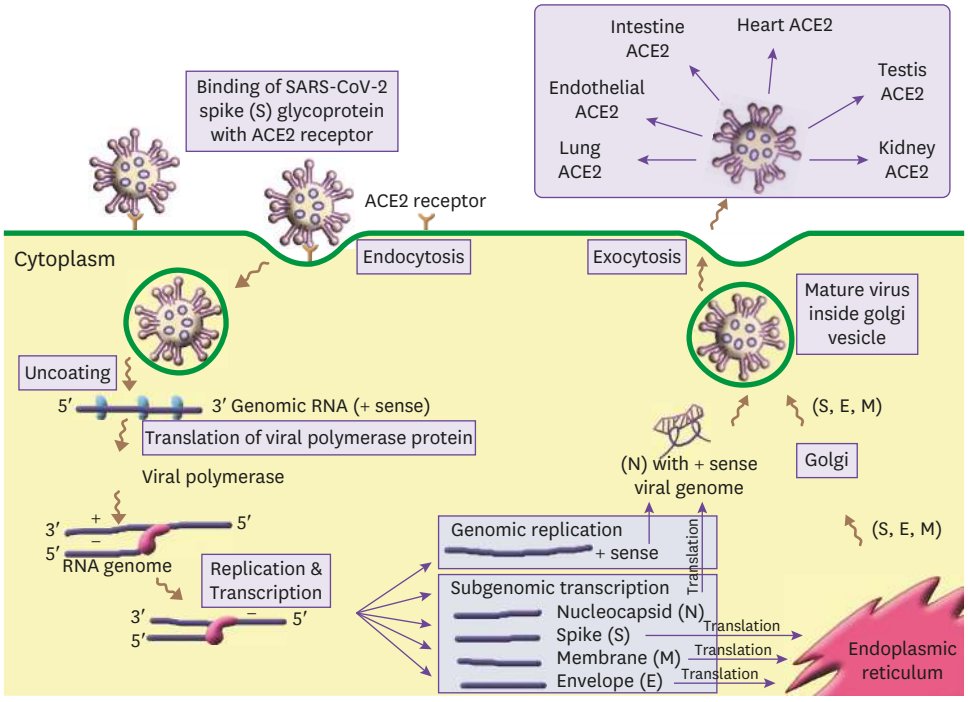

Figure 1. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike (S) glycoprotein binds with host cell angiotensin converting enzyme 2 (ACE-2) receptor. Subsequently, the virus enters the host cell either through membrane fusion or endocytosis and releases its positive sense ribonucleic acid (RNA) in the host cell cytoplasm via uncoating. The host ribosomes translate viral polymerase protein from positive sense RNA. The viral polymerase replicates negative sense RNA from the positive sense RNA. The viral polymerase then utilizes negative sense genome to produce more positive sense RNA (genomic replication) and mRNAs for nucleocapsid (N), spike (S), membrane (M), envelope (E) (subgenomic transcription). After the translation of viral structural proteins, S, E, and M proteins are processed in Endoplasmic Reticulum-Golgi (ERG) intermediate compartment. Nucleocapsids are assembled in the cytoplasm and then bud into the lumen of the ERG intermediate compartment. Finally, the mature virus inside the Golgi vesicle is released from the infected cell through exocytosis. A mature virus is capable of infecting the lung, endothelium, intestine, heart, testis, kidney through ACE-2 receptors.

of these fatty acids as antimicrobial agents has not yet received much attention in clinical medicine worldwide.

Nowadays, the novel coronavirus has resulted in a pandemic that has spread with sheer rapidity across the globe. In this literature review, we provide information on omega-3 FAs and the possible use of this natural, inexpensive, and safe compound as an alternative treatment for those who are at high risk or have contracted the disease.

The principal source of omega-3 FAs in the human diet comes from eating fresh fish, particularly oily fish, including mackerel, salmon, herring, flounder, cod, and mullet, as shown in **Table 2**. This happens because most fish foods such as microalgae and other invertebrates are rich in DHA and EPA [45]. Besides this, most microorganisms such as marine protists and dinoflagellates, such as species of Thraustochytrium, Schizochytrium, and Crypthecodinium are rich sources of DHA. On the other hand, microalgae like Phaeodactylum and Monodus are sources rich in EPA [45]. However, we also can find omega-3 amounts in non-marine foods such as cereals, seeds, nuts, and some fruits and vegetables [46, 47].

Omega-3 FAs are PUFAs that are abundantly available in nature. Various forms in which fatty acids exist are free fatty acids (FFAs), ethyl esters, triglycerides, and phospholipids [47, 48]. Dietary lipids after ingestion are hydrolyzed in the intestinal lumen. FFAs and

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Table 2. Selected food sources of DHA and EPA [49]

Food	Grams per serving DHA	Grams per serving EPA
Salmon, Atlantic, farmed, cooked, 3 oz.	1.24	0.59
Salmon, Atlantic, wild, cooked, 3 oz.	1.22	0.35
Herring, Atlantic, cooked, 3 oz.	0.94	0.77
Sardines, canned in tomato sauce, drained, 3 oz.	0.74	0.45
Salmon, pink, canned, drained, 3 oz.	0.63	0.28
Mackerel, Atlantic, cooked, 3 oz.	0.59	0.43
Sea bass, cooked, 3 oz.	0.47	0.18
Trout, rainbow, wild, cooked, 3 oz.	0.44	0.40
Oysters, eastern, wild, cooked, 3 oz.	0.23	0.30

DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid.

monoglycerides are hydrolysis products that are incorporated into micelles that contain bile salt and get absorbed in enterocytes mostly by passive diffusion [49]. Within the enterocytes, FFAs get incorporated in chylomicrons and via lymphatic circulation will enter the circulation from where lipids are delivered to various organs for further oxidation, storage, or metabolism [49]. Factors like intestinal pH, bile secretion, microorganisms, type of chemical bond, concomitant food intake and presence of some other components like calcium affects the absorption and thus the bioavailability. A diet that consists of FFAs has a higher bioavailability than an ester [50]. Absorption of EPA in triglyceride form is 90% whereas it is 60% in the form of ethyl ester [46]. ALA has low bioavailability due to a higher rate of oxidation, whereas DHA is more bioavailable as a result of being a poor β-oxidation substrate [50]. Binding of long-chain omega-3 FAs in sn-⅓ position to glycerol increases bioavailability by facilitating the bond's lipase hydrolysis. A study on hamsters conducted by Cholewski and colleagues, showed that DHA when present in sn-2 position facilitates the absorption of fatty acids in the intestine and its tissue incorporation [51]. Metabolism occurs mainly in the liver [52]. ALA gets converted to EPA and DHA by process of desaturation and elongation [53, 54]. Studies show that in healthy young men, approximately 8% of dietary ALA is converted to EPA and 0 - 4% is converted to DHA. Whereas in healthy young females, 21% dietary ALA is converted to EPA and 9% to DHA [55]. ALA with the help of Δ6-desaturase forms Stearidonic acid which then forms Eicosatetraenoic acid via elongation. EPA and DHA are formed by desaturation with the help of Δ5-desaturase [50]. The half-life of EPA is 37 hours and that of DHA is 46 hours [52].

EPA binds and activates PPARα whereas DHA binds and activates PPARγ [56]. When omega-3 FAs are incorporated into the cell membrane, it induces production of eicosanoids and resolvins which then compete with arachidonic acid for the activity of phospholipase A2. FAs are then liberated inside the cytosol and via cyclooxygenase-2 (COX-2), 5-lipoxygenase and thromboxane synthetase activity gets degraded into PGs, LTs, and TX respectively. Thus, omega-3 FA is responsible for decreasing the synthesis of eicosanoids derived from arachidonic acid (AA) like PGI2, PGF2α, PGE2, and LTB4 which are responsible for pro-inflammatory responses and increase the synthesis of LT5 and PGE3 from EPA which have weak effects on inflammation [57, 58].

The guidelines have remained unchanged since 2003 when the American Heart Association recommended consuming at least 0.5 g/day of omega-3 FA to prevent the risk of cardiovascular disease [59]. Despite this, a study conducted by Richter and colleagues showed that more than 90% of American people consumed less than the recommended optimal value for omega-3 FAs in the diet (0.17 g/day) [46]. Aside from maintenance of normal health, omega-3 FAs are also recommended in specific dosages for a variety of inflammatory conditions, as mentioned in **Table 3**.

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Table 3. Omega 3 fatty acid optimal dosage for various health conditions

Health Conditions	Optimal Dosage
Rheumatoid arthritis [84]	2.7 g/day EPA + 1.8 g/day DHA
Systemic Lupus Erythematosus [85]	0.18 g/day EPA + 0.12 g/day DHA
Multiple sclerosis [86]	0.4 g/day EPA + 0.5 g/day DHA
Type 1 Diabetes Mellitus [85]	0.4 g/day EPA + 0.6 g/day DHA
Sjogren's Syndrome [86]	0.42 g/day EPA + 0.28 g/day DHA

EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

Omega-3 FAs belong to a category of supplements known as GRAS (generally recognized as safe). Omega-3 FAs will rarely cause a few mild, non-distressing adverse effects such as unpleasant taste, bad breath, and change in body odor. Some mild gastrointestinal symptoms such as nausea, vomiting, loose stools, and increased stool frequency may be associated with omega-3 FAs. Few patients might report neurologic symptoms such as dizziness and insomnia; however, most symptoms are very mild and self-limiting [50, 57]. Elderly people are at risk of bleeding when they combine long chain PUFA such as fish oil with other anticoagulants such as warfarin and aspirin. The anti-atherosclerotic and anti-lipidemic effects of omega-3 FAs are well known; however, in patients who combine warfarin and fish oil supplements, the risk of bleeding is increased due to inhibition of platelet aggregation. This is the reason which leads to irreversible coagulopathy in elderly patients taking the combination even after suffering blunt head trauma [8, 60].

OMEGA-3 FATTY ACIDS AND INFLAMMATION

A study conducted by Gutierrez and colleagues showed that omega-3 FA is incorporated throughout the body into the bi-phospholipid layer of the cell membrane of neutrophils and produces different mediators such as prostaglandins, leukotrienes, and maresins. So, if the injury occurs the byproducts of those cell membranes may produce less inflammatory provoking mediators compared to omega-6 FAs, which are more prevalent in the Western diet [58]. Sheppard and colleagues showed that children and adults in the US did not consume sufficient EPA and DHA in their diets. In other terms, Western diets predispose to have a high omega-6/omega-3 ratio which may promote the pathogenesis of many diseases [61, 62]. Further, there is evidence that omega-6 may inhibit the anti-inflammatory effect of omega-3 FAs [63].

Previous studies have been done to clarify the role of omega-3 on anti-inflammatory mechanisms. For example, Saifullah and colleagues carried out a study to know the outcomes of adding EPA and DHA to the diet of hemodialysis patients for 3 months, showing a modest reduction in serum C-reactive protein, which is an inflammatory mediator produced in the liver in response to inflammation [10].

Microorganisms like bacteria, viruses, fungi, protozoa, and worms can all cause infections. Sepsis may occur following infections which can disturb the homeostasis of the body leading to uncontrolled inflammation and ultimately organ failure, shock, and death. A study was done with omega-3 FA lipid emulsion in the cases of sterile peritonitis and murine polymicrobial sepsis demonstrated anti-inflammatory properties of omega-3 FAs. In this study, omega-3 FAs reduced neutrophil infiltration, pro-inflammatory mediators, and classical monocytes while it enhanced non-classical monocyte/macrophage recruitment and efferocytosis in sepsis [64].

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Omega-3 FAs include EPA and DHA. Saedisomeolia and colleagues conducted a study to determine the anti-inflammatory properties of DHA and EPA in airway epithelial cells infected with Rhinovirus. In this study, the researchers incubated airway epithelial cells with EPA, DHA, and AA for 24 hours and then infected them with rhinovirus for 48h. They measured IL-6, IL-8, and interferon-gamma-induced protein-10 (IP-10) released by cells using enzyme-linked immunosorbent assay. The investigators found that DHA significantly reduced the release of IL-6 and IP-10 from the cells infected with different strains of rhinovirus. This could be explained by the efficiency of omega-3 FA reducing inflammation by inhibiting AA metabolism to eicosanoids and finally reducing pro-inflammatory cytokines and immune cell function [65].

OMEGA-3 FATTY ACIDS AND OXIDATIVE STRESS

Omega-3 FAs have been found to exhibit antioxidant activity through various mechanisms including upregulating nuclear factor erythroid 2-related factor 2 (NRF2) mediated antioxidant effects, reducing F2 isoprostanes formed during the oxidation of arachidonic acid, inducing PPARγ and modulating toll-like receptor 4 (TLR4) receptors which all lead to a reduction in κβ phosphorylation and thus reduce NF-κβ which in turn reduces inflammatory markers like IL-6, TNFα, and tissue growth factor beta (TGFβ). They also induce mitogen activated protein kinase (MAPK) phosphatases and upregulate glutathione also known as GSH, which is an antioxidant molecule, and upregulate genes responsible for the production of heme-oxygenase, which is cytoprotective. N-3 fatty acids also inhibit lipid peroxidation. They are ultimately metabolized to anti-inflammatory molecules like resolvins, protectins, and maresins [66-68].

OMEGA-3 FATTY ACIDS AND IMMUNE SYSTEM

There is a plethora of ongoing research on the effects of omega-3 FAs and its modifications to the immune system. Omega-3 FAs are considered to be a polyunsaturated fatty acid, which upregulates the activation of immune cells specifically in macrophages, neutrophils, T-cells, B-cells, dendritic cells, natural killer cells, mast cells, basophils, and eosinophils. Omega-3 FA plays a role in the host cellular membrane which regulates membrane fluidity and intricate lipid raft assembling [9]. This is demonstrated in the **Figure 2**.

Omega-3 FAs also increase the function of neutrophils which are the first responders of infection in the body. The study showed that omega-3 FAs incorporate phospholipids of the cell membrane of neutrophils and produce different mediators such as prostaglandins, leukotrienes, and maresins. In addition, neutrophils strengthen the immune function by promoting neutrophil migration, phagocytic capacity, and production of reactive free radicals to kill microbes. Omega-3 FAs help activate the function of T cells by promoting antigen-presenting cells (APC), for example, macrophages or dendritic cells. Subsequently, that promotes activation of different subgroups of T cells such as CD4 cells, Th17 cells, and regulatory T cells. B cells are also activated by omega-3 FAs, producing more antibodies utilizing heavy chain immunoglobulin rearrangements and further differentiation. The study claims that omega-3 FAs also increase the population of B cells in the study mice [9]. Omega-3 improves the function of the macrophages by secreting cytokines and chemokines, promoting the ability of phagocytosis, and activating macrophages by polarization [69].

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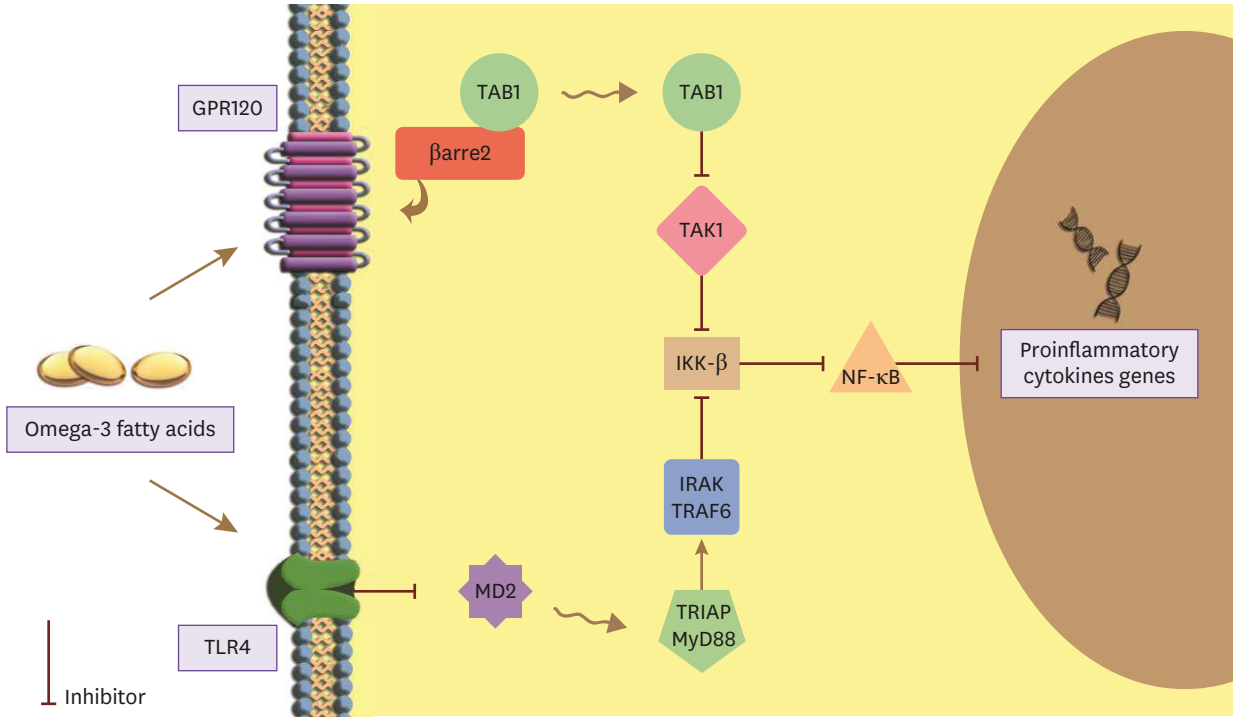

Figure 2. How omega-3 fatty acids impact the cellular immune response.
Nuclear factor kappa B (NF-κB) is a pro-inflammatory cytokine triggering an inflammatory response via activation of transcription of genes for further pro-inflammatory proteins. Omega-3 fatty acids potentially exert their anti-inflammatory effect via toll-like receptor 4 (TLR4) pathway and G-protein coupled receptor 120 (GPR120) pathway to inhibit the NF-κB and consequently the inflammatory cascade.
TAB, TGF-beta activated kinase; TAK, tat-associated kinase; IRAK, interleukin 1 receptor-associated kinase; TRAF6, tumor necrosis factor receptor associated factor 6; TRIAP, TP53 regulated inhibitor of apoptosis; MD2, myeloid differentiation factor 2.

Moreover, the omega-3 FA has appeared to block the activity of NF-κB through decreasing the degradation of the inhibitory subunit of the NF-κB called IkB, in cultured pancreatic cells and human monocyteds. Since NF-κB is responsible for cytokine production in immune cells, by blocking that pathway, its decreasing cytokine storm, and complication [70]. Omega-3 FAs are also known to down-regulate NF-κB. NF-κB is considered to be a transcription factor involved in cell signaling to initiate an inflammatory response by the innate immune system. Furthermore, omega-3 FAs intake upregulates vagal response which in turn down-regulates inflammation and cytokine production. To our understanding omega-3 FAs have multiple effects on the inflammatory response; however, analytic data has not yet recognized its role in critically ill patients. Future research may indicate that supplementation of omega-3 FA fish oils may play a crucial role in SARS-CoV-2 treatment [71].

OMEGA-3 FATTY ACIDS AND VIRAL INFECTION

Omega-3 FAs could be a potential antimicrobial drug with little potential for drug resistance [72]. The metabolites of both omega-3 and omega-6 play an important role in the synthesis of different mediators such as prostaglandins, leukotrienes, thromboxanes, protectins, and resolvins [9]. The study shows that fish oil enhances antiviral response by inducing interferon (IFN) which inhibits viral replication [69]. The anti-inflammatory effect by omega-3 FAs is stronger in DHA compared to that of EPA, and their secretion of cytokines IL-10 is further increased by omega-3. CD_8 T cells are responsible for fighting against viruses by inducing the

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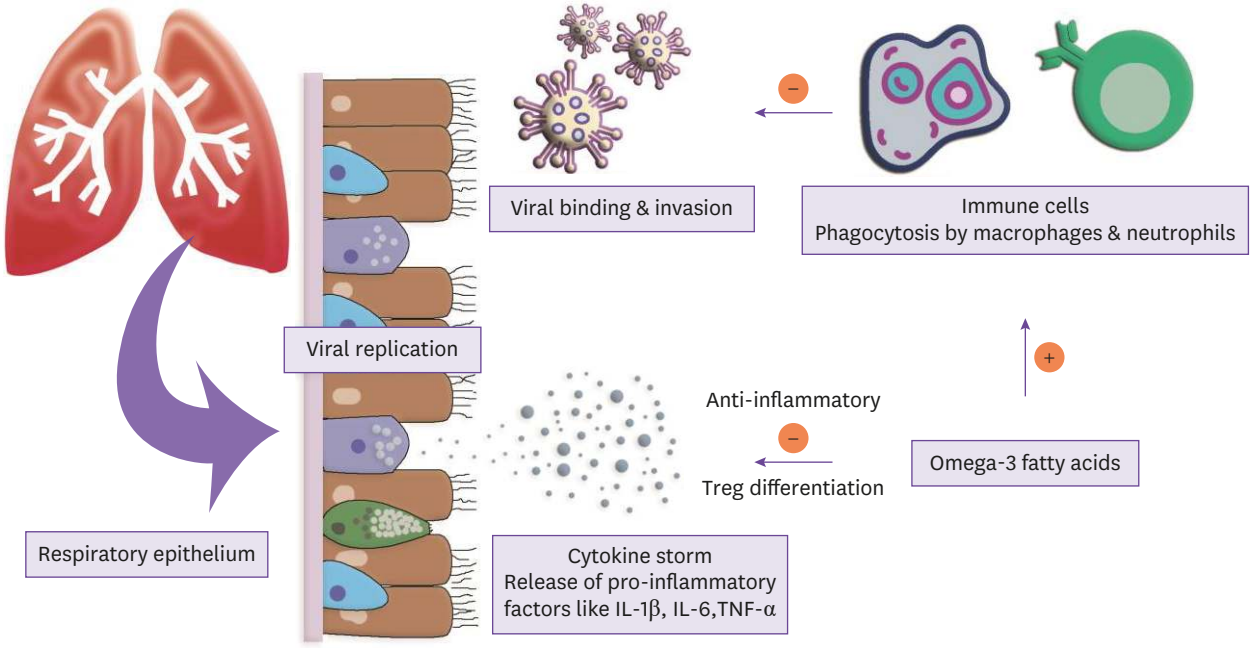

Figure 3. Omega-3 fatty acid acting on different elements of the immune response.
Omega-3 fatty acids, through their anti-inflammatory mechanism, inhibit the production of pro-inflammatory mediators like interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α and prevent cytokine storm. Some studies also suggest that they dampen the inflammatory response through regulatory T cells (Treg) differentiation. They also exert an anti-viral effect by enhancing the phagocytic activity of cells of the innate immune system- Neutrophils and Macrophages.

production of different cytokines in the body, such as Tumor Necrosis Factor-alpha (TNF-alpha) and granzyme B. However, the surge of cytokines by CD_8 T cells to defend influenza viruses impose unintended lung damage and further deteriorate the clinical outcome. Omega-3 FAs weaken the antiviral response by CD_8 T cells and could potentially be used to modulate cytokine responses as antiviral responses, and this process is further explained in **Figure 3** [73].

OTHER BENEFITS OF OMEGA-3 FATTY ACIDS

Omega-3 PUFAs include α-linolenic acid (ALA; 18:3 ω-3), stearidonic acid (SDA; 18:4 ω-3), eicosapentaenoic acid (EPA; 20:5 ω-3), docosapentaenoic acid (DPA; 22:5 ω-3), and docosahexaenoic acid (DHA; 22:6 ω-3). The health benefits of omega-3 FA are encompassing and cover a wide range of different organ systems and targets including cardiovascular disease, diabetes, cancer, Alzheimer's disease, dementia, depression, visual and neurological development, and maternal and child health. Numerous studies have been done that enumerate the reduction in clinical disease rates and mortality rates in patients suffering from a vast array of diseases. Research has been conducted involving humans and omega-3 FA for well over 40 years [74]. Albert and colleagues demonstrated that diets rich in fish and seafood containing high levels of omega-3 PUFAs lead to a statistically significant reduction in mortality from cardiovascular events. The study population included Inuit people who had a diet naturally predominated by seafood and marine life. Men who consumed fish at least once every seven days had a multivariate relative risk of sudden death of 0.48 (95% confidence interval, 0.24 - 0.96; $P = 0.04$) compared to men who consumed fish less frequently than once per month, demonstrating that diets rich in omega-3's can reduce the risk of death for men from the cardiovascular event by half [11]. Omega-3 supplementation

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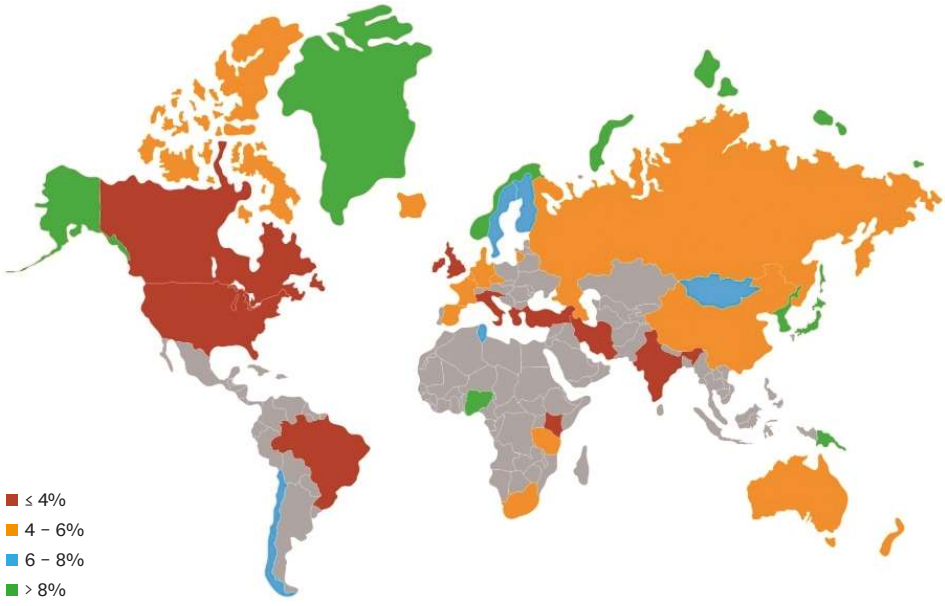

Figure 4. The global view of omega-3 index levels is shown in this figure.
The omega-3 index risk zones are as follows:

- High Risk ≤ 4%.
- Intermediate risk = 4 - 8%.
- Low risk > 8%.

has also been studied in the setting of ARDS. In a study done in 2015, it was determined that natural antioxidants like omega-3 only lead to a statistically significant decrease in mortality in those suffering from ARDS [75]. Due to the survival rate of COVID-19 patients suffering from ARDS standing at 25%, it is therefore imperative that methods that could potentially provide therapeutic relief or treatment are investigated thoroughly [12]. Although the role of ω-3 supplementation in ARDS needs to be further elucidated, its vital role in reducing reactive oxygen species and pro-inflammatory cytokines, such as TNF-α, IL-1β, IL-6, and IL-8, is widely documented. Therefore, ω-3 PUFAs could be considered for potential interventions for COVID-19 [75].

Omega-3 index, which is the EPA + DHA, is a a percent of total red blood cell fatty acid and is regarded as a new risk factor for death from coronary heart disease (CHD) (**Fig. 2**). The value of about 8% is estimated to be cardioprotective while that of less than 4% is associated with an increased risk of CHD death [76]. As per our discussion, omega-3 FAs are less prone to the production of different inflammatory markers compared to omega-6 that could initiate a cascade of the cytokine storm. It is evident that the regions with a low index like the USA, few European countries experiencing higher COVID-19 related deaths than those with high index. Omega-3 FAs may play a role in COVID-19 by reducing inflammatory markers and may lower the coronary complications. **Figure 4** shows the Global View of Omega-3 Index Levels.

CONCLUSION

There are various benefits of omega-3 FA and taking it as a supplement might be associated with the prevention of the viral entry by changing the composition of fats in the bilipid membrane of cells. Omega-3 FAs, such as DHA and EPA, perform their role by being

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incorporated in the cell membrane and affecting the clumping of toll-like receptors and thus preventing signals that activate NF-κB and help to ameliorate complications of COVID-19 by producing fewer pro-inflammatory mediators. DHA and EPA are precursors of particles called resolvins D and E, which reduce the proinflammatory mediators thereby reducing pulmonary neutrophils recruitment, increasing apoptosis by macrophages, and subsequently decreasing broncho-alveolar IL-6 production and as a result, decreasing inflammation of the lung. Omega-3 FA plays a role in increasing the phagocytic capacity of macrophages due to the changes in the composition of the cell membrane bilipid layer. Omega-3 FAs also play a role in mediating inflammatory processes and immunomodulation for both innate and acquired immune systems.

It is necessary to understand that the link between omega-3 FA-rich diet and the clinical outcome could be far more complex than previously considered when treating COVID-19 patients. At the very least, this information could serve as the impetus that initiates further conversation and investigation into dietary supplementation that can be considered in both hospitalized patients and patients at home. Several clinical trials are being conducted to investigate the most appropriate treatment for SARS-CoV-2. Due to its anti-inflammatory, immunomodulatory, and other various beneficial properties, omega-3 FA is a natural, inexpensive, and could play a role as a healthier choice of supplement during this ongoing pandemic situation. Future larger randomized blinded clinical trials are warranted and sufficient confirmatory results are required which could further shed light on this topic.

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