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Omega-3 Polyunsaturated Fatty Acids as Adjunctive Therapy for COVID-19 Management: Review

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Patients with severe Coronavirus disease 2019 (COVID-19) experience thrombotic complications, cytokine storm, immune disorder, hypoxia, numerous disturbances in iron homeostasis, and increased oxidative stress. In addition to the appearance of the classic onset symptoms of COVID-19 which are cough fever and chest pain. Dietary supplements or nutraceuticals can be used as an adjunct treatment to improve patients' recovery. Omega 3-polyunsaturated fatty acids (ω-3PUFAs) in particular, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) exhibit anti-inflammatory, anticoagulant, and immunomodulatory properties that, when combined with the appropriate therapeutic intervention, may improve patient outcomes. Upon oxidation, EPA and DHA produce specialized pro-resolving lipid mediators (SPMs) that induce resolution of inflammation through inhibiting neutrophil migration, enhancing macrophage phagocytosis, and decreasing proinflammatory mediators which are risk factors for COVID-19 and increasing its severity. Moreover, ω-3PUFAs have many pathways to ameliorate various metabolic changes induced by viral infection. In this review, we attempted to summarize the available literature to understand the actual role of ω-3PUFAs that might improve or protect against COVID-19 and to determine whether it is possible to administer ω-3PUFAs as a co-therapy with conventional COVID-19 treatments.

Keywords: COVID-19, inflammation; Immunity; Iron homeostasis; Pro-resolvins ω-3 PUFAs.

The coronavirus disease 2019 (COVID-19) originated in Wuhan, China in 2019. A novel member of the coronavirus family was identified and caused this pandemic which is severe acute respiratory syndrome coronavirus-2 (SARS-COV2). It is worth noting that person-to-person transmission is the main cause of the rapid spread over the world. Until recently, the number of positive and death-related cases is still growing all over the world [1]. COVID-19 common symptoms at the onset of infection include cough, fever, dyspnea, and myalgia. Besides, intestinal, hepatic, dermatological, and neurological manifestations may also present in COVID-19 patients [2]. COVID-19 endangers elderly people, patients with chronic diseases such as diabetes, hypertension, or cardiovascular diseases, and individuals with compromised immunity. COVID-19 could cause sepsis, septic shock, and multiple organ dysfunctions. Multiple disturbances in blood tests

such as leukopenia, lymphopenia, raised hepatic enzyme activities, D-dimer level, and many abnormalities in tomography of the chest [3]. There is a strong correlation between our immune response and the progression of COVID-19. Various types of immune cells and inflammatory markers have been implicated in the disease process [4,5]. In this context, Wong postulated that inflammation is a crucial feature of COVID-19 outcomes where an overwhelming of cytokines (cytokine storm) may lead to mortality [6]. Moreover, many investigators have shown that alterations in iron metabolism like hypoferremia, hyperferritinemia, and hepcidin dysregulation may contribute to multiple organ failures in COVID-19 [7, 8]. On the other hand, some researchers have postulated that the presence of iron deficiency anemia (IDA) may increase both the severity of COVID-19 and the mortality rate [9, 10]. But in fact, it is still a matter of debate if iron deficiency contributes to COVID-19 pathophysiology and its outcomes [11].

Omega-3 polyunsaturated fatty acids (ω-3PUFAs) are necessary nutrients. They include EPA DHA and á- linolenic acid (ALA). EPA and DHA are the most important for human health. They should be obtained from foods because the body can only produce a limited amount of them by converting ALA. EPA and DHA can be found in fish, microalgae, and fungi. Meanwhile, soybeans and flaxseed are good sources of ALA. ω-3PUFAs have several health benefits. They can reduce inflammation in inflammatory conditions and chronic diseases like cardiovascular and neurological ones [12]. They have immunosuppressive effects in critical illnesses [13]. Chang [14] added that ω-3PUFAs have a marked potential for modulating the various symptoms of COVID-19. The molecular mechanisms responsible for ω-3PUFAs health benefits effects may include the production of pro-resolving mediators that modulate and resolve inflammatory responses [15]. Herein we tried to summarize the hypotheses and trials that explained how ω-3PUFAs could ameliorate the serious metabolic disorders that accompanied covid-19 especially, on iron homeostasis and inflammation.

Iron homeostasis and COVID-19

Iron (Fe) is an important transition metal that can participate in oxidation-reduction reactions by accepting and donating electrons. It has an essential role in many biological processes. Also, iron in heme is incorporated into multiple proteins such as hemoglobin, cytochrome proteins, nitric oxide synthases, and myoglobin. Iron complexes with sulfur are in respiratory complexes, coenzyme Q10, and DNA primase. The presence of iron-sulfur complex in DNA primase, an essential enzyme for DNA replication, contributes to enzyme activity [16]. Also, iron-sulfur clusters in CoQ10 are responsible for its redox activity [17]. Therefore, iron is essential for vital cellular functions like oxygen transport, nucleic acid metabolism, xenobiotic metabolism, and cell signaling [18]. Red blood cells contain the majority of Fe in the form of hemoglobin. Iron is bound to transferrin and circulates in the bloodstream. It is stored mainly in macrophages and hepatocytes. Meanwhile, all other body cells contain smaller quantities of iron for their essential processes. The liver plays an important role in iron homeostasis through its important synthetic, regulatory, and storing functions [19]. The bone marrow is the primary iron consumer in the body, as it is the site of erythropoiesis, whereas the reticuloendothelial system is responsible for iron recycling via erythrocyte phagocytosis. The circulating iron level is about 2-4 mg [20]. Notably, the diet provides 1-2 mg of iron and its excretion is minimal. Figure (1) shows systemic iron homeostasis [21].

Dietary iron is absorbed as nonheme, heme, and ferritin. Excess iron is stored in the form of ferritin in an inert form to control the production of reactive species. Systemic delivery of iron is performed by ferroportin in the ferrous form (Fe^{2+}) which is oxidized to ferric (Fe^{3+}) by three ferroxidases which are ceruloplasmin, hephaestin, and zyklopen to be loaded on transferrin, the main carrier for iron in the bloodstream [22]. However, ferritin, heme, and hemoglobin also circulate in plasma. The iron hormone hepcidin is the major regulatory factor at the systemic level. Hepcidin limits the entry of iron into circulation by binding to ferroportin and inducing its degradation. It was noted that stimulating hepcidin expression inhibits iron absorption [23]. Consequently, iron deficiency anemia may be the result.

Anemia is a common global disorder. It is a public health problem that affects both developing and developed countries with significant clinical consequences for human health and economic development. The occurrence of anemia is the

magnitude of various red blood cell (RBC) defects. For instance, RBC production defects result in aplastic anemia, maturation defects cause megaloblastic anemia and abnormal hemoglobin (Hb) synthesis leads to IDA.

Malnutrition affects one-half of the world's population and leads to diseases especially related to iron. Women, infants, and children are the most vulnerable people affected by such deficiencies, especially in developing countries like Egypt. IDA is the major anemic type that affects about one-fourth of the world population and accounts for one-half of anemic cases. The World Health Organization (WHO) defines anemia in non-pregnant women as having Hb concentration of less than 12g/dl. Mild to moderate anemia may be asymptomatic. Meanwhile, some anemic individuals have chronic fatigue, weakness, shortness of breath, headache, pica, hair loss, brittle nails, cold insensitivity, and restless leg syndrome [24]. Besides, iron deficiency significantly impairs many immune responses like those regulated by interferon-γ (IFγ) such as T-cell proliferation, natural killer cell activity, and those responses that are down-regulated by interleukin 10 (IL10) like respiratory bursts [25]. Moreover, it is documented that iron deficiency disrupts the balance between pro-inflammatory and anti-inflammatory cytokines with concomitant effects on both innate and cell-mediated immunity [26]. In addition, IDA markedly influences and decreases cognition, motor, and social-emotional activity in the animal model and human [27-28]. Interestingly, iron deficiency during pregnancy affects the genomic profile of the developing hippocampus of the fetus which persists despite iron supplementation [29]. Iron induces these changes by affecting neurochemistry, neurometabolic, and neuroanatomy during development. Therefore, proper management of IDA improves the quality of life and significantly reduces symptoms and complications of anemia.

Oral iron is frequently poorly tolerated, with up to 70% of patients reporting gastrointestinal problems; this can make it difficult to stick to a treatment regimen. Furthermore, due to their underlying condition, many individuals will not respond to oral iron. Intravenous iron is increasingly being utilized to replenish iron reserves [30-31]. However, IV iron may be undesirable and unsafe in very high doses or when ferritin concentrations are high. IV iron administration may expose patients to toxicity due to increased oxidative stress and ferroptosis. However, the guidelines for treating IDA lack consensus [32]. Consequently, a recent strategy for managing anemia is to use functional foods as iron adjuvants to enhance their bioavailability and reduce their side effects [33].

The prevalence of anemia was strongly associated with the severity of respiratory diseases, poor outcomes, and increased mortality in patients with pneumonia [34-35]. Other studies indicate that IDA induces a 2-6 times greater risk of mortality in chronic pulmonary diseases [36-37]. A recent meta-analysis demonstrated that anemia is closely associated with a 41% and 33% elevated risk of general mortality, and cardiovascular mortality [38]. The same results were obtained when comparing heart failure patients with and without anemia, or stroke patients with and without anemia, anemic patients usually have a higher mortality risk than non-anemic [39]. In this context lower hemoglobin levels in patients with heart failure are associated with increased mortality rates [40].

COVID-19 patients have decreased hemoglobin levels, indicating anemia and increased ferritin values [41]. Each anemia and hyperferritinemia are strong predictors of mortality as mentioned above [38] especially in pregnant patients [42]. Anemia reduces the oxygen delivery to the tissue and therefore it may cause hypoxia and mortality in COVID-19 patients. It should be noted that increased anemia severity is directly proportional to the severity of COVID-19. The respiratory symptoms of COVID-19 in mild (Hb11.6 g/L) and moderate (Hb10.3 g/L) anemic patients are less than in those with severe anemia (Hb7.2 g/L) [10]. Ferritin levels are increased in inflammatory cases as an acute phase reactant and as a contributor to the development of a cytokine storm [43]. Where the H-chain of ferritin activates macrophages to increase the secretion of inflammatory cytokines; interleukin 6 (IL-6) and tumor necrosis factor (TNFα). The persistence of hyperferritinemia in patients with COVID-19 is accompanied by increased disease severity, poor patient performance, and severe pulmonary deterioration [9]. These are the cases that could not overcome the virus. On the other hand, in those patients who recovered from the viral infection,

ferritin as an acute phase reactant induces IL-6 production which increases the concentration of hepcidin, the master regulator of iron homeostasis. Hepcidin reduces cellular iron efflux via binding to ferroportin-1 with concomitant iron retention in the macrophages and a reduction in duodenal iron absorption [43]. The increase of macrophage iron supports the innate immune system to fight viral invasion by decreasing the bioavailability of iron required for viral replication [44]. Meanwhile, other cytosolic iron overload leads to cell death and ferroptosis. Figure (2) demonstrates the interrelationship between anemia and COVID-19.

ω-3PUFAs and COVID-19

Functional foods are defined as any food or food ingredients that may provide health benefits beyond their nutritional values. They are similar in appearance to conventional foods, but they demonstrate physiological benefits and may reduce the risk of various diseases. Also, they provide the body with its requirements from different nutrients [25]. Some vitamins, minerals, carbohydrates,

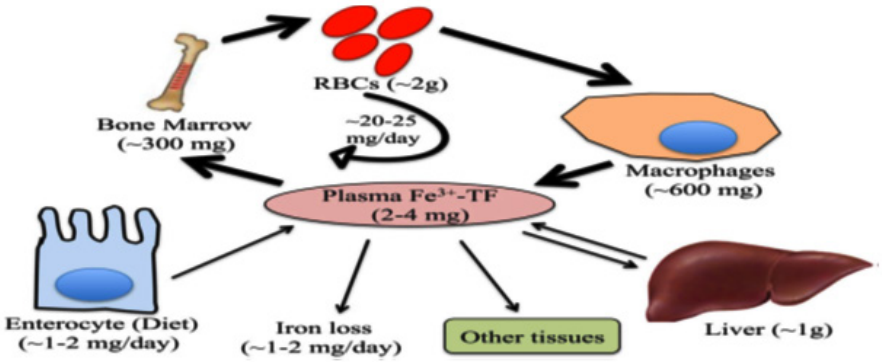

Fig. 1. Systemic iron homeostasis[21]

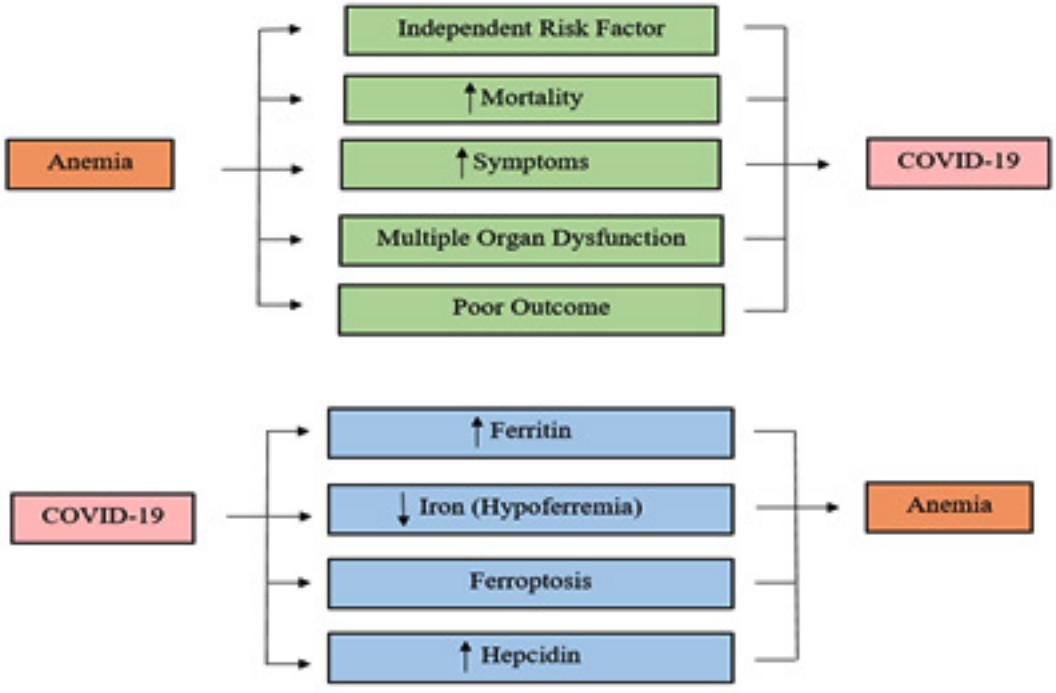

Fig. 2. Anemia and COVID-19 Interrelationship

proteins, fibres, certain fats, edible herbs, and phytochemicals are examples of functional foods.

ω-3PUFAs are derived from essential polyunsaturated fatty acids (EFAs) such as linolenic acid. EFAs play a vital role in promoting human health. Alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) are the three major types of ω-3PUFAs. They are documented to be effective in cases of depression, anxiety, and many mental health disorders [46]. Also, they are anti-inflammatory, antithrombotic, immunomodulator, antiarrhythmic, and anti-tumour agents. Recently, they are put in nanoforms using nanotechnology to increase bioactivity and bioavailability and reduce their oxidative deterioration[47]. ω-3PUFAs are precursors of some bioactive compounds and exert multifaceted roles in enhancing membrane fluidity, cell signaling, receptor functioning, and preventing oxidative damage and inflammation [48]. Fish oil contains DHA and EPA which may help to reduce cardiovascular mortality, the prevalence of some cancers, and inflammatory diseases [49]. In addition, flaxseed oil is a natural source of ALA (about 56%) which is a precursor to EPA and DHA and has potential anti-inflammatory [50,51] and antiviral activities [52].

ω-3PUFAs and anaemic COVID-19 patients

It is noted that iron affects ω-3PUFAs metabolism via iron-dependent hepatic desaturases, which convert essential fatty acids to long-chain polyunsaturated fatty acids (LCPUFAS), as well

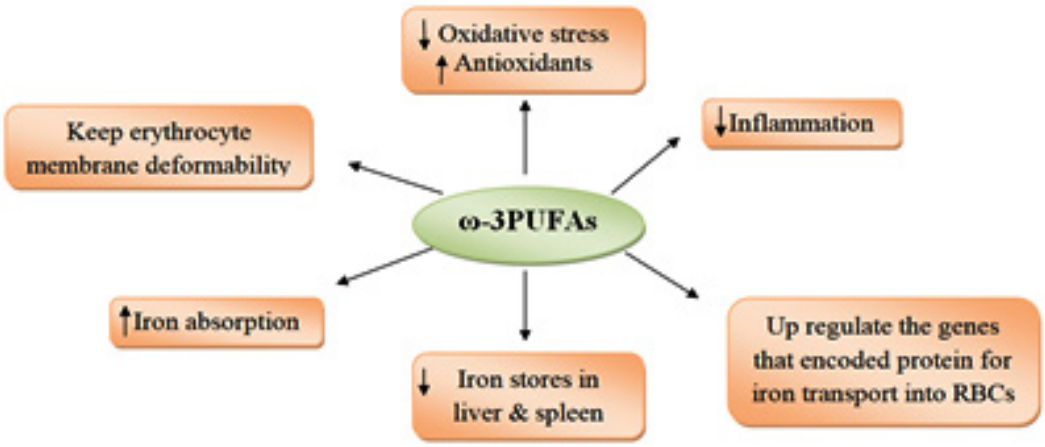

Fig. 3. Pathways of antianemic effects of ω-3PUFAs

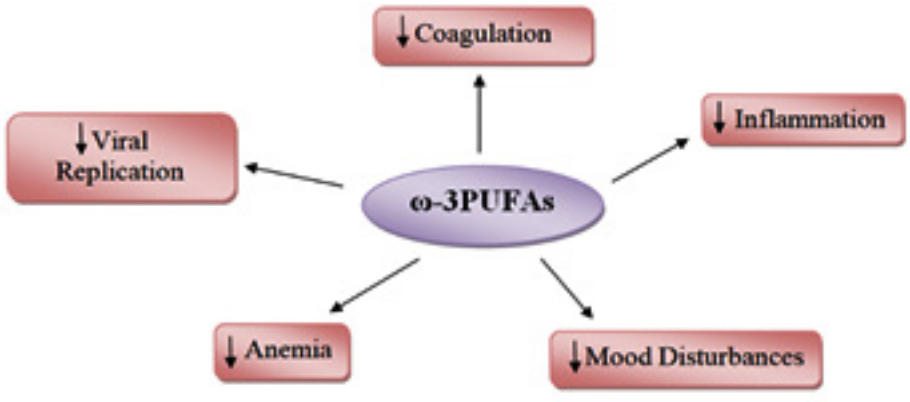

Fig. 4. Various Pathways of ω-3PUFAs against COVID-19

as iron-dependent cyclooxygenase (COX) and lipoxygenase (LOX), which participate in the synthesis of eicosanoids from LCPUFAS [53-54]. On the other side, ω-3PUFAs can affect iron metabolism. They are extensively used as adjunctive therapy for anaemia treatment [48, 55]. Therefore, ω-3PUFAs can be used to manage anemia associated with COVID -19 (9, 10). It is worth noting that ω-3PUFAs supplementation can change the n6 to n3 ratio which may modulate inflammatory mediators. Furthermore, they participate in the production of anti-inflammatory eicosanoids, which inhibit the production of pro-inflammatory eicosanoids through competitive inhibition. Consequently, prostaglandinE_2 (PGE_2) concentration is limited. Inhibiting PGE_2 reduces the production of IL-6, IL-1β, and TNF-α, which may mediate the inflammation associated with anaemia [56]. Okpala [57] and Khan [58] demonstrated that ω-3PUFAs could reduce the number of crises and haemolysis in sickle anaemia by reducing inflammation. Moreover, it was noticed that ω-3PUFAs reduced ferritin, an acute-phase protein, in anaemic haemodialysis patients. In this case, ferritin was more indicative of inflammation than iron stores [48]. Besides, the anti-inflammatory properties of ω-3PUFAs, they resemble a structural cornerstone in RBCs. Premenopausal women having IDA were found to have a lower ω-3PUFAs level in the erythrocyte membrane than premenopausal women without anaemia [59-60]. As a consequence, IDA is characterized by decreased RBCs deformability due to anomalies in the structure and function of the erythrocyte membrane and hypochromia [61]. Also, ω-3PUFAs membrane deficiency exposes RBCs to oxidative stress. RBCs of rats supplemented with fish oil (0.4g/kg/day) had increased catalase activity and reduced malondialdehyde (MDA) and nitric oxide (NO) levels [62].

Pregnant women were given 400ml of DHA-fortified milk per day in two doses of 200ml each.

The duration of the intervention is from the 28th week of pregnancy to the delivery. The iron concentration in this woman's plasma and umbilical cord vessels was significantly higher. Besides, the expression of key genes (divalent metal transporter 1 (DMT1), Ferroportin 1 (FPN1), Transferrin 1 Receptor (TfR1), and hepcidin antimicrobial peptide 1 (Hamp1)) and proteins involved in iron metabolism were up-regulated. ω-3PUFAs supplementation, also enhanced iron transfer and boosted neonates' iron stores [63]. The increase of RBCs iron by ω-3PUFAs in those women may be attributed to the up-regulation of DMT-1(divalent metal transporter 1) mRNA expression which enhances the uptake of iron by erythrocytes. This effect was also seen in inflamed rats and was attributed to high erythrocyte turnover [64]. Figure (3) shows the pathways of the anti-anaemic effects of ω-3PUFAs

Anti-inflammatory, anticoagulant, and antidepressant activities of ω-3PUFAs in COVID-19 patients

COVID-19 patients had various complications after two weeks of infection. They may have acute respiratory distress syndrome (ARDS) and kidney, liver, or other organ failure depending on host immunity and the viral load. In addition, if the virus reaches the alveoli, it will strongly replicate and induces the adaptive immune response for cytokine storm. Moreover, the virus increases platelet aggregation with a concomitant increase in blood coagulation [65-66]. On the other hand, mood disturbance was documented to be associated with COVID-19 [15].

There are global efforts underway to develop and implement a variety of medications and vaccines to combat COVID-19. However, the consumption of functional foods may have the potential to relieve symptoms or aid in the treatment of COVID-19 patients. Vitamins D, C, and E, selenium, zinc, and ù-PUFAs act against COVID-19 by boosting immunity [67]. The higher levels of circulating PUFAs, which protect against severe COVID-19, omega-3 PUFAs, particularly DHA and EPA, were linked to lower COVID-19 susceptibility [68, 69]. Potential evidence has shown that ω-3PUFAs could counteract COVID-19 through their antidepressant, anti-inflammatory, and anticoagulant, activities [15, 70]. Both EPA and DHA are oxidized via COX, LOX, or cytochrome P450, and specialized pro-resolving mediators (SPMs) like resolvins, protectins, and maresins are produced. These metabolites have an important immune-regulating function [71]. SPMs play an essential direct role in inflammation resolution via inhibition of the neutrophil migration, activation of macrophage phagocytosis of apoptotic neutrophils, and also via suppression of pro-inflammatory

chemokines and cytokines [72-73]. In general, EPA and DHA and their metabolites can modulate the immune response and its function in many ways. They could inhibit leukocyte chemotaxis, disruption of lipid rafts, reduction of adhesion molecule expression and leukocyte-endothelial adhesive interactions, inhibition of nuclear factor-kappa B (NK-κB), activation of anti-inflammatory transcription factors like peroxisome proliferator-activated receptor gamma (PPARγ), and also binding to G-protein-coupled receptor(GPCR) [74]. Furthermore, they and their metabolites can modulate migration, increase phagocytotic ability, and decrease both ROS and cytokine production of macrophages and neutrophils. Also, they ameliorate the T cell activation by altering the activation of antigen-presenting cells (APCs) such as macrophages and dendritic cells. Stimulation of immunoglobulin M (IgM) is significantly increased by ω-3PUFAs [75].

It is worth noting that the inhibition of cytokine storm especially of IL-6, the main cause of mood disorders in COVID-19 patients will lead to mood improvement by ù-PUFAs and their metabolites. Also, the alteration of the hypothalamus-pituitary-adrenal axis and the modulation of neurotransmission via changing lipid rafts by ω-3PUFAs may improve mood disturbances accompanied by COVID-19 [70].

Coagulopathy is usually found in severe cases of COVID-19 [66]. Recent research indicated that SARS- COV infected patients, those non-survivors had markedly higher levels of D-dimer and fibrin degradation products, as well as a longer prothrombin time compared to survivors [76]. Dietary administration of DHA and EPA may alter platelet aggregation and their lipid membrane phospholipids composition; consequently, fish oil may alter the progression and thrombotic complications in COVID-19 [77]. Wander and Patton [78] hypothesized that a moderate fish diet could have a moderately positive effect on platelet aggregation, increasing bleeding time and elevating the EPA content of the platelet fatty acids. This could be explained by the action of EPA and DHA on COX-1 and LOX-12 with concomitant reduction of both thromboxane release and platelet aggregation [79].

It should be noted that the dysregulation of human lipid metabolism is associated with the increased spread of coronavirus. Linolenic acid supplementation significantly reduced viral replication by correcting the linolenic to arachidonic acid ratio [52] and by inhibiting virus entry through the Angiotensin-Converting Enzyme 2 (ACE2) receptor [80,81]. Based on the above-mentioned effects of ω-3PUFAs, Arnardottir [82] tried intravenous ω-3PUFAs for elderly hospitalized COVID-19 patients and reported that this intervention seems to possess positive effects on the immune response to cope with the virus. Moreover, Doaei [81] agreed with Arnardottir [82], they used a fortified formula with ω-3PUFAs for critically ill patients infected with COVID-19. The survival rate of patients was increased by one month and their biochemical parameters were improved as a control. Also, Asher [83] postulated that the levels of EPA and DHA in the RBCs may be inversely associated with the risk of death from COVID-19. Figure (4) depicts the various pathways through which ω-3PUFAs may improve COVID-19 prognosis.

Adverse effects of ω-3PUFAs

However, some studies documented that high doses of EPA and DHA can increase susceptibility to viral infection [84]. Also, both of them could replace arachidonic acid in phospholipids of the cell membrane that are prone to oxidative damage when there is an increase in ROS [85]. Besides, some evidence suggests that chronic ω-3PUFAs administration may increase the risk of some cancers but the obtained results are conflicting [86]. Therefore, the guideline emphasized that patients administered, ù3 fatty acids (especially high doses), should be closely monitored for gastrointestinal and dermatological adverse effects. Also, the guideline further suggested a clinical examination before ω-3PUFAs prescription, EPA/DHA ratio should be more than 2 and one dosage should be 1-2g of net EPA. On the other hand, the US Department of Health and Human Services National Institutes of Health Office of Dietary Supplements (USdhhs) recommended that the daily intake of EPA + DHA dose of up to 3g/day is potentially safe. Moreover, the European Food Safety Authority (EFSA) permitted that chronic consumption of ω-3PUFAs at doses of up to 5g/day is safe [87].

CONCLUSION

In conclusion, we hypothesized here that alterations in iron homeostasis have a critical

potential role in the severity, progression, outcome, multiple organ dysfunction, and mortality of COVID-19 patients. To date, no conventional medicines have been developed to combat COVID-19 except for the recently developed vaccines.

ω- 3PUFAs may be useful as an adjuvant in the treatment of COVID-19 and its associated anemia. In anemic corona patients, PUFAs may increase iron bioavailability in a variety of mechanistic ways including increased absorption, up-regulating genes that help iron transport into RBCs, decreasing oxidative stress and inflammation, and maintaining erythrocyte membrane fluidity. Other ω-3PUFAs pathways for modulating COVID-19 symptoms are to decrease clotting, viral replication, and inflammation, and improve mood disorders. The effects of ω-3PUFAs mentioned above are achieved by ω-3PUFAs themselves as well as their important metabolites SPMs such as resolvins, protectins, and maresins. However, ω-3PUFAs supplementation should be done in controlled doses with constant monitoring of the patient's condition. Excessive doses of ω-3PUFAs may have some adverse effects.

Conflict of interest

The authors declared no conflict of interest.

Ethical approval

Not applicable.

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