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REVIEW

Assessment of Polyunsaturated Fatty Acids on COVID-19-Associated Risk Reduction

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Abstract

Pooled evidence conveys the association between polyunsaturated fatty acids and infectious disease. SARS-CoV-2, an enveloped mRNA virus, was also reported to interact with polyunsaturated fatty acids. The present review explores the possible mode of action, immunology, and consequences of these polyunsaturated fatty acids during the viral infection. Polyunsaturated fatty acids control protein complex formation in lipid rafts associated with the function of two SARS-CoV-2 entry gateways: angiotensin-converting enzyme-2 and cellular protease transmembrane protease serine-2. Therefore, the viral entry can be mitigated by modulating polyunsaturated fatty acids contents in the body. α-Linolenic acid is the precursor of two clinically important eicosanoids eicosapentaenoic acid and docosahexaenoic acid, the members of ω-3 fats. Resolvins, protectins, and maresins derived from docosahexaenoic acid suppress inflammation and augment phagocytosis that lessens microbial loads. Prostaglandins of 3 series, leukotrienes of 5 series, and thromboxane A_3 from eicosapentaenoic acid exhibit anti-inflammatory, vasodilatory, and platelet anti-aggregatory effects that may also contribute to the control of pre-existing pulmonary and cardiac diseases. In contrast, ω-6 linoleic acid-derived arachidonic acid increases the prostaglandin G_2, lipoxins A_4 and B_4, and thromboxane A_2. These cytokines are pro-inflammatory and enhance the immune response but aggravate the COVID-19 severity. Therefore, the rational intake of ω-3-enriched foods or supplements might lessen the complications in COVID-19 and might be a preventive measure.

Keywords Anti-inflammatory · Efferocytosis · Immune system · Pro-resolving lipid mediators · Platelet aggregation · Viral replication

Introduction

Coronavirus disease-19 (COVID-19) costs above 195 million infections and 4.18 million deaths globally from December 2019 to July 2021 (WHO 2020). Countries are approaching to combat the outrageous form of the pandemic. However, they have to face different issues such as low efficacy of the vaccine, shortage of vaccine production facilities, the origin of more virulent SARS-CoV-2 variant, difficulty in the world vaccine management system, and inability to develop effective antiviral drugs (Johnson et al. 2021). So, the day-by-day, COVID-19 is becoming ferocious with multiform infections. That is why, from the outbreak to now, health experts suggest minimizing the risk by practicing standard hygiene and taking nutritious foods (de Finger et al. 2021). A nutrient-rich diet helps to reduce the risk of comorbidity and boost the body's immune response. Polyunsaturated fatty acids (PUFAs) are fatty acids that contain more than one double bond in their backbone. This class includes many important compounds, such as essential fatty acids that give drying oils their characteristic property. Their pivotal role in improving health has been well-documented (Saini and Keum 2018; Sokoła-Wysoczańska et al. 2018).

α-Linolenic acid (ALA) and linoleic acid (LA) are two essential PUFAs which give rise to other clinically important PUFAs like eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and arachidonic acid (AA). They impart a vital role to body homeostasis (Saini and Keum 2018). Dietary supplementation of omega-3 (ω-3) PUFAs improves the clinical condition in obesity, inflammation, hypertension,

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dyslipidemia, atherosclerosis, diabetes mellitus, metabolic syndrome, neurological/neuropsychiatric disorders, and eye diseases and helps fetal neurological developments (Yashodhara et al. 2009). On the other hand, eicosanoids derived from omega-6 (ω-6) PUFAs enhance the inflammatory response, concurring that the increased ratio of ω-6 and ω-3 in food may increase in chronic inflammatory diseases (Patterson et al. 2012).

Nevertheless, recent pooled evidence has consistently reported that chronic diseases like chronic obstructive pulmonary disease (COPD), cardiovascular disease (CVD), cancer, cerebrovascular accident (CVA), diabetes, hypertension, and chronic kidney disease have an association with the severity among COVID-19 patients (Baral et al. 2021). So, polyunsaturated fatty acids may have an essential role in lessening the risk of these comorbidities and improving the health of COVID-19 positive cases (Asher et al. 2021). Furthermore, the anti-inflammatory metabolites of AA, EPA, and DHA, collectively named as specialized pro-resolving lipid mediators (SPMs) such as lipoxins, resolvins, protectins, and maresins, suppress inflammation. The augmented phagocytosis of macrophages and other immunocytes decreases the microbial load and enhances the healing process (Das 2020). The present review aims to demonstrate the effect and rational selection of PUFAs to lessen COVID-19 severity with probable mechanisms.

Search Strategy

The study focused primarily on the buildup of all possible outcomes of polyunsaturated fatty acids in COVID-19 patients. Then, we had a recourse on multiple works about fatty acids' role in viral infection published before the COVID-19 outbreak to analyze and support the outcomes. Both prospective and retrospective trials and supportive articles were picked up from PubMed, Google Scholar, and Web of Science databases from 15th May 2021 to 30th June 2021 using the English language. The more frequent searching keywords were "polyunsaturated fatty acids" or "omega-3" or "omega-6" or "PUFAs" with "COVID-19" or "coronavirus" or "SARS-CoV-2" or "severe acute respiratory syndrome-2." We collected data from articles published by peer review journals from the 1980s to 30th June 2021.

Discussion

Classification

The hydrocarbon containing a one-end carboxyl group and the other end methyl group is chemically known as fatty acids. Few substantive features like the chain length in numbers of carbon, the number of carbon–carbon double bonds (unsaturations), and the position of the double bonds determine the fatty acids' biological reactivity (Patterson et al. 2012). Human physiology can synthesize fatty acids where few acids cannot be synthesized. According to these features, the acids can be classified in four ways (Fig. 1). Although the general notion "polyunsaturated fat" indicates only multiple levels of unsaturation, its character and functions depend on all the features mentioned above.

According to a chain length of fatty acids, they are classified in three types: short-chain FAs (SCFAs) (C_{2-6}), medium-chain FAs (MCFAs) (C_{6-12}), long-chain FAs (LCFAs) (C_{12-18}) and very-long-chain FAs (> 18)

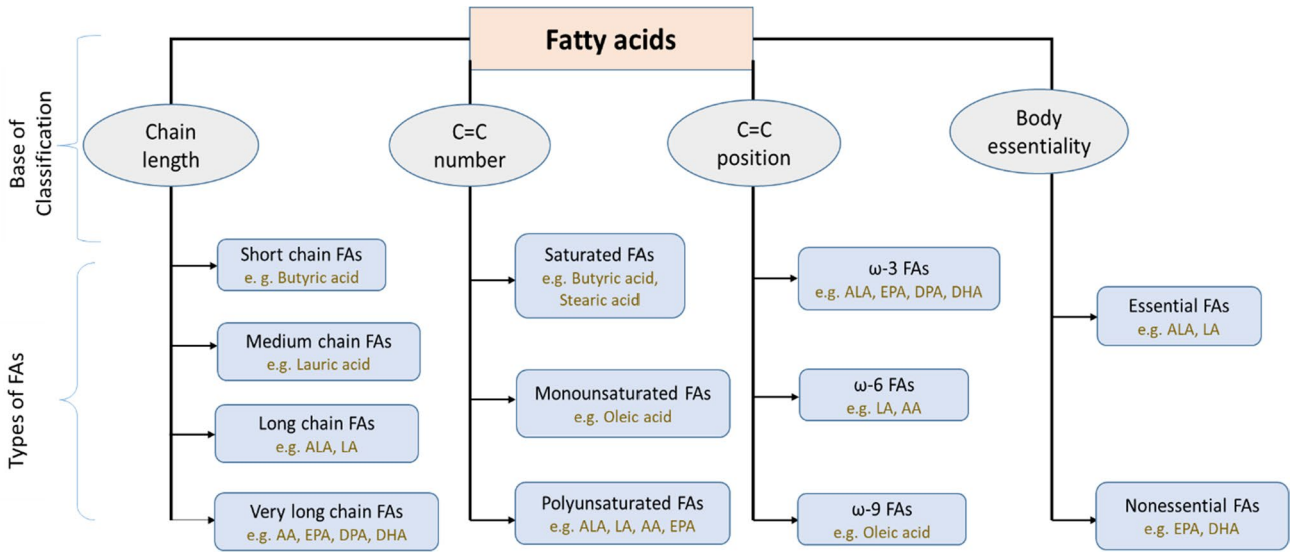


Fig. 1 Classification of fatty acids

(VLCFAs). LCFAs and VLCFAs are more abundant in plants and animals, but SCFAs and MCFAs also present in comparatively small amounts (Schönfeld and Wojtczak 2016). SCFAs and MCFAs are mainly present in triglycerides in some plant oils and milk. Furthermore, SCFAs are also produced in the gut of human and other mammals by bacterial fermentation of non-starch polysaccharides and amylase-resistant starch (Wong et al. 2006). LCFAs are usually referred to as free fatty acids or unsaturated fatty acids with an even carbon count. It is synthesized in animals or plants from acetyl-CoA and is then degraded via β-oxidation reactions (Kaneko et al. 2008). VLCFAs are derived from parental 18-carbon molecules by several biochemical reactions (Agostoni and Bruzzese 1992).

The second way of classification is the degree of unsaturations. When FAs have no unsaturated bonds, it is termed as saturated fatty acids (SFAs). Very few FAs like oleic acid have only a single double bond, called monounsaturated fatty acids (MUFAs), e.g., omega-7 and omega-9 fats. Most naturally occurring FAs have more than one unsaturated double bonds, commonly known as polyunsaturated fatty acids (Agostoni and Bruzzese 1992; Saini and Keum 2018). The first double bond starting from the methyl-end (the opposite side of the molecule) is counted to categorize FAs and denoted by omega, ω, or n − FAs. All unsaturated FAs are characterized, by using this classification, in three prominent families: ω-3, ω-6, and ω-9. Alpha-linolenic acid (ALA, 18:3, n-3; $C_{18}H_{30}O_2$) and linoleic acid (LA, 18:2, n-6; $C_{18}H_{32}O_2$) are two FAs that cannot be synthesized within the human body, referred to as essential fatty acids (EFAs), whereas other FAs are known as nonessential FAs (Yashodhara et al. 2009).

Clinically Significant PUFAs

The essential PUFAs ALA and AA cannot be generated in humans and are therefore regarded as parent PUFAs, whereas eicosapentaenoic acid (EPA, 20:5, n-3), docosahexaenoic acid (DHA, 22:6, n-3), and γ-linolenic acid (GLA, 18:3, n-6) are endogenous nonessential PUFAs belonging to the ω-3 and ω-6 families, respectively. Dietary ALA and LA have crucial roles in maintaining ω-3 and ω-6 LC-PUFAs levels in tissue (Barceló-Coblijn and Murphy 2009). However, when there is a lack of EFAs, pathophysiological ω-9 PUFAs are synthesized in increased amounts (Burdge 2011). PUFAs exert a wide range of beneficial effects on lipoprotein concentration, regulation of blood pressure, the function of membrane enzymes and receptors, membrane fluidity, modulation of eicosanoid production, and metabolism of minerals (Simopoulos et al. 1999). Among different PUFAs, ω-3 and ω-6 fatty acids are synthesized and accumulated in specific tissues and clinically play significant roles (Saini and Keum 2018).

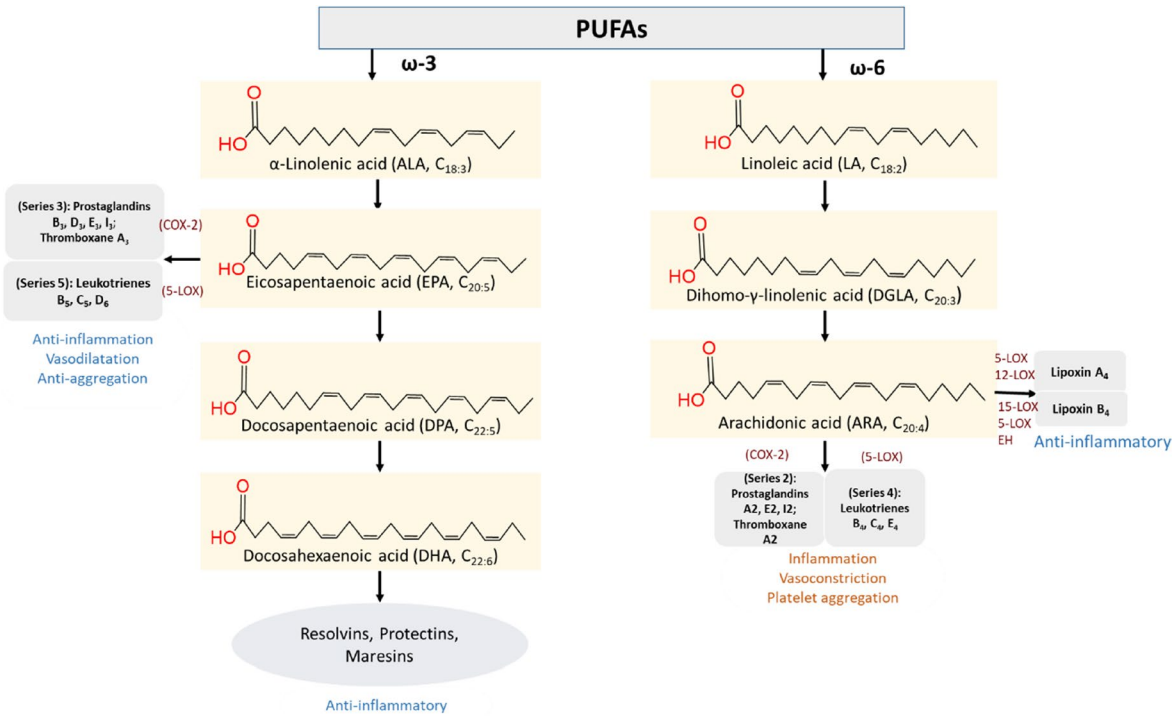


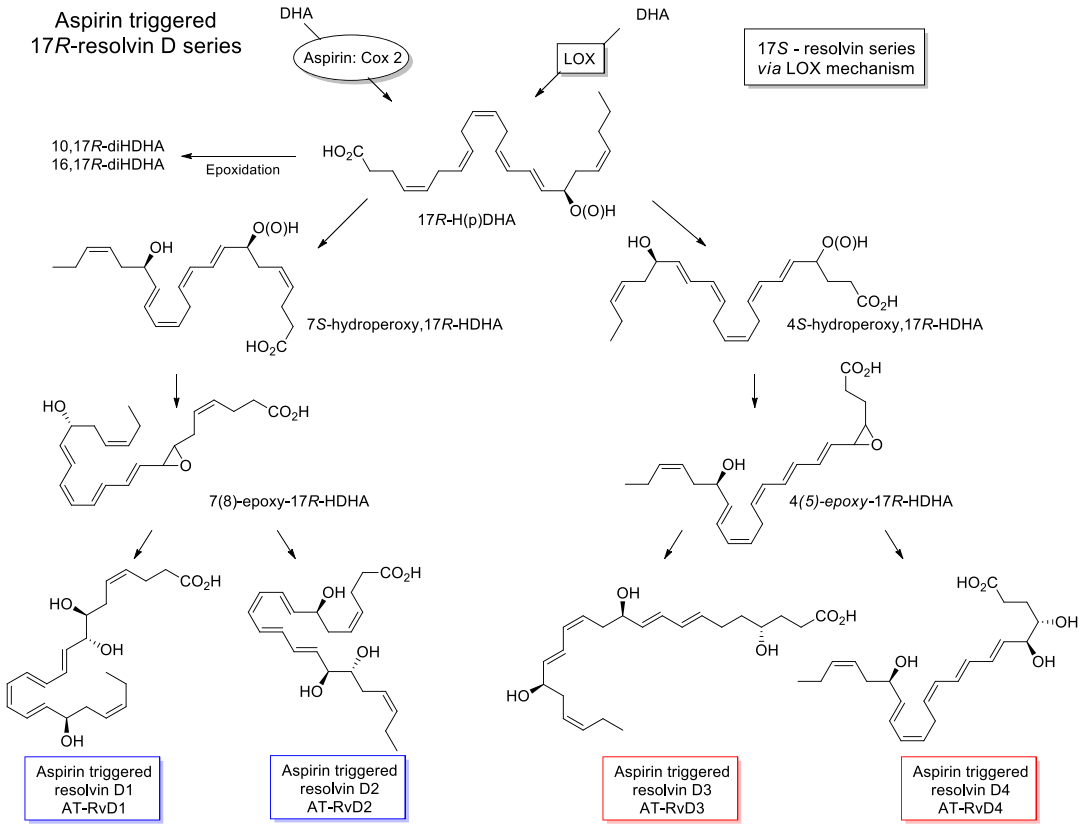
Fig. 2 Clinically significant polyunsaturated fatty acid families: ω-3 and ω-6 and their members associated with the pathophysiology of humans; COX, cyclooxygenase; LOX, lipoxygenase; EH, epoxide hydrolase

Omega-3 PUFAs

The first member of ω-3 PUFAs series is all-*cis*-9,12,15-octadecatrienoic (α-linolenic acid, ALA 18:3). The more important few ω-3 PUFAs derived from ALA are all-*cis*-5,8,11,14,17-eicosapentaenoic (EPA 20:5), all-*cis*-7,10,13,16,19-docosapentaenoic (DPA 22:5), and all-*cis*-4,7,10,13,16,19-docosahexaenoic (DHA 22:6) (Fig. 2). Bioactive signaling lipids, commonly known as eicosanoids, are derived from oxidation of EPA and DHA by several enzymes like cyclooxygenase (COX-1 and COX-2), lipoxygenase (5-LOX and 15-LOX), and epoxygenases (cytochrome P450 or CYP450).

Eicosanoids are not produced in a steady ratio. However, after biosynthesis, esterified EPA and DHA are stored in neutral triglycerides or phospholipids, and when required, they can be mobilized to form eicosanoids and other autacoids. COX-2 mobilizes EPA to series 3 eicosanoids (PG B_3, D_3, E_3, I_3, and TXA_3), and 5-LOX mobilizes to series 5 eicosanoids (LT B_5, C_5, and D_6) (Calder 2003; Sabater et al. 2011). These are anti-inflammatory mediators which cause vasodilatation and anti-aggregation of platelets. Additionally, DHA metabolizes SPMs of the lipoxin, resolvin, protectin, and maresin families during inflammation (Scheme 1).

The SPMs initiate the process of resolution which include restriction or cessation of neutrophil infiltration, counter-regulation of chemokines and cytokines, induction of the neutrophils apoptosis and subsequent efferocytosis (the process by which apoptotic cells are removed by phagocytic cells) by macrophages, the conversion of macrophages from classically activated (M1) to alternatively activated cells (M2), return of non-apoptotic cells to the vascular system or lymphatic vessels, and the start of the healing process. These events facilitate proper return to the homeostasis balance (Park et al. 2020; Lee 2021). For example, resolvin D_1 (**1**) and D_2 (**2**) impart in resolving inflammation and protecting organ damage in injury (Duffield et al. 2006; Spite et al. 2009). In addition, resolvin D1 promotes the targeting and clearance of necroptotic cells (Gerlach et al. 2020). Another anti-inflammatory mediator resolvin D_6 (**3**) induces nerve reaeration and post-infection healing (Pham et al. 2020). Neuroprotectin D_1 (**4**) is also an anti-inflammatory mediator that reduces oxidative stress in several pathological events

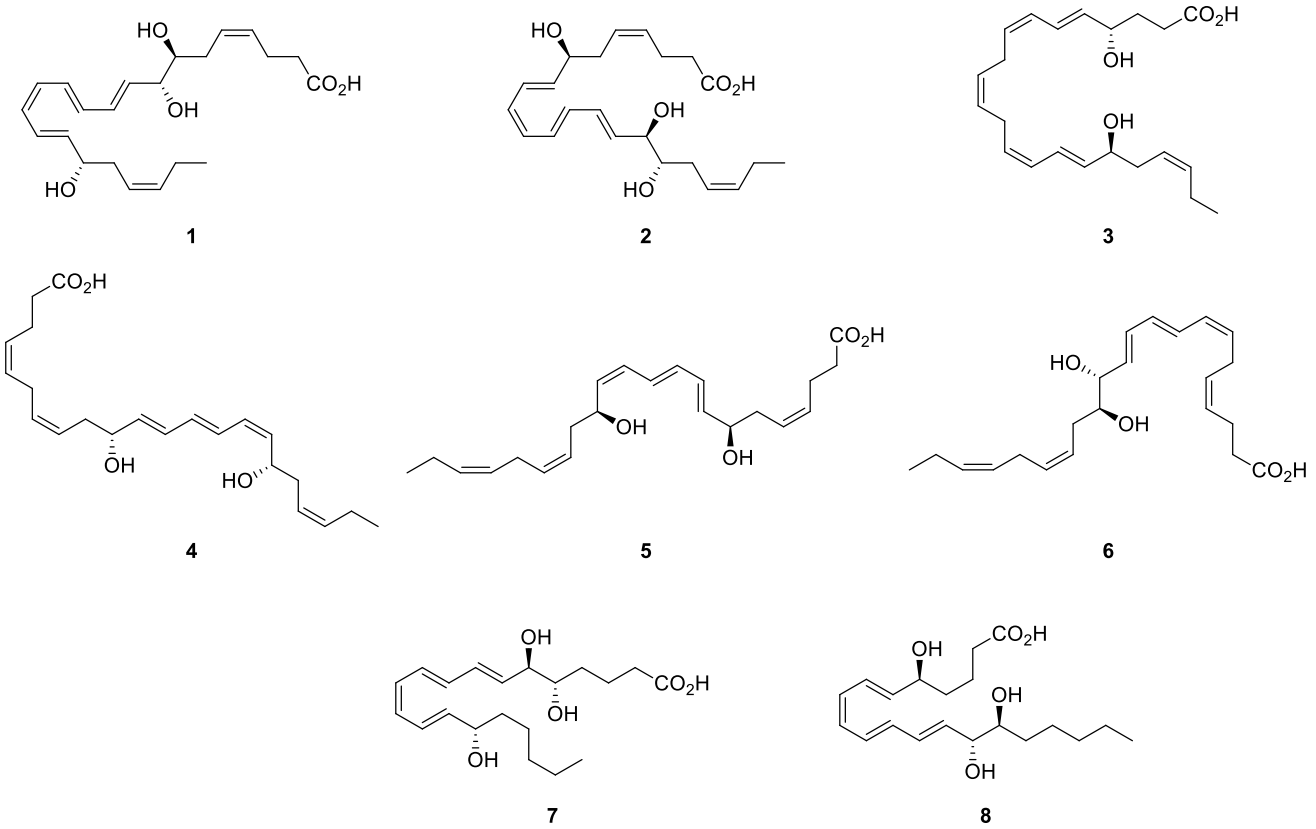


Scheme 1 Aspirin activated biosynthesis of specialized pro-resolving mediators from docosahexaenoic acid (DHA). Aspirin not only blocks the biosynthesis of prostaglandins, but also stimulates the endogenous production of anti-inflammatory and pro-resolving lipid mediators termed aspirin-triggered specialized pro-resolving mediators (AT-SPMs), such as aspirin-triggered resolvins (AT-RvDs) and lipoxins (AT-LXs)

like stroke, retinal degenerations, and Alzheimer's disease (Bazan 2005; 2009). Furthermore, maresins MaR_1 (**5**) and MaR_2 (**6**) act as anti-inflammatory and pro-resolving factors in wound healing (Wang et al. 2015; Tang et al. 2018). Ma R_1 promoted de novo generation of regulatory T cells and interacted with type 2 innate lymphoid cells to inhibit TGF-β-dependent cytokine production, which effectively reduced lung inflammation and attenuate pulmonary fibrosis (Li et al. 2020). Lipoxin A_4 (**7**) and B4 (**8**) attenuates or prevents an inflammatory response via the immunosuppressive activity of stem cells of the apical papilla through the activation of its receptor, ALX/FPR2 (Gaudin et al. 2018).

LTE_4) are synthesized by lipoxygenases (5-LOX) from AA (Fig. 2). Additionally, various hydroperoxy- and hydroxyl-eicosatetraenoic acid (HPETE and HETE) derivatives and lipoxin A4 are also produced from AA (Schmitz and Ecker 2008).

Most cell signaling molecules from DGLA and AA are pro-inflammatory, vasoconstrictor, platelet aggregator, and disease-propagating (Robinson and Stone 2006). However, in the case of inflammatory modulation, PGE_2 exerts both pro- and anti-inflammatory roles. PGE_2 induces COX-2 and 15-LOX, producing pro-inflammatory IL-6 and anti-inflammatory lipoxins, respectively (Serhan et al. 2003). In



Omega-6 PUFAs

Parental all-*cis*-9,12-octadecadienoic (linoleic acid, LA, 18:2) of ω-6 family produces two important PUFAs: all-*cis*-8,11,14-eicosatrienoic (dihomo-γ-linolenic acid, DGLA, 20:3) and all-*cis*-5,8,11,14-eicosatetraenoic (arachidonic acid, AA, 20:4). Series 1 prostaglandin PGs (PGE_1, PGF_1, thromboxane A1) and series 3 leukotrienes (LTs), such as LTA_3, LTC_3, and LTD_3, are produced by the enzyme COX and LOX, respectively (Yashodhara et al. 2009). Like EPA and DHA, AA is stored in esterified form and mobilized by phospholipase A2 (PLA2) to form eicosanoids. COX-2 converts AA to series 2 eicosanoids (PGA_2, PGE_2, PGI_2, and TXA_2). Similarly, series 4 eicosanoids (LTB_4, LTC_4, and

contrast, 5-lipoxygenase inhibition of PGE_2 decreases the pro-inflammatory series 4 LT level (Levy et al. 2001).

PUFAs in COVID-19 Infection

PUFAs play essential roles in the cell activity of each organ and tissue in the human body. PUFAs with structural and physiological significance have a beneficial effect on pathological conditions such as infection or inflammation. Given that COVID-19 is a viral illness associated with significant inflammation of the respiratory tract, there is a possibility of benefiting from PUFA supplementation (Lee 2021). The potential beneficial effects of PUFA supplementation based on research evidence are depicted in Fig. 3.

Role on Respiratory System

The essential PUFAs ω-3 and ω-6 modulate the inflammatory response that potentially influences respiratory health involving chronic inflammatory and infectious processes (Lemoine et al. 2020). However, PUFAs (especially ω-3) affect blood rheology, host–microbial interactions, and surfactant production in the lung (Knapp, 1995). So, commonly PUFAs are thought to be essential nutrients to prevent lung diseases like acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD), asthma, and allergies. Nevertheless, the exact modes of these effects on the respiratory system remain primarily unknown. SPMs, such as protectins, resolvins, and maresins, from ω-3 PUFAs counter-regulate airway eosinophilic inflammation against the pro-inflammatory mediators of ω-6 PUFAs and promote the resolution of inflammation *in vivo* (Miyata and Arita 2015).

Two studies demonstrated that dietary fatty acid supplements in infants or children at the age range of 6 months to 5 years decreased wheeze prevalence and lessened bronchodilator use at 1.5 years of age (Mihrshahi et al. 2004). Moreover, such clinical intervention reduced the prevalence of cough allergic sensitization at 3 years of age; however, the effects on the prevalence of asthma were not observed (Damsgaard et al. 2007). Other clinical studies with ω-3 PUFAs supplementation diminished the production of LTs from polymorphonuclear cells in athlete and asthmatic adults and decreased bronchoconstriction after exercise (Mickleborough et al. 2006). Another work on ω-3-rich supplementation revealed the beneficial and suppressive effects on exhaled NO levels before and after the intervention (Schubert et al. 2009).

Masclans et al. (1999) determined plasma levels of TXB_2, $PGF_{1\alpha}$, and LTB_4 in peripheral arteries, pulmonary arteries, and venous system within 48 h of 21 ARDS cases. Eicosanoids were considerably more significant in ARDS patients than in the healthy control group. Furthermore, survivors presented higher eicosanoid levels in systemic pulmonary arteries than nonsurvivors. However, Auner et al. showed that LTB_4 concentrations were considerably more significant in patients with respiratory problems, and it explained LTB_4 levels as biochemical markers of respiratory disorders such as pneumonia, ARDS, respiratory failure, and pulmonary embolism (Auner et al., 2012). Another study also observed pro-inflammatory eicosanoid LTB_4 as a correlating mediator between lung injury and severe ARDS patients (Masclans et al., 2007). Therefore, these studies draw an apparent connection between respiratory health and PUFAs, and probably the effect of ω-6 FAs family is opposed by ω-3 FAs.

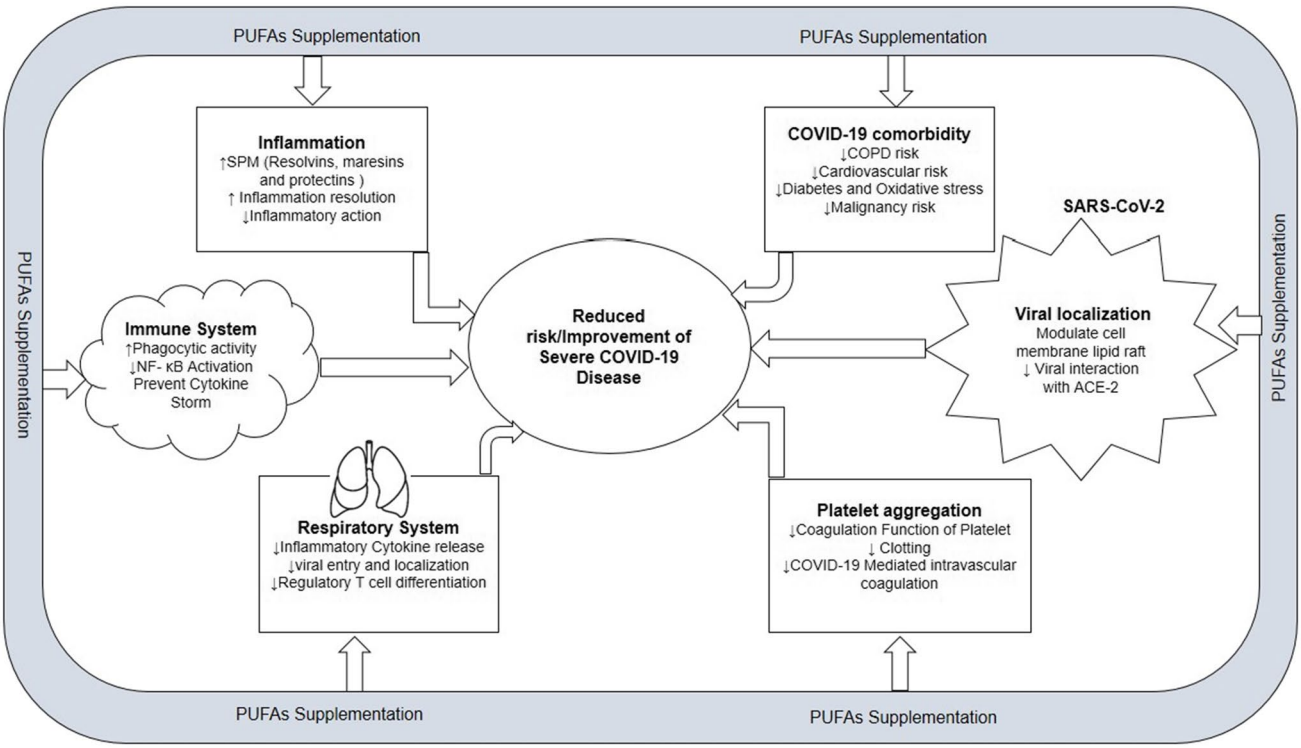


Fig. 3 Potential beneficial effect of PUFA supplementation in severe COVID-19 patients. PUFAs, polyunsaturated fatty acids; SPM, specialized pro-resolving mediators; NF-κB, nuclear factor kappa-B; COPD, chronic obstructive pulmonary disease; ACE-2, angiotensin-converting enzyme-2

Role Against Viral Replication

Long-chain and very-long-chain PUFAs EPA, DHA, AA, and ALA have a substantial role in the immunological defense against viral entry, localization, and replication to new copies (Calder et al. 2020). PUFAs can control membrane features such as membrane fluidity and protein complex formation in lipid rafts since they are the components of membrane phospholipids. Angiotensin-converting enzyme-2 (ACE2) and cellular protease transmembrane protease serine-2 (TMPRSS-2), which are the entry gateway for SARS-CoV, are most commonly found in lipid rafts (Ballout et al. 2020). ACE2 and TMPRSS2 expression, stability, and enzymatic activity may be affected by the quantity and size of lipid raft and non-raft domains. A study on Vero E6 cells showed the involvement of lipid raft on SARS-CoV entry (Lu et al. 2008), and another study by Glende et al. suggested that ACE-2 mediated viral entry can be attenuated by modulation in lipid raft (Glende et al. 2008). Comparing to other PUFAs, DHA is the most potent fatty acid to participate in lipid raft formation (Wassall et al. 2018).

Metabolic reprogramming of cells in pro-inflammatory stimulants is a recurring event. Transcription factors sterol regulatory element-binding proteins (SREBPs) and their isomers are reprogramed with metabolism in the cell if they are virally infected. Modulation of biomolecules including enzymes connected with numerous signals affecting normal and pathological cell activity is favorable for the long-chain ω-3 fatty acid. One of the strategies of the virus is to reprogram host lipid metabolism to supply sufficient lipid molecules necessary for virion replication membrane formation. One manner in which MERS-CoV might influence lipid metabolism of host cells and remodel de novo SREBP-dependent lipogenesis pathway is by maintaining an abundance of circulating fatty acids (Yuan et al. 2019). It has also been demonstrated that SREBPs are active during flavivirus infection (Pombo and Sanyal 2018). Following this, a potential therapeutic intervention against viral infection is designed targeting SREBP ½. As ω-3 PUFAs like EPA and DHA block the conversion of SREBP1 from its inactive to active mature form and accelerate the breakdown of mRNA for SREBP-1c, it may prevent the viral activating mechanism and shorten the duration of its replication. The outcome of this suppression is that cell concentrations of the matured SREBP are reduced overall, and lipogenic gene codes, especially acetyl-CoA carboxylases, fatty acid synthases, and stearoyl-CoA desaturases, are reduced (Deckelbaum et al. 2006). Viruses can cause large-scale changes in the host cell's metabolism, including the activation of fatty acid production in human hepatocytes by the hepatitis C virus (HCV) and the consumption of cellular lipid reserves in hepatocytes by the dengue virus (Matheson et al. 2015).

Role Against Inflammation

PUFAs are crucial for membrane phospholipid structural integrity and flexibility. Immune cells such as lymph nodes or splenic lymphocytes collected from laboratory mice often contain 15–20% of PUFAs as AA and include relatively few EPA and DHA (Calder et al. 1994). Modulation of the composition of fatty acid of these animals' diets results in changes to the fatty acid content of their immune cells, and thus, the AA-, EPA-, or DHA-enriched diet improves the accumulation of these PUFAs in the immune cell (Peterson et al. 1998). PUFAs also affect gene expression and offer a component for lipid mediator production, like cytokines (Calder, 2001). The role of the AA cascade on inflammation through viral stimulation is well-documented, while EPA- and DHA-derived eicosanoids have the anti-inflammatory potential (Ripon et al. 2021). The PLA2 enzyme activity triggered by physiological or pathological events results in the mobilization of AA for the development of inflammatory cytokines in the promotional phase of inflammation (Innes and Calder, 2020). Three individual enzymes named COX, LOX, and cytochrome P450 (CYP450) play a role in the enzymatic oxidization of AA to inflammatory and anti-inflammatory cytokines, as represented in Fig. 2. It can be said that ω-6 PUFAs have been shown to activate the inflammation promotion phase. Secondly, the affected cell or tissue tries to restore as a homeostasis process is the resolution phase of inflammation, and ω-3 PUFAs can stimulate this resolving phase at the inflammation site.

The principal precursors to inflammation resolution are EPA and DHA. Calder demonstrated that ω-3 PUFAs like EPA and DHA are incorporated across the body into the phospholipid layer of neutrophils' cell membranes and produce various mediators, including PGs, LTs, and maresins. As a result, in case of injury, the by-products of these cell membranes can produce less inflammatory eliciting mediators than ω-6 PUFAs like AA and LA, more frequently found in the western diet (Calder 2011). EPA- and DHA-mediated SPMs known as resolvins, maresins, and protectins impede the synthesis of pro-inflammatory cytokines by diminishing NF/kB pathway (Basil and Levy 2016). E-series and D-series resolvins synthesized from EPA and DHA have potential anti-inflammatory activity by reducing the infiltration of leukocytes at the damaged tissue, whereas the DHA-derived maresins can resolve inflammation through inducing macrophage phagocytosis of neutrophils (Rius et al. 2012). Western diets are predisposed to a high ω-6/ω-3 ratio that can enhance many diseases' pathogenesis; again US adults and children consume the insufficient amount of DHA and EPA (Sheppard and Cheatham 2018). Furthermore, a laboratory study suggested that the anti-inflammatory action of ω-3 PUFAs is inhibited by ω-6 counterparts (Innes and Calder 2018). Morin et al. (2014) suggested another minor ω-3

PUFA, docosapentaenoic acid (DPA), as significant to the inflammatory resolution of the lungs.

Enormous *in vivo* and *in vitro* studies have been launched, highlighting the anti-inflammatory role of PUFAs. One study with ω-3 PUFA emulsion to sterile peritonitis and murine polymicrobial sepsis condition showed potential anti-inflammatory activity by diminishing infiltration of neutrophils and pro-inflammatory mediator synthesis (Körner et al. 2018). Another study conducted by Saedisomeolia et al. (2009) to identify the anti-inflammatory potential of AA, DHA, and EPA in airway epithelial cell inflammation induced by a virus named rhinovirus demonstrated that DHA significantly diminished the release of IP-10 and IL-6 release from airway epithelial cells. The mechanisms underlying the anti-inflammatory activity are inhibiting the synthesis of eicosanoids from AA and decreased cellular immune function. A clinical study launched for 3 months on patients with hemodialysis showed that an additional diet with DHA and EPA lowered the serum level of C-reactive protein (CRP), which is a biomarker of inflammation (Saifullah et al. 2007). Supplementation with EPA and DHA has been shown to enhance both fatty acids in blood lipids, blood cells, and other tissue regions. Another clinical trial launched by Gerling et al. (2019) shows a 12-week supplementation of fish oil equivalent to 3 g EPA + 2 g DHA/day to healthy young men increases the ω-3 PUFA content in the mitochondrial membrane and whole muscle at the same time reduces the ω-6/ω-3 ratio. Overall, the study's outcome represents that the incorporation of DHA and EPA in diet can reduce the AA level for eicosanoids synthesis, thus inducing anti-inflammatory potentials.

A clinical study for 8 weeks by De Souza et al. (2020) demonstrated that fish oil enriched with 1.44 g EPA and 0.96 g DHA when supplemented to obese type 2 diabetes patients diminished the inflammatory biomarker (IL-1β and IL-6 and TNF-α) level. The inhibition of leukocyte chemotaxis, reduction in cell adhesion molecule expression and leukocyte–endothelial adhesive interactions, interrupting lipid rafts, inability to activate nuclear factor kappa-B (NF-κB), activation of peroxisome proliferator-activated receptor gamma (PPARγ), and binding to G protein-coupled receptor (GPCR) are the underlying measures of anti-inflammatory action of EPA and DHA. Again, the synthesis of SPMs such as resolvins, maresins, and protectins from enzymatic oxidation of EPA and DHA can resolve inflammation by interrupting the trans-endothelial neutrophil migration and chemokine and cytokine production (Calder 2013). Inflammatory biomarkers such as tumor necrosis factor-α (TNF-α), IL-1, IL-2, IL-6, IL-7, IL-10, IL-12, IL-17, macrophage colony-stimulating factor (M-CSF), granulocyte colony-stimulating factor (G-CSF), chemokine CXCL-10 (IP-10), monocyte chemoattractant protein-1 (MCP-1), and macrophage inflammatory protein-1α (MIP-1α) were shown to be raised in the plasma of COVID-19 patients admitted to the hospital and requiring intensive care in the clinical research (Costela-Ruiz et al. 2020; Huang et al. 2020). Moreover, pro-inflammatory TNF-α and IL-6 block desaturases, which are required to synthesize AA, EPA, and DHA from their substrates LA and ALA, accordingly. In addition, during COVID-19 infection, there is a higher level of inflammation and overexpression of inflammatory TNF-α and IL-6 that result in the shortage of AA, EPA, and DHA at the cellular level. As a result, anti-inflammatory mediators such as lipoxins, resolvins, protectins, and maresins are synthesized at a lower rate. In this case, a diet or supplement containing PUFAs can compensate for the shortage and aid in resolving inflammation while also preventing cytokine storms in severe COVID-19 (Das 2019).

Role in the Immune System

PUFAs play a critical part in the immune system's function. Various saturated and unsaturated fatty acids provide fuel for energy production in the immune cells. ω-6 PUFAs, like AA, are one of the most critical components of the cell membrane phospholipids supporting physical and biochemical functions. In another way, PUFAs have potential in the genetic signaling process, thus regulating cellular functions. Various PUFAs like AA, DHA, and EPA serve as a precursor for synthesizing various functional eicosanoids like PGs, LTs, lipoxins, resolvins, and proteins. As a result, changes in the PUFA composition in the membrane phospholipid structure through supplementation or any other stimuli can change the immune system function (Calder 2001; Innes and Calder 2018).

Immune cell phospholipids such as lymph nodes or splenic lymphocytes contain the highest (15–20%) concentration of AA as fatty acid; for this reason, this ω-6 PUFA is considered as the primary precursor for eicosanoids which synthesis accelerated due to external stimuli like microbial infection or cellular injury (Calder et al. 1990, 1994). Among various AA-mediated inflammatory eicosanoids, PGE_2 and LTB4 are predominant. The synthesis of AA-mediated inflammatory eicosanoid type depends on inflammatory cells (PGE_2 synthesis is predominant in monocyte cells where PGD_2 is predominant in mast cells) and the nature of stimuli. The incorporation of increased levels of EPA and DHA in cell membranes has been well-documented to reduce the production of AA-derived eicosanoid mediators such as PGE_2. Peterson et al. (1998) suggested that EPA- and DHA-enriched diet to rat modified the level of AA content in the immune cell membrane phospholipids along with its predominant precursor PGE_2 production. It is partially due to the reduced availability of AA as a substrate material and the inhibition of metabolic processes of AA. In contrast, oral administration of AA at a dose of 1.5 g/day to healthy humans raised

the synthesis of PGE_2 and LTB_4 by peripheral blood mononuclear cells (Kelley et al. 1998). As EPA acts as a substrate for COX and LOX enzymes, if EPA can be incorporated into the membrane phospholipids, EPA-mediated eicosanoids (5 series LTs and PGE_3) synthesis will be stimulated in immune cells. Research evidence supports this hypothesis, as Grimm et al. (2006) and Wachtler et al. (1997) suggested that the ω-3-enriched fish oil supplementation increases the production of 5 series LTs from neutrophils.

The fundamental step of the immune response against a pathogen or foreign substance is phagocytosis. This process involves the binding, in the end, a phagocytic vacuole of the pathogen or supplementary or antibody-coated pathogens on the surface receptor and subsequent invagination of the cell membrane around the pathogen. Phagocytosis also initiates acquired immunity in response to microorganisms. In addition, the level of PUFA content in the phagocytic cell membrane has a substantial role in the immune cells' phagocytic capacity. Several *in vitro* and *in vivo* research approaches support this statement. It is suggested that the uptake of the foreign pathogen by macrophage is highly influenced by the uptake and incorporation of saturated and unsaturated fatty acid (Calder et al. 1990). The higher the uptake of PUFAs, the higher the increased in the phagocytic activity by phagocytic cells. A study conducted with human peripheral blood mononuclear cells from healthy volunteers suggested that about 80% of total neutrophils and 25% of monocytes are active. The phagocytic activity of those cells was highly correlated with the PUFA composition in membrane phospholipid. Both neutrophils and monocytes' phagocytic activity were positively correlated with the total PUFA content, total ω-6 PUFAs, and total ω-3 PUFAs but negatively correlated with a palmitic acid content and the saturated to PUFAs ratio (Samantha Kew et al. 2003a, b). As there is a negative correlation between the phagocytic activity of the immune cell and the ω-6 to ω-3 fatty acid ratio, it can be considered that the ω-3 PUFAs have the potential to improve phagocytic activity. The outcome of clinical research on healthy volunteers also supports this, claiming that administering a mixture of ω-3 PUFAs (DHA + EPA) at a dose of 1.5 g/day improves about 40% of neutrophil and 200% of monocyte phagocytic activity (Kew et al. 2003a, b).

T cell functioning and signaling are also highly influenced by PUFAs. The underlying mechanisms behind this are (i) changes in the level of inflammatory cytokine synthesis, which influences T cell functioning; (ii) alteration in the plasma membranes' physical structure; (iii) alteration of genetic signaling; and (iv) influence on lipid raft (Miles et al. 2003; Zeyda and Stulnig 2006). *In vitro* study suggested that supplementation with fish oil alters the phosphorylation of phospholipase C-λ1, a primary signaling event of T cell (Sanderson and Calder 1998). Another study on mice also demonstrated the reduced proliferation of T cell and IL-6 production, but the extent to which the human T cell lipid raft is modulated by PUFA supplementation is not studied yet (Fan et al. 2004).

An antigen-presenting cell (APC) is a cell that expresses antigen on its membrane surface via major histocompatibility complex (MHC) proteins, and this complex is recognized by T lymphocyte cells. MHC-1 and MHC-2 are involved in the presentation of pathogen-mediated antigens to T cells, resulting in the death of APCs. An *in vitro* study by Calder et al. (2007) suggested that antigen presentation via MHC II and expression are reduced when APCs are exposed to EPA or DHA. Sanderson et al. (1997) found a decreased expression of dendritic cells MHC-2 in fish oil-treated rats, which correlates with decreased antigen presentation by T cells. Another *in vitro* study examined the effect of PUFAs (AA, DHA) on MHC-1 expression and concluded that exposure to PUFAs decreases MHC-1 expression and that the effect is concentration sensitive (Shaikh and Edidin 2007). These findings of the action of AA and DHA in inhibiting MHC-1 expression provide insight into the mechanism by which PUFAs reduce antigen presentation; however, EPA has not been studied.

Role in Platelet Aggregation

PUFAs have a substantial influence on platelet structure and function. Supplementation with ω-3 and ω-6 PUFAs may alter the plasma membrane's phospholipid composition. As a result, the platelet clotting or aggregation function may be diminished, which benefits patients with coagulopathy or cardiovascular complications. A review of *in vivo* and *in vitro* studies on the role of different PUFAs on platelet functions by Adili et al. (2018) agreed with the above statement. This is due to the action of PUFAs on the metabolizing enzyme COX-1, 12-lipoxygenase (12-LOX), and CYPs in platelets that convert the fatty acids into oxylipin products. These oxylipin products regulate platelet aggregation and thrombosis function. Barre and Holub (1992) demonstrated that AA is the primary fatty acid component (13.5%) in platelets and synthesizes various PGs that promote the coagulation process. However, supplementation with ω-3 fatty acids like EPA or DHA can modulate the AA composition in the membrane phospholipids of platelets and decrease the AA-mediated coagulation function. Another 28-day study on healthy volunteers supplemented by EPA stated that platelet function was significantly reduced, but DPA has no such function (Park and Harris 2002).

Intravascular coagulation is commonly noticed in severe cases of COVID-19. A study with 183 COVID-19 patients revealed that a significant proportion did not recover from the infection and had significantly higher levels of D-dimer, prothrombin time, and fibrin degradation products and lower levels of anti-thrombin and fibrinogen than recovered patients (Tang et al. 2020). Again, in patients with

COVID-19, acute cardiac injury is particularly prominent and is correlated with severe clinical outcomes (Huang et al. 2020). However, all the heart failure cases (23%) noticed in hospitalized COVID-19 patients were not pre-existing cardiomyopathy (Zhou et al. 2020). Intra-arterial coagulation or thrombosis may promote the development of acute myocarditis. Considering these issues, it has been recommended that anticoagulants (e.g., heparin) can be used actively in patients with severe COVID-19 patients (Tang et al. 2020).

In COVID-19 patients, a moderate dose of ω-3 fatty acid can also perform heparin-like functions. A study conducted by Wander and Patton (1991) supports the correlation between ω-3 fatty acid consumption and improvement of COVID-19 coagulopathy. They demonstrated that a moderate consumption of EPA-containing fish salmon + sablefish + dover sole = 200 g/day for 18 days by healthy volunteers had increased bleeding time, increased platelet EPA content, and decreased platelet aggregation. Although substantial clinical research has not yet been conducted regarding the effect of PUFA supplementation against thrombosis in severe COVID-19 cases, a positive effect is highly expected.

Role in COVID-19 Comorbidities

Comorbidities of infectious illness increase the chances and severity of infection. In COVID-19, chronic respiratory disease, cardiovascular diseases, hypertension, diabetes, malignancy, and kidney diseases are suggested as the most influential morbidities. A tremendous report on PUFAs demonstrated a positive impact on these morbidities, although some conveyed double standards. PUFAs have both anti-inflammatory and anti-oxidative effects. Therefore, it has been mentioned to improve chronic respiratory complications like COPD. Two cohort studies of 120,175 participants revealed that fish consumption was negatively linked to the risk of COPD. Nonetheless, the effect of fatty acids and ω-3 PUFAs was non-significant (Varraso et al. 2015). Another study demonstrated the impact of ω-3 fatty acids cigarette smokers against COPD and showed an inverse relation with the risk in a quantity-dependent fashion (Shahar et al. 1994). However, interestingly, as like as ω-3, epidemiological evidence of ω-6 PUFAs inconsistently reported COPD prevention by several studies (Hirayama et al. 2010; Varraso et al. 2015).

In the 1970s, the first Greenland Eskimos have reported a lower prevalence of cardiovascular diseases (CVD) than populations taking typical Western diets. The study drew a relation between fish consumption and cardio-protection that the presence of ω-3 PUFAs series in marine food prevents ischemic processes by decreased platelet aggregability (Dyerberg and Bang 1979). A recent umbrella review found a significant reduction of CVD risks by ω-3 PUFAs, with RRs (95% CIs) range from 0.89 (0.82–0.98) to 0.90 (0.85–0.96) (Chareonrungrueangchai et al. 2020). Another pooled estimate by a meta-analysis on ω-3 effects reduced coronary heart disease and myocardial infarction risks compared to the control group (Hoang and Kim 2020). A randomized control trial in the USA on 28,100 women testified that dietary ω-3 and ω-6 PUFS was not associated with the risk of hypertension (Wang et al. 2010). In contrast, a very recent study described the vasodilatory effects of DHA and EPA, which ultimately lessen blood pressure (Bercea et al. 2021).

Moreover, several studies reported that PUFAs could prevent diabetes and attenuate the oxidant stress in chemically induced diabetic animals (Suresh and Das 2003). The Asian population intake more fish and marine ω-3 PUFAs compared to the Western population. Therefore, Asian people are at less risk of diabetes than the western population, and the same finding is described by Rice Bradley (Bradley 2018). Despite a paucity of information from various communities, few studies failed to show the association of PUFAs with end-stage renal disease (Malhotra et al. 2016). In terms of malignancy, Donat-Vargas et al. (2017) reported that EPA-DHA intake reduces the 80% risk of malignant melanoma. In comparison, a meta-analysis on 57 cases reported non-significant and weak relations between ω-3 PUFAs and different types of malignancy (Lee et al. 2020).

Safety Considerations

The ω-3 and ω-6 PUFAs are essential nutrients that should be kept in the daily food calendar to prevent nutritional deficiencies. Though the optimal daily requirements of PUFAs remain unknown, very high intakes may carry a risk of adverse effects. Clinical interventions support the notion against ω-6 PUFAs that a large intake of the FAs may enhance *in vivo* lipid peroxidation. Nevertheless, the influence of a high ω-3 PUFA intake on lipid peroxidation has been uncertain (Eritsland 2000). The peroxidative breakdown results in groups of products such as cyclic peroxides, aldehydes, and ketones. These molecules are involved in the free radical generation, leading to chronic and lethal pathogenesis such as inflammation, atherosclerosis, and cancer (Spiteller 2005).

High intake of ω-3 PUFAs replaces arachidonic acid with eicosapentaenoic acid in platelet membranes and results in more thromboxanes and prostacyclins. It enhances the vasodilatory and anti-aggregatory profile, leading to prolonged cutaneous bleeding (Dyerberg et al. 1978). Hypothetically, excessive n-3 PUFA intake could weaken defensive mechanisms against infections, but so far, there is no such clinical data (Eritsland 2000). However, excessive intake of PUFAs may be associated with immunosuppression, disturbance in glucose homeostasis, and hyperlipidemia. Although well-documented *in vitro* and *in vivo* assays ascertain the potential benefits of ω-3 fatty acids to lessen COVID-19-related complications, the risk of high dose supplementation during SARS-CoV-2 infection must be well-investigated.

Sources, Supplements, and Dose of PUFAs

COVID-19 patients have been reported significant improvement after ω-3 PUFA administration in few studies. So, these FAs should be suggested as palliative medicine. Effective outcomes from the treatment arise few vital questions: what are the sources of ω-3 fatty acids, do they have any supplements, which route is efficient to effective delivery, and what dose should be taken?

Nature is the best repository of essential PUFAs. Each one can take adequate ω-3 and ω-6 PUFAs from foods derived from animals and plants. The professional bodies recommend fish consumption to meet the daily needs of ω-3 PUFAs for health benefits. However, vegetable oils also contain significant amounts of ω-3 FA. The following seed oils are presented in descending order of ω-3 PUFAs: linseed oil, flaxseed oil, pumpkin seed oil, canola oil, soybean oil, safflower oil, and sunflower oil (Yashodhara et al. 2009). Box 1 elucidates ω-3 and ω-6 PUFAs enriched foods along with a recommendation, should it eat or avoid. Olivieri's recommendation mainly focused on avoiding cardiovascular disease but may apply to COVID-19 due to similar positive/negative impacts of the two types PUFAs (Olivieri 2019).

Box 1. PUFA-enriched common foods and suggestions base on relative components.

Fatty acid types	ω-3 PUFAs (ALA, EPA, DHA)		ω-6 PUFAs (LA, AA)	
	Recommended	Avoid	Recommended	Avoid
Long-chain: ALA, LA	Relatively more ALA: flax, walnuts, green leafy vegetables	Relatively low ALA: canola oil, soybean oil	-	Relatively more LA: sunflower oil, safflower oil, corn oil, cottonseed oil, soybean oil
Very-long-chain: EPA, DHA, AA	Relatively more EPA and DHA: mackerel, salmon, anchovies, sardines, tuna, herring, squid, shellfish, wild animal meats, grass-fed animal meats	-	Relatively low AA: eggs, poultry, beef, pork, liver, human breast milk	Relatively more AA: farm-raised fish, rain feed animal milk

Besides these dietary sources, different supplements of ω-3 FA are now available in the market. Oral capsule and intravenous lipid injection emulsion are recommended for intensive care patients. Many patients with digestive intolerance can take lipid emulsions enriched with fish oil (Sabater et al. 2011). A study on 19 septic shock patients was designed with ten patients randomly assigned to receive a ω-3 FA emulsion (350 ml/day, equivalent to 14 g DHA + EPA) intravenously for 3 days. The emulsion achieved a ratio of 2.5:1 for ω-3 and ω-6 PUFAs and significantly decreased pro-inflammatory mediators TNF-α, IL-6, and IL-8 (Mayer et al. 2003). Different dosage forms with a convenient route of administration are involved in PUFA supplement to adjust the required amounts.

The ω-3 FA content of the diet must achieve nutritional adequacy to prevent deficiency symptoms. However, exact dose requirement is difficult to measure for few reasons: interindividual variability in ω-3 FA metabolism based on genetic determinants, age, and gender; dietary composition, high ω-6 PUFA, and saturated FAs interfere with the functions of ω-3; availability of certain foodstuffs, such as wild fish; and food contaminants (Molendi-Coste et al. 2011). An ideal balanced diet is deduced from ancestral nutrition, where fat should represent below 20–30% of the total energy uptake. Moreover, the fat portion should meet 5–6 g/day of EPA- + DHA-enriched ω-3 PUFA, and the ω-6-to-ω-3 ratio should average 1 (Sanders 2000). Consumption of cold water fish or specific enteral feeding formulas can provide insufficient EPA and DHA (nearly 1 g/day). Nevertheless, Bistrian (2020) suggested 4–6 g/day of EPA and DHA to manage a hyper-inflammatory state in critically COVID-19-infected patients. PUFAs, especially ω-3 FAs, are a potential medicine to provide palliative care in coronavirus infection. Therefore, proper investigation on dosage form, dose, and administration route of its supplements is required to ensure their safety and efficacy.

Perspectives and Future Directions

PUFAs are well-known for their constructive and beneficial impact on health. A sort of study on viral infection revealed the fats and viral interaction pathway to modulate immunochemistry. Therefore, PUFAs are promising molecules considered as curative and risk reductive medicine in COVID-19 treatment worldwide. Nevertheless, negligible studies on the fats against SARS-COV-2 have been conducted till now. Most of the investigations are hypothetical based on previous works on infectious diseases.

Moreover, the viral characteristics are very complex with the implicit mode of actions. That obviously asks for comprehensive studies about the sites of interaction with biomolecules and the extent of interference using PUFAs.

COVID-19 is an obdurate contagion of this decade and has recently considered its parallel coexistence with time. And so, the potential subject should be concisely explored to reduce the risks of the infection. Future studies should be highly focused on immunological effects, hematological parameters, respiratory healing, and comorbid stress reductions that will make a thorough direction for disease management.

Conclusions

SARS-CoV-2 is a highly contagious virus which spread through respiratory droplets. Besides the respiratory system, multisystem and multi-organ involvement of the virus triggers a cytokine storm that is an indicator of disease severity. Polyunsaturated fatty acids, a cluster of clinically significant fats, are the considerable option to lessen the severity. It has a substantial role in the immunological defense against viral entry, localization, and replication to new copies. However, it is also associated with respiratory health by controlling blood rheology and surfactant production in the lung. To add more, PUFAs might significantly benefit COVID-19 comorbidities such as cardiovascular disease, COPD, and diabetes. However, all PUFAs are not functionally the same. The members of ω-3 PUFAs (ALA, EPA, and DHA) are associated with anti-inflammatory action, whereas ω-6 PUFAs (LA, AA) are pro-inflammatory. Exceptionally, few SPMs like lipoxin derived from the AA show anti-inflammatory action that might lessen COVID-19 severity. Therefore, the ω-3 PUFA-enriched food or supplements is a good option in the emergence cytokine race and might decrease COVID-19 complications. Further clinical and retrospective study for the use of PUFAs in COVID-19 management is warranted.

Author Contribution PKB and MTA equally contributed to the design and draft of the research; MMR was associated with the conception and correction of the text; MSH contributed to the conception and design of the research. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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