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Review Article

Elucidating Potential of Dietary PUFAs (Ω-3) In Tackling Cytokine Storm Syndrome by Attenuation of Pro-Inflammatory Cytokines

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ABSTRACT

The study aims to examines PUFAs precisely ω-3 potential in tackling Cytokine storm syndrome. Study also investigates PUFAs: ω-3 in regulation of pro-inflammatory and anti-inflammatory cytokines associated with acute respiratory distress syndrome during respiratory viral infections. To find the most relevant studies, an in-depth review of the literature published in PubMed, Embase, the Cochrane library and China National Knowledge Infrastructure (CNKI) was conducted. The most relevant studies associated role of PUFAs in regulation of pro inflammatory cytokines, anti-inflammatory cytokines, acute respiratory distress syndrome was considered for the data extraction and interpretation of findings. PUFAs and their catalytic products via lipoxygenase and Cyclooxygenase results in an array of bioactive lipid mediators called as specialized pro-resolving mediators effectively resole the inflammation. Here, pro inflammatory cytokines such as IL-6, IL-8 and TNF-α in case of SARS-CoV2 and IFN-γ, TNF-α, IL-15 and IL-17 in respiratory viral infection reported up regulated and pose uncontrolled production of other immune mediator leading to CSS. PUFAs: ω-3 not only down regulates pro-inflammatory cytokines but also up regulates anti-inflammatory cytokine and facilitates resolution of inflammation. Dietary intake of PUFAs: ω-3 offer a protective role in the acute respiratory distress syndrome associated with cytokine storm. PUFAs: ω-3 and enzymatic metabolites decrease risk of systemic inflammation, multi-organ dysfunction and multi-organ failure due to the respiratory viral infection associated complications. Clinical evidences demonstrated that the dietary PUFAs (ω-3) and their enzymatic catalytic products i.e. SPMs possess anti-inflammatory potential by down regulating production of pro-inflammatory cytokines.

Keywords: Cytokine Storm Syndrome, Respiratory Virus Infections, Acute Respiratory Distress Syndrome, Inflammatory Cytokines, Poly Unsaturated Fatty Acids, Omega 3.

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INTRODUCTION

Fats are necessary dietary constituents for every living being. Carbon chain of Fatty Acid (FA) molecules is variable in length, having a carboxylic acid head group and a methyl terminal.[1] Carbon chains can be classified according to how saturated they are. The maximum amount of hydrogen atoms is found in saturated Fat Acids (FAs), whereas monounsaturated and Polyunsaturated Fat Acids (PUFAs) have one, two, or more double bonds, respectively.[2,3] Based on where the first double bond is located in relation to the chain's methyl terminus, PUFAs can be further segmented. Two of the most biologically significant PUFAs groups, for instance, are ω-3 and FAs ω-6, which have their initial double bond on the third and sixth carbons from the chain terminus, respectively.[4] Because the last carbon in the FA chain is commonly referred to as the omega carbon, these FAs are frequently referred to as omega-3 or omega-6 PUFAs. Polyunsaturated Fatty Acids (PUFAs) rich diet had an impact on numerous physiological functions. Function of ω-3 Polyunsaturated Fatty Acids (PUFAs) in the prevention and treatment of cardiovascular disease has garnered significant attention due to the results of several epidemiological researches and clinical trials.[5] The current emphasis of research is to clarify the routes and processes underlying the biological action of PUFAs ω-3. It is well acknowledged that dietary management is essential to both patient therapy and the general preservation of human health. Further, 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) are examples of omega-3 Polyunsaturated Fatty Acids (PUFAs). Alpha-Linolenic Acid (ALA) and linoleic acid are the precursors of long-chain Polyunsaturated Fatty Acids (PUFAs) that are produced from Essential FAs (EFAs).[6]

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More emphasis has to be placed on including. PUFAs ω-3 in the diet because most diets are already quite high in PUFAs ω-6. Although they are not widely available, dietary sources of n-3 PUFAs are. ALA can be found in a wide variety of foods, such as walnuts, dairy products, flaxseed and vegetables.[7] A great source of the long-chain derivatives of ALA, Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA) is fatty fish, such as mackerel, herring and salmon. Clinical trials have found positive effects of PUFA ω-3 supplementation and fish consumption on human health.[8,9]

Acute Respiratory Infections (ARIs) are major factors for higher morbidity and mortality.[10] Over the last two decades several repeated respiratory viral outbreaks were reported globally. These viral primarily infect upper reparatory tract i.e. reparatory epithelia and trigger prompt and massive immune response.[11] As a result, a cascade of immune mediators mainly pro-inflammatory cytokines pose pulmonary oedema, hypoxia and impaired functioning of respiratory organs results in acute respiratory distress syndrome.[12] As per World Health Organization Report (WHO) in the last five years 2018-2019 (49.5%), 2019-2020 (39.65%), 2020-2021 (41.52%) and 2021-2022 (34.50%) a striking hike of respiratory viral infections were reported including SARS-CoV (COVID-19) pandemic.[13] These grown and repeated respiratory infections are key concern for the various programs under the continuous diagnosis, surveillance, treatment and vaccination. Repeated outbreak of respiratory viruses, their novel variants with altered pathogenecity poses another challenge to healthcare where existing approaches; therapeutic reported ineffective.[14] The lethal outcome of respiratory viral infections is ARDS and cytokine storm syndrome remains associated with multi organ failure. The cause of ARDS and CSS is essentially to the over activity of immune system and release of pro inflammatory cytokine to the lung and other organs.[15] The previous studies have reported that poly unsaturated fatty acids mainly ω-3 capable in tackling over activity of immune system via down-regulating pro-inflammatory immune mediators and up regulating anti-inflammatory mediators. PUFAs ω-3 reported superior in tacking inflammatory response of immune system over the PUFAs ω-6.[16,17] PUFAs ω-3 molecular mechanism for the resolution of inflammatory cascade is complex and diverse however least explored in the context of respiratory illness mainly ARDS and CSS.[18,19] The present study investigate role of PUFAs ω-3 in tackling and attenuating pro-inflammatory immune response during infection of respiratory viruses. In the present study, role of pro-inflammatory cytokine has been illustrated in the onset and progression of ARDS and CSS that often lead to high morbidity and mortality. Study also provides a scientific rationale and structure a scientific basis how these PUFAs ω-3 beneficial in managing ARDS and CSS based on findings from clinical, *in vivo* and *ex vivo* studies.

Respiratory viral infections

Respiratory infections are leading and most frequent causative agents for acute respiratory illness across the globe.[20] As per WHO report, it has been reported that more than 400 million viral pneumonia cases occur every years affecting children and adult population across the globe.[21] A wide range of respiratory viruses including *Coronavirus (CoVs), influenza, Respiratory Syncytial Virus (RSV), Parainfluenza Virus 1-4, Human Metapneumovirus, Adenoviruses, Enteroviruses and Parechoviruses* infect upper and lower respiratory tissue and trigger life threatening inflammatory responses.[22] These respiratory viruses infect all age group where bronchiolitis and pneumonia are key clinical manifestations in severe condition. Respiratory viruses primarily infect upper and lower respiratory tissues while bacteria such as *Streptococcus pneumoniae* and *Klebsiella pneumonia* infect upper respiratory tissues.[23] Interestingly majority of upper respiratory infection are viral driven that account nearly 60% of all the infections including bacterial and viral. These infections are associated with common cold, pharyngitis, epiglottitis and laryngotracheitis. On the contrary, lower respiratory infections are virus and bacteria driven cause bronchitis and bronchiolitis. Several viruses infect respiratory system, leading to a variety of clinical symptoms ranging from a minor involvement of the upper airways to the potentially lethal ARDS.[24] Respiratory viral infections that worsen chronic inflammatory diseases are lethal and involve wide range pro inflammatory mediators.[25] Respiratory viruses primarily infect and multiply in epithelial cells, triggering an immunological response and the production of a variety of immune players that promote inflammation.[26]

Acute Respiratory Distress Syndrome (ARDS)

ARDS emerged lethal outcome in upper and lower respiratory viral infection. In case of severe ARDS patients experience non-carcinogenic pulmonary oedema, hypoxaemia and that require mechanical ventilation is a life-threatening pathophysiological event.[27] Research and clinical studies have demonstrated that ARDS develops more frequently under the pneumonia condition primarily caused by bacterial and viral infections. Non-pulmonary sepsis is another cause of ARDS along with the transfusion associated acute lung injury.[28] ARDS is defined as complex immune phenomenon with several risk factors involved including drug overdose, hemorrhagic shock, re-perfusion injury, frozen plasma transfusion and pancreatitis etc.,[29] ARDS is common clinical manifestation in the respiratory infections where based on level of oxygenation defines severity of ARDS: mild, moderate and severe (Figure 1).[30] The mortality rate for ARDS, fast inflammatory deteriorates respiratory tissues, is severe and varies from 30 to 46%.[31] The most frequent condition causing ARDS is infectious pneumonia, with viral infections accounting for 22-40% of patients. The two viruses most frequently found in viral pneumonias are influenza and rhinovirus, parainfluenza, adenovirus, respiratory syncytial

virus, coronavirus and human metapneumovirus.[32] Recently, it was discovered that adenoviruses can cause infection in ARDS patients, whether they are ventilated or not. The percentage of viral pneumonia that develops into ARDS is unknown and it is also unclear how seriously these viral infections affect patient outcomes.[33]

Respiratory viral infections and inflammation

Inflammatory response (quick/prompt) and inflammation (severe) remain associated as central pathophysiological phenomenon with respiratory viral infections including *Coronavirus (CoVs), influenza, Respiratory Syncytial Virus (RSV), Parainfluenza Viruses* (type I-IV), *Human Metapneumovirus, Adenoviruses, Enteroviruses and Parechoviruses.*[25] Inflammation is defined as protective immune response against the viral infection and other stimuli where causative agent trigger/activate (up regulate and or down regulate) a wide range of inflammatory mediators: pro-inflammatory and anti-inflammatory.[34] Inflammation is double edged sword where failed immune response enables a persistent infection while severe case of immune response leads to chronic or systemic inflammatory diseases; cytokine storm in case of respiratory viral infections (Coronavirus and others).[24] Immune response function in two segment one innate immune recognize causative agent (Pathogen Associated Molecular Pattern; PAMPs).[35] Recognition of causative agents leads to over expression of downstream signaling pathways resulting massive outrange of pro-inflammatory immune molecules.[36] Causative agents recognition triggers inflammasome primarily involve in the death of inflammatory cells along with cleave of pro-inflammatory family e.g. IL 1 family. Inflammasome activation also leads to the pyroptosis process via generation of bioactive forms of interleukins; IL-1β and IL-18. It is important to note here host immune response under respiratory virus infections require a balance between pathogen recognition and virus clearance.[37] A complicated, multifaceted response reported in pulmonary epithelia, different immune cells control adaptive immune cells necessary for viral clearance and infection resolution.[38,39]

Respiratory viral infections and inflammatory cytokines

A cytokine is a class of signaling molecule that is unlashed by immune cells e.g. helper T cells (Th) and macrophages, as well as several other cell types that induce inflammation.[40] Cytokines can be either pro-inflammatory or inflammatory. Respiratory viral infection *Coronavirus (CoVs), influenza, Respiratory Syncytial Virus (RSV), Parainfluenza Viruses (type I-IV), Human Metapneumovirus, Adenoviruses, Enteroviruses and Parechoviruses* trigger a massive volume and variety of pro-inflammatory immune molecules that affect the vital organs.[41] Interestingly pro-inflammatory mediators with the higher trigger potential reported equal across various viral infection is not explored completely. Numerous studies have shown that viral infections may result in a variety of problems in patients,

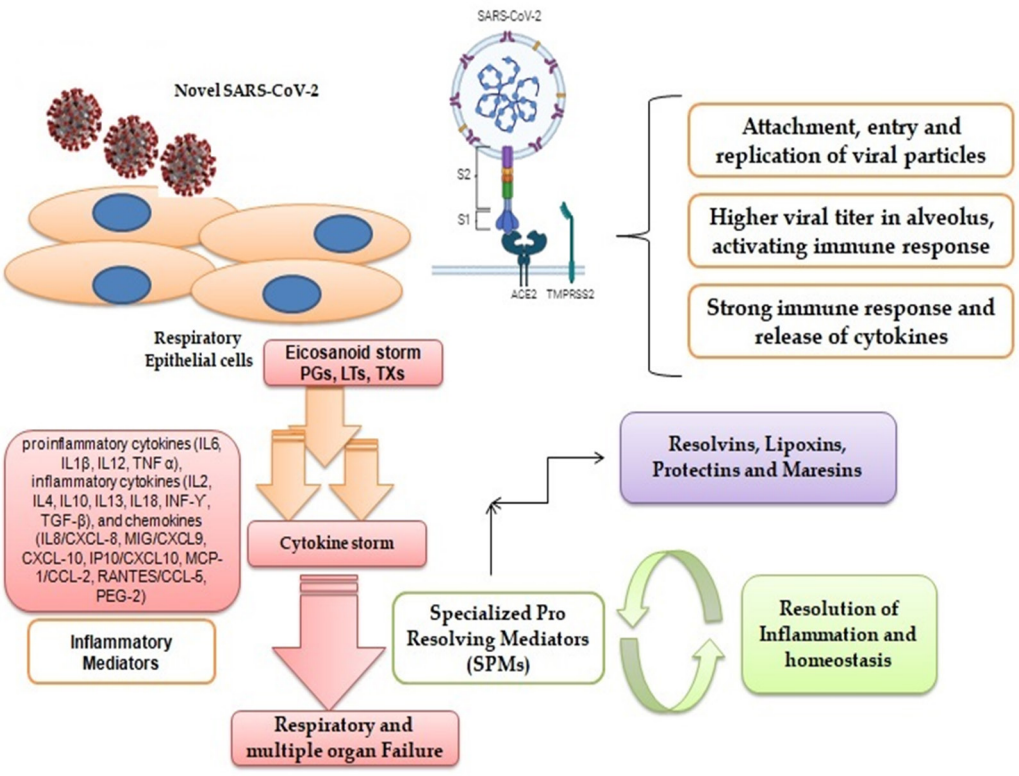


Figure 1: The figure depicts the mechanism of novel SARS-CoV-2 mediated inflammation via cytokine storm and the role of SPMs in resolving inflammation.

leading to impaired functioning of many organs.[42] It might due to overreacting to the viruses, which could harm important organs, increase pathogenecity and increase death.[43] Studies have demonstrated that influenza variants H5N1 activate/triggers a cytokine storm, along with IFN-β, IL-6, IP-10 and SARS patients demonstrated an up-regulated pro-inflammatory cytokines in serum [e.g., IFN-γ, IP-10, IL-1b, 6,12 and MCP-1, linked with pulmonary inflammation and extensive lung damage.[44] Up-regulated pro-inflammatory mediators e.g. TNF, IL-15 and IL-17, have been linked to the MERS infection. Further studies have demonstrated that the inflammatory signaling molecules higher inflammatory potential across various virus infections not yet explored completely.[45] There are lacks of *in vitro* and *in vivo* platforms for accurate prediction of dynamics of these cytokines and it is unclear which of these cytokines is the most important in tackling ARDS.

Respiratory viral infections and Pro-Inflammatory cytokines

Viral infection primarily targets and infects epithelia of upper respiratory tissues and triggers a prompt immune response.[46] Among the virus mediated immune response cytokine and interferon are key immune mediators associated with entire immune cascade. Given that cytokines direct and activate the adaptive immune response, pro-inflammatory cytokines are thought to be crucial in pig respiratory infections.[47] Despite the findings of earlier co-infection research, lesser scientific evidences are available in context with one virus affects another in terms of the local immune response. Because they direct and activate the adaptive immune response, pro-inflammatory cytokines are thought to be crucial in animal respiratory infections.[48] A high cytokine level, however, can cause tissue damage and worsen the course of the disease. In the recent viral outbreak i.e., SARS-CoV-2 that bind to ACE2 receptor ubiquitous express on the epithelial cell of respiratory tract. Severe lung injury linked with massive expression of pro-inflammatory cytokines IL-6, 8, TNF-α under NF-kB up-regulations.[49] ACE2 is key receptor/target for the SARS-CoV-2 that alters rennin Angiotensin system (RAS) via a catalytic breakdown of Angiotensin II to Angiotensin 1-7. In severe case of COVID-19, the key cytokine as pro-inflammatory mediator IL 6 that stimulates mono nuclear cells to express tissue factors mediate a massive inflammatory mediator flow into the injuries lung tissues.[50] Outrange of cytokines and other immune molecules e.g. TNF, IL-1, IL-6-8, MAS causes' expression of TF by neutrophil, endothelial cells and macrophages in the lungs, which starts and intensifies microvascular thrombosis and pulmonary coagulopathy.[51] Increasing clinical evidences demonstrated the up-regulated level of inflammatory mediators as pro inflammatory cytokines in severely chronic COVID-19 patients are IL6, 8, 12, IFN-γ, MCP1 and IP10 (Table 1).[52] Earlier in the outbreak of MERS-CoV infected patients showed a prompt pro-inflammatory Th1/Th17 response releases IFN-γ, TNF-α, IL-15 and IL-17. Other respiratory viral infection also triggers innate immune response and release of pro-inflammatory mediators.[53] Research and clinical studies demonstrated avian influenza infection leads to two classes of immune responses where in first phase immune cell releases RANTES, IFN-α, IFN-β, MCP-1, IL-8 and IFN-κ as early responses.[54] However, infected macrophages in the lower respiratory tract releases IL-1α/β, IL-6, TNF-α, IL-18, IFN type I, MCP-1, MIP-1α, MIP-1b, RANTES, MCP-3, MIP-3α and IP-10.[55]

Respiratory viral infections and Cytokine Storm

A condition referred to as Cytokine Release Syndrome (CRS), referred as cytokine storm or cytokine-associated toxicity reported when immune system reacts excessively to an infection.[58] Multiple Organ Failure (MOF), hyperferritinemia, haemodynamic instability and overwhelming systemic inflammation are all symptoms of the urgent clinical condition known as "cytokine

Table 1: Table summarizes key pro inflammatory cytokines and chemokines associated with key respiratory viral infection in CSS.[56,57]

Virus and serotypes	Immune cells	Pro inflammatory cytokines
SARS-CoV	Macrophages, Activated Th1 cells, NK cells.	IP-10, IL-8, IFN-γ, IL-1, TGF-β, MCP-1, MIG, IL-6, IL-12.
MERS-CoV	Macrophages, Activated Th1 cells, NK cells Antigen Presenting Cells (APCs).	IL-2, IL-6, IL-8, CCL-5, IFN-α, IL-1β, MCP-1, MIP-1a.
SARS-CoV2	Macrophages, Activated Th1 cells, NK cells Activated Th2 cells, CD8+ T and B.	Interleukin 1, 6, 8, 12, IFN-γ MCP-1 and IP-10.
Influenza	Macrophages, neutrophil B cells, macrophages.	IFN-γ, TNF-α, IL-6-9, IL15-17, IL-12p70.
Respiratory Syncytial Virus	Macrophages Lymphocytes T cells, monocytes.	IFN-γ, TNF-α, IL-1β, IL-2, sIL2Rα, IL-6, IL-10, IL-12, IL-18.

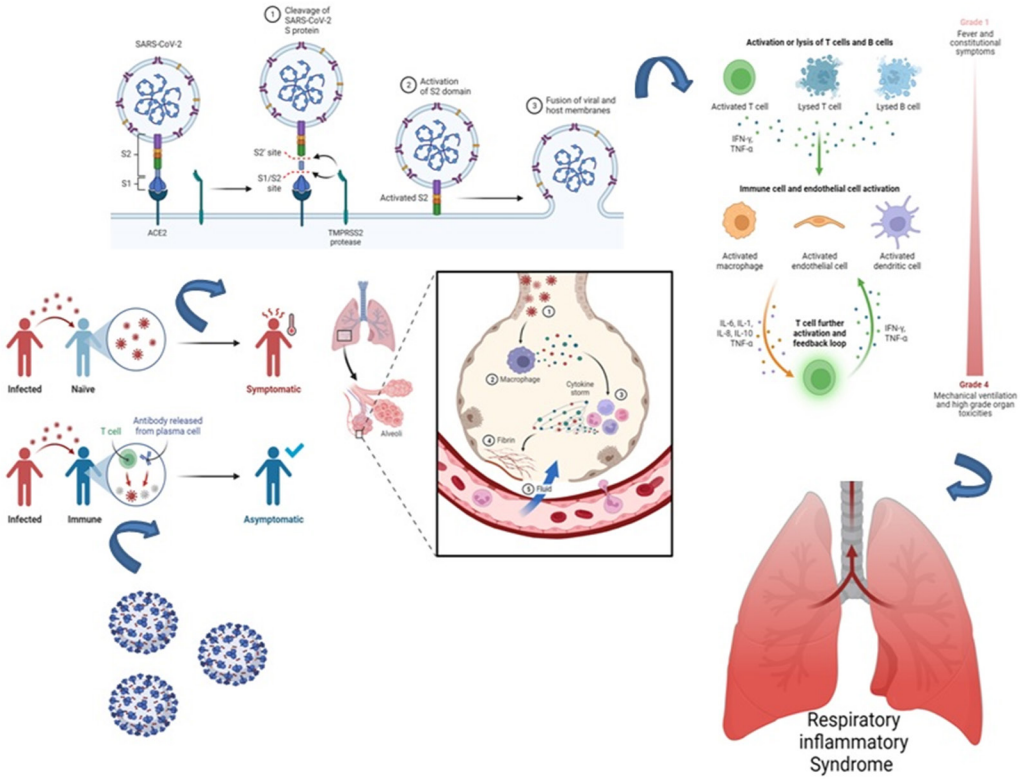
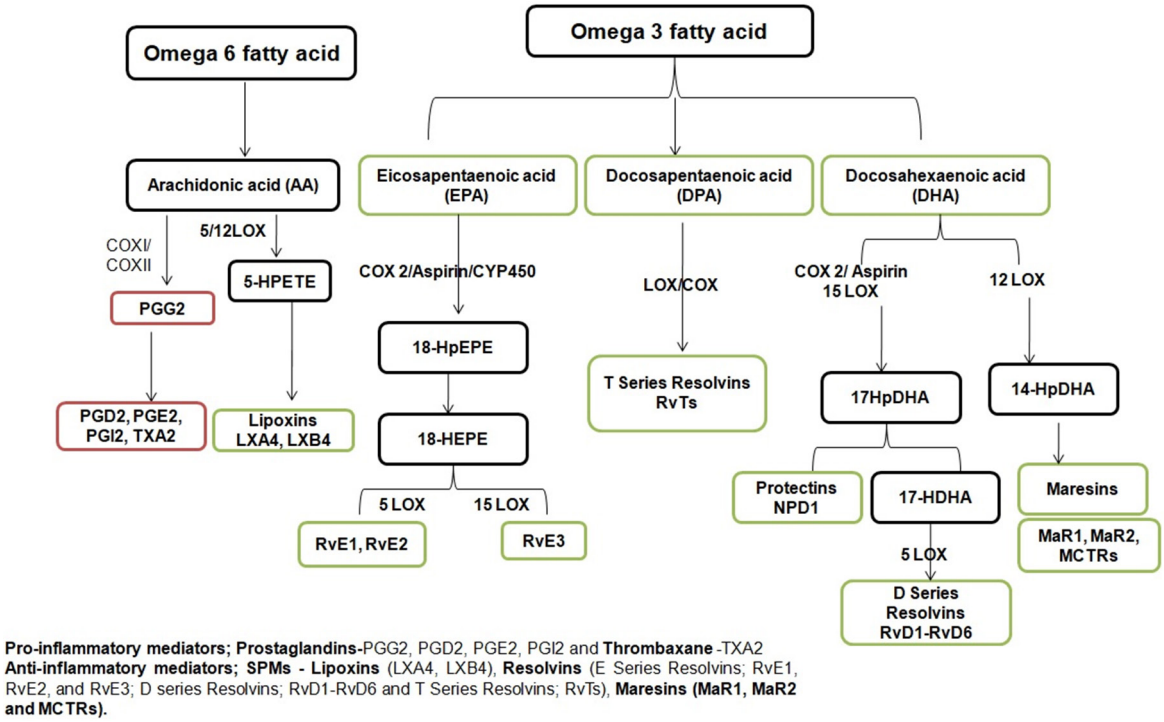


Figure 2: The figure demonstrates the mechanism of cytokine storm syndrome associated with the respiratory viral infection triggering a massive immune response.



Pro-inflammatory mediators; Prostaglandins-PGG2, PGD2, PGE2, PGI2 and **Thrombaxane** -TXA2
Anti-inflammatory mediators; SPMs - Lipoxins (LXA4, LXB4), **Resolvins** (E Series Resolvins; RvE1, RvE2, and RvE3; D series Resolvins; RvD1-RvD6 and T Series Resolvins; RvTs), **Maresins (MaR1, MaR2 and MCTRs).**

Figure 3: The figure describes the biosynthesis of Specialized Pro-resolving Mediators (SPMs). Both PUFAs ω-3 and ω-6 serves as the substrate for enzymes, including LOX/COX for the biosynthesis of SPMs.

storm syndrome," or CSS.[58] For individuals with SARS-CoV or MERS-CoV infections, ARDS is the main cause of death.[59] It is now recognized that an array of pro-inflammatory cytokines, including CCL2, CCL5, IP-10, IL-6, IL-8 and IL-1, reactive oxygen species and granulocyte-macrophage colony-stimulating factor. Cytokines are pro-inflammatory molecules produced by various immune cells.[59] Coronaviruses are enveloped viruses with RNA single strand as genetic material range up to 30kb. These viruses infect animals and complete the life cycle in five stages, including attachment, penetration, biosynthesis, maturation and release.[60] The physiological association of pro-inflammatory cytokines in HCoVs infections has been established in animal models. A successful infection and entry of coronaviruses primarily affect the respiratory system; lower respiratory tract. The viruses rapidly replicate and increase the cellular load and simultaneously trigger immune system for an immune response where both innate and humoral immunity get involved (Figure 2).[61] T cells initiate a preliminary reaction against SARS-CoV-2 infection via antigen presentation utilizing dendritic cells and macrophage.[62] These T cells with viral antigen as an Antigen-Presenting Cell (APC) travel to the lymph node where CD+4 and CD8+T cells are involved in a critical immune response against these cells. CD+4 and CD+8 cells work differentially in response to APC. CD+4 T cell stimulates B cells to produce SARS-CoV-2 specific immune molecules such as antibodies and inflammatory cytokines, while CD+T cells act as killer cells.[63] The immunological response can correlate patients' symptoms, such as asymptomatic, mild, moderate, severe and chronic. Under SARS-CoV-2 infection, a series of immune mediators are produced as a result of host immunological response, including pro-inflammatory cytokines (IL6, IL1β, IL12, TNF α, etc.), inflammatory cytokines (IL2, IL4, IL10, IL13, IL18, INF-ϒ, TGF-β, etc.) and chemokines (IL8/CXCL-8, MIG/CXCL9, CXCL-10, IP10/CXCL10, MCP-1/CCL-2, RANTES/CCL-5 and PEG-2).[64,65] There is growing research findings have demonstrated that the SARS-CoV-2 infection also damages the lymph node may affect T cell function, antigen-presenting cells.[66] Further, a drastic rise in pro-inflammatory, inflammatory cytokines and chemokines during SARS-CoV-2 conditions, primarily lower respiratory tract; lung epithelia trigger massive inflammation, accumulation of fluid and mucus leading to respiratory collapse.[67,68]

Anti-inflammatory cytokines

Anti-inflammatory mediators/cytokines are classes of bio-molecules regulate inflammatory immune activity primarily antagonize the effect of pro-inflammatory cytokines.[69] The IL-1 receptor antagonist, IL-4 and IL10-13 are important anti-inflammatory cytokines. Depending on the situation, the CLIF, INFα, IL-6 and TGF are anti-inflammatory and pro-inflammatory.[70] Pro-inflammatory cytokines are inhibited by specific cytokine receptors for IL-1, TNF-α and IL-18. For effective resolution of inflammation and tackling of cytokine storm syndrome role of anti-inflammatory cytokines becomes crucial.[71] Among, anti-inflammatory cytokines IL-10 reported most potent by inhibiting the expression of pro-inflammatory cytokines by activated macrophages such TNF-α, IL1, 6. In addition, endogenous anti-cytokines and pro-inflammatory cytokine receptors can both be regulated by IL-10.[72] The binding of long-chain fatty acids, particularly DHA but not eicosapentaenoic acid, to the GPR120 receptor in macrophages attenuate NF-kB activation and lower the generation of inflammatory cytokines.[73] Above action demonstrates that EPA and DHA may demonstrate anti-inflammatory benefits irrespective of altering the synthesis of lipid mediators or integrating into cell membranes.[74]

Poly Unsaturated Fatty Acids (PUFAs)

PUFAs are long chain unsaturated fatty acids essential for physiology. PUFAs ω-3 and ω-6 with longer carbon backbone synthesized from the Essential Fatty Acids (EFAs) Alpha-Linolenic Acid (ALA) and linoleic acid, respectively.[75] N-6 polyunsaturated fatty acid consumption vastly outpaces that of n-3 polyunsaturated fatty acid (Figure 3).[76] PUFAs ω-6 such as arachidonic acid produces the eicosanoid family of inflammatory mediators (prostaglandins, leukotrienes and related metabolites), which in turn controls the immune system's various balances and the activities of immune system and immune cells involve in inflammatory cascade.[77] The numerous double bonds of PUFAs ω-3 can physically alter how proinflammatory chemicals are expressed when NF-kB is activated.[78] The double bonds may block the generation of H_2O_2, activates NF-kB and the induce expression cell surface molecules such as adhesion molecule, by inactivating $O2^{\bullet-}$ synthesized in cytokine-induced intracellular signal transduction.[79,80] It has been suggested that administering an adequate concentration of PUFAs ω-3 could advance recovery of COVID-19 patients since PUFAs ω-3 diminish inflammatory immune response, which are highly common in critically ill COVID-19 patients and may also decrease virus replication.[81] Contrary to anti-inflammatory medications utilized during therapy and fail to offer prophylactics, PUFAs ω-3 can function as a preventative against viral.[82]

Anti-inflammatory potential of PUFAs

PUFAs ω-3, mainly EPA and DHA, possess strong anti-inflammatory property. Anti-inflammatory property of PUFAs ω-3 is due to their ability to restrict the eicosanoids synthesis derived from n-6 PUFAs (e.g., Arachidonic acid), which have proinflammatory and immunoactive functions.[83] PUFAs ω-3 fatty acids derived EPA and DHA is active metabolites with an immense potential for the resolution of inflammation.[84] During the inflammation several cellular events such as leucocyte chemotaxis, adhesion molecule expression, interactions between leucocytes and endothelial cells, biosynthesis of eicosanoids like prostaglandins and leukotrienes from the PUFAs ω-3 such as AA and the biosynthesis of pro-inflammatory cytokines, can

be partially inhibited by these fatty acids.[85] Additionally, EPA and DHA form eicosanoids such as Resolvins, protectins and Maresins, which are mediators that reduce inflammation and frequently have lesser biological efficacy than those made from AA.[86] EPA and DHA anti-inflammatory response are mediated by changing cell membrane phospholipid fatty acid composition, disruption of lipid rafts, inhibition of nuclear factor-B activation, which decreases the expression of inflammatory genes and activation of peroxisome proliferators-activated receptor, which inhibits NF-kB activation.[87]

PUFAs in tackling cytokine storm syndrome

Eicosanoids are signaling molecules derived from enzymatic and or oxidative outcome of Arachidonic acid and PUFAs.[88] These are signaling molecules are more closely associated with the controlled immune response against infections and injury.[89] Eicosanoid signaling is primarily related to pro-inflammatory response, but recent findings demonstrated that a selected eicosanoid, bioactive lipid mediators are anti-inflammatory and pro-resolving (Figure 4).[90] The formation of inflammasome in response to infection and injury drives a local immune response via the accumulation of bioactive lipid mediators, leukotrienes and prostaglandins result in a pro-inflammatory cascade.[91] During nSARS-CoV-2 infection, a massive rise in pro-inflammatory eicosanoids also triggers cytokine storm as well. Eicosanoids offer antiviral properties via enhancing B cell production and lymphocyte activity[92] These selected eicosanoids will be an ideal candidate to resolve eicosanoid storm and valuable in the CoVID-19 caused nSARS-CoV-2.[93] In fact, 17-hydroxy Docosahexaenoic acid (17-HDHA) in combination with other SMPs had shown a promising response as an adjuvant in influenza vaccine development.[94] Thrombosis remains a key hallmark in CoVID-19, primarily in chronic infection of nSARS-CoV-2 hence, Resolvins and EETs are crucial to diminish thrombotic complications. These eicosanoids reported promising in offering a resolution of inflammation over conventional COX inhibitors. Several SPMs (EETs and others) were evaluated to resolve local and systemic inflammatory responses and could be a potential candidate for CoVID-19. In moderate and chronic SARS-CoV-2, a severe inflammatory response is a hallmark and anti-inflammatory therapeutics is crucial in CoVID-19 management.[95] Specialized Pro-Resolving Mediators (SPMs) are enzymatic lipid-derived bio-active molecules and intermediates possess the immense capacity to balance inflammatory cascade.[96]

The growing research evidence demonstrated that Specialized Pro-resolving Mediators (SPMs), including Resolvins, lipoxins and protectin, mediate endogenous resolution by stimulating macrophage phagocytosis of cellular debris and countering the release of pro-inflammatory cytokines/chemokines.[97] The preponderance of research data on SPMs shows that omega 3 fatty acids are ideal sources of Eicosapentaenoic Acid (EPA), DHA and DPA. These fatty acids, through a series of enzymatic degradation, give rise to a series of SPMs and most studies E series (EPA) and D series Resolvins (DHA). The SPMs possess potent

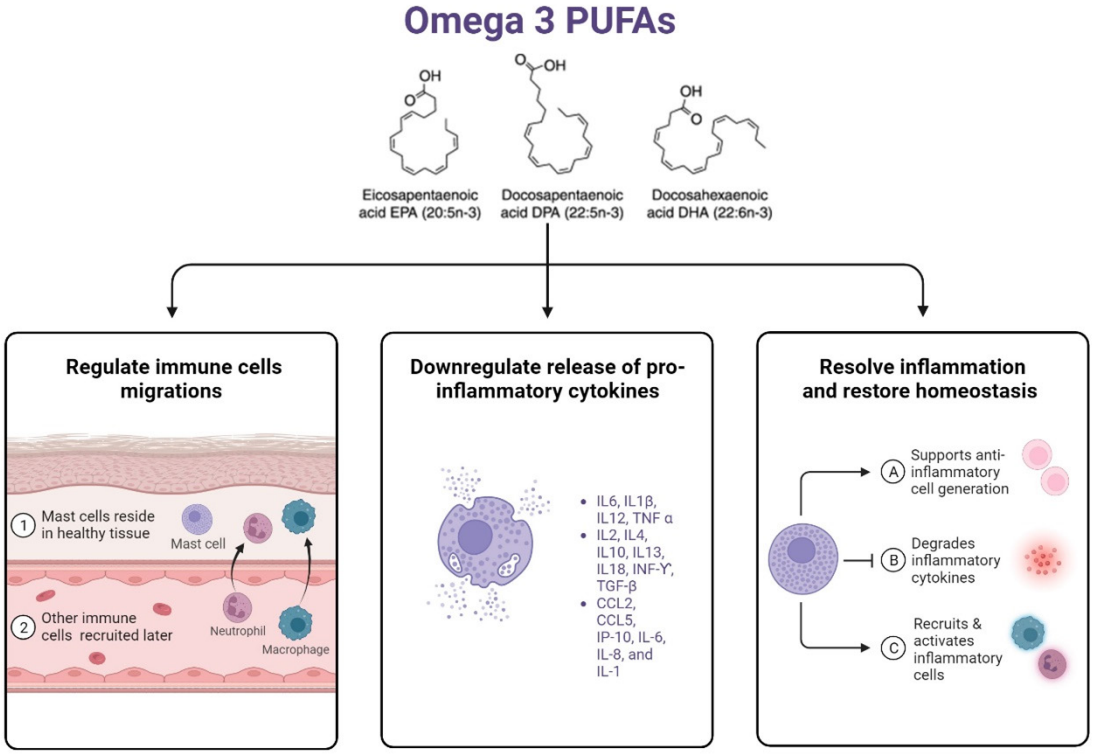


Figure 4: Figure demonstrates anti inflammatory role of PUFAs (ω-3) in cytokine storm syndrome as major clinical manifestation of respiratory viral infections.

and diverse pharmacological activities that include blocking Polymorphonuclear Neutrophil (PMN) recruitment at the site of inflammation, reduction of chemotaxis, blocks prostaglandins and leukotrienes and reduce cytokine release and functions as well. Additionally, SPMs remain associated with enhanced antimicrobial defense mechanisms and clearance at the mucosal surface, updating and removing apoptotic PMN and microbial particles by macrophages. The major precursor of SPM in humans is reported as AA, EPA, DHA and Docosapentaenoic Acid (DPA).[98] Through a series of enzymatic degradation/conversion, these molecules result in bioactive lipoxins, Resolvins (E and D series) and protectins. In a recent finding, Halade *et al*. 2018 studied new aspects of fatty acid drug discovery, including biosynthesis and the biological role of various SPMs in humans.[99] The enzyme involves in the biosynthesis of SPMs from PUFAs ω-3 are COX, LOX and their isoforms. There are growing studies, Verma *et al*. 2016, 2017 has shown enzymes are highly promiscuous and may catalyze multiple reactions resulting in a series of products and intermediate. Biosynthesis of a wide range of bioactive SPMs from omega 3 fatty acids under COX/LOX (12/15LOX) is likely due to enzyme promiscuity.[100,101]Prophylactic role of PUFAs (ω-3) in respiratory illnesses via cytokine modulation

Virus based respiratory infections accounts for 60% of respiratory illness including mild, moderate and severe cases of ARDS. The overwhelming clinical, *ex vivo* and *in vivo* have demonstrated that dietary intake of PUFAs primarily ω-3 reduces risk of severe case of COVID-19 and other respiratory illnesses. Integrated research demonstrates that polyunsaturated fatty acids and infectious illnesses are related. Studies have demonstrated the (ω-3) PUFAs offer effective resolution of inflammation via down regulating pro inflammatory cytokines biogenesis and trigger anti-inflammatory cytokines. Baral *et al*., 2022[102] evaluated respiratory illness reduction under dietary intake of PUFAs and reported Docosahexaenoic acid-derived Resolvins, protectins and Maresins reduce inflammation and promote phagocytosis, which reduces microbial load. In an 8-week clinical trial, De Souza *et al*. 2020[103] reported supplementing patients with 1.5 gm EPA and 1.0 gm DHA reduced levels of the inflammatory biomarkers (IL-1,6, TNF-α). PUFAs both ω-3 and ω-6 along with their enzymatic metabolites offer anti-inflammatory activity via different modes.[104] The underlying mechanisms of EPA and DHA's anti-inflammatory action include disabling leukocyte chemotaxis, down regulation of cell surface molecules e.g. adhesion molecule and leukocyte-endothelial adhesive interactions, lipid rafts disabling, fail to trigger NF-kB, activation of Peroxisome Proliferators-Activated Receptor gamma (PPAR) and binding to GPCR.[105] Desaturase, which are necessary to produce AA, EPA and DHA from their substrates LA and ALA, are blocked by pro-inflammatory TNF-α and IL-6. Additionally, an up-regulated immune activity and an up regulation of pro-inflammatory TNF-α and IL-6 during COVID-19 infection led to a cellular deficiency in AA, EPA and DHA.[106]

As a result, the synthesis of anti-inflammatory mediators e.g. SPMs are reduced. Intake of PUFAs ω-3 rich diet can make up for the deficiency, help to reduce inflammation and guard against cytokine storms in severe COVID-19.[107] Respiratory viral infection triggers prompt immune response that involves recognition of pathogen, release of pro-inflammatory cytokine and immune clearance. Previous findings demonstrated that the dietary consumption of PUFAs ω-3 boost immune function in recognition of pathogen, phagocytosis, release of inflammatory cytokines and immune clearance.[107] In general, PUFAs have a significant impact on the signaling and operation of T cells as well. The amount of PUFAs present in the phagocytic cell membrane significantly affects the immune cells' ability to phagocytose. It is proposed that the intake and integration of fatty acids (*Cis and Trans*) have a significant influence on the engulf of virus by macrophage.[76] The amount of phagocytic activity by phagocytic cells increases in direct proportion to the amount of PUFAs. Anti-inflammatory activity during respiratory viral infection and illness is affected by function of Antigen Presenting Cells (APC). APC is a cell that expresses antigen via the Major Histocompatibility Complex (MHC) proteins on its membrane surface. T lymphocyte cells can identify this complex.[108] Lymphocyte that present pathogen antigen, which causes the demise of APCs, involves MHC-1 and MHC-2. Studies have shown that higher plasma level of EPA and DHA reduced expression of APC and drive a poor immune response. PUFAs ω-3 have a significant impact on the composition and operation of platelets.[109] Phospholipid content of the plasma membrane may change in response to PUFAs ω-3 and ω-6 supplementation. The respiratory viral infections and associated illness linked with impaired platelet's function that further trigger systemic inflammation via release of wide range of pro-inflammatory.[110]

As it comes to SARS-CoV-2 human infection, limited research work have examined the immune-modulator potential of ω-3: PUFAs on respiratory epithelial cells or respiratory cell infected *ex vivo* models.[111] Earlier, Szabo *et al*., 2020[112] reported expressions level of pro inflammatory cytokines under the EPA and DHA supplementation in Calu-3 human lung epithelial cells. Here study reports no change in the release of pro inflammatory cytokines in DHA treated Calu-3 cells. On the contrary, EPA treated Calu-3 cells showed a sharp decline pro-inflammatory cytokines i.e., IL-6 and IP-10 from infected cells. Another study where A549 human alveolar epithelial cells exposed with DHA trigger and releases anti-inflammatory cytokine IL-10.[113] Earlier, Cotogni *et al*., 2011[114] reported exposures of DHA and EPA in 1:2 ratios reduce COX2 level and trigger PEG2 expression. These events further promote NF-kB translocation into the nucleolus and release of anti-inflammatory cytokine IL-10 via PRARy activation. PUFAs, ω-3; EPA and DHA have shown tremendous potential in immune modulation; down regulation of pro-inflammatory cytokines (IL-1β, IL 2, 6, 8, IFN-α, MCP-1, MIP-1a, CCL-5) and up-regulation of anti-inflammatory cytokines (IL-4 and

IL-10-13). In primary human and murine macrophages as well as in macrophage cell lines, EPA and DHA suppressed the NLRP3 inflammasome.[111] Additionally; PUFAs ω-3 capacity to down regulate M1 macrophage polarization and promote M2 polarization in mouse macrophages and macrophage cell lines is what allows them to decrease the generation of pro-inflammatory cytokines by macrophages against LPS stimulation.

These studies clearly demonstrate dual role of PUFAs; ω-3; EPA and DHA in tackling respiratory illness via modulating pro-inflammatory cytokines (down regulation) and anti-inflammatory cytokines (up-regulation). Additionally, PUFAs ω-3; EPA and DHA also boost immune functioning by alleviation of pathogen recognition, phagocytosis and clearance. PUFAs; ω-3; EPA and DHA and enzymatic products offer a vital potential while tackling respiratory illness associated with the influenza infection. Schultz *et al*., 2019[115] showed PUFAs metabolites 12-HETE, 15-HETE, 17-HDoHE inhibits influenza infection. Morita *et al*., 2013[116] reported PUFAs enzymatic metabolite PD1 inhibits nuclear export of influenza mRNA. Oguin *et al*., 2014[117] investigated PUFAs metabolite PLD promotes host innate immune evasion by influenza. PUFAs; ω-3; EPA and DHA derived bioactive lipid mediators called as SPMs mediate resolution of inflammation is well established and validated; however, potential in the case of COVID-19 is recently hypothesized. There is no direct clinical evidence showing the potential of SPMs in tackling cytokine storm and resolution of inflammation in the case of COVID-19 disease but based on similar findings such as influenza, a precise dose of endogenous lipid mediators can resolve inflammation and create homeostasis in local tissue. These endogenous lipid-derived molecules and intermediates are immensely active and potent in promoting B cell antibodies and lymphocytes activity. The growing scientific literature demonstrated SPMs, including protectins and Resolvins (E and D series), are competent to resolve the inflammation and restore functions. In COVID-19 disease, ARDS and multiple organ failure provide a challenging task for SPMs to combat cytokine storms and eicosanoid mediated cytokine storms.[118] Several studies are underway using SPMs as candidates for clinical trial studies to resolve inflammation (NCT04308889 and NCT03606252).[116-119] The outcomes from such clinical trials provide candidature of SPMs in COVID-19 disease management. As there is no specific therapeutic available for COVID-19 and vaccine development is underway, a trial on SPMs, will be worth a try. Considering the research database, these mediators' pro-resolution actions are exemplified by their role in pulmonary inflammation primarily caused by viral infections, including influenza and others.[120]

CONCLUSION

Upper and lower respiratory infections mainly viral are leading pose of ARDS where coronaviruses and influenza infections account for more than 70%. Respiratory illness due to respiratory virus infections triggers prompt immune responses where an array of pro-inflammatory cytokine causes respiratory collapse due to the cytokine storm syndrome. The key respiratory viruses that *infect upper respiratory epithelia are Coronavirus (CoVs), influenza, Respiratory Syncytial Virus (RSV), Parainfluenza Virus 1-4, Human Metapneumovirus, Adenoviruses, Enteroviruses and Parechoviruses.* ARDS and multiple organ failure as a result of cytokine storm is the primary cause of death in case of COVID-19 and other respiratory viral infections. Inflammatory mediators mainly pro-inflammatory cytokines (over expression) and anti-inflammatory cytokines (under expression) are key immune players involve in the ARDS and CSS. Studies have reported the PUFAs precisely ω-3 attenuate of pro-inflammatory cytokine, same time promote expression of anti-inflammatory cytokines. Dual role of PUFAs (ω-3) in regulation of inflammatory immune mediators offer a protective role in respiratory viral infection mediated ARDS and CSS. There are grown clinical and animal studies demonstrated that ω-3 PUFAs reduce hospital stay of patients during chronic respiratory viral infections including SARS-CoV. On the contrary, studies have showed that PUFAs ω-3 possess potential to resolve the inflammation compare to the PUFAs ω-6. Further, it has been reported that the PUFAs ω-3 possess higher affinity with LOX/COX compare PUFAs ω-6. Hence, a new strategy using endogenous specialized pro-resolving mediators is being explored to control cytokine storms and restore the vital function of respiratory tissue. These endogenous bioactive molecules and intermediates are synthesized from PUFAs (ω-3) such as EPA, DHA and DPA. COX and LOX enzymes and their iso-forms catalyze the biosynthesis of a series of bioactive lipid mediators, including Lipoxin, resolving, Protectins. The COX is also associated with the biosynthesis of pro-inflammatory cytokine based on available substrates. Dietary PUFAs are potential substrates for COX and LOX in the biosynthesis of SPMs. The preliminary clinical evidence shows that SPMs may resolve inflammation caused by a cytokine storm in the case of COVID-19, but based on previous studies; there is a growing consensus that SPMs will be part of future therapeutic against respiratory viral infection driven ARDS and CSS.

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CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

ABBREVIATIONS

ARDS: Acute respiratory distress syndrome; **SARS-CoV-2:** Severe Acute distress syndrome Coronavirus 2; **COVID19:** Coronavirus disease 2019; **CDC:** Centre for Disease Control; **COX:** Cyclooxygenase; **LOX:** Lipoxygenase; **WHO:** World Health Organization; **SPMs:** Specialized pro Resolving Mediators; **ACE:** Angiotensin-Converting Enzyme; **PMN:** Polymorphonuclear neutrophil; **EPA:** Eicosapentaenoic acid; **DHA:** Docosahexaenoic acid; a **DPA:** Docosapentaenoic acid; **CoVs:** Coronavirus; **RSV:** Respiratory Syncytial Virus; **CSS:** Cytokine storm syndrome; **IFN:** Interferon; **IL:** Interleukin; **MOF:** Multiple organ failure **TGF:** Transforming growth factor; **EFAs:** Essential FAs; **GPCR:** G protein-coupled receptor; **NF-B:** Nuclear Factor Kappa-B; **PPAR:** Peroxisome proliferators-activated receptor gamma; **APC:** Antigen-Presenting Cell; **HETE:** Hydroxydocosahexaenoic acid; **HDoHE:** Hydroxyeicosatetraenoic acids.

AUTHOR CONTRIBUTIONS

FFA conceptualized, structured and retrieved scientific literature interpreted the results and wrote the manuscript. FFA reviewed, edited and submitted to the journal.

SUMMARY

Respiratory viral infections trigger release of a wide array of inflammatory mediators and these immune players not only hamper respiratory functions but also pose risk of human health. Among the viral respiratory infection, a massive outrage of immune molecules triggers acute respiratory distress syndrome and cytokine storm syndrome. In the last two decades several viral outbreaks *Coronavirus (CoVs), influenza, Respiratory Syncytial Virus (RSV), Parainfluenza Viruses (type I-IV), Human Metapneumovirus, Adenoviruses, Enteroviruses and Parechoviruses results in a large number of patients with the* acute respiratory distress syndrome and cytokine storm syndrome symptoms. Uses of conventional therapeutics are effective however associated with the several complications as most of them work via anti-inflammatory mechanism. Resolution of Inflammation is reversal of inflammation where lipid mediators derived from PUFAs mainly omega 3 are promising one. Omega 3 PUFAs offer a wide array of bioactive lipid mediators called as Specialized Pro resolving Mediators (SPMs) with enormous potential in resolving inflammation. These bioactive lipid molecules are capable to tackle acute respiratory distress syndrome and cytokine storm syndrome as major clinical manifestation of respiratory viral infection.References

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