Review

How Fish and Shark-Derived Oils Affect Antiviral Immune Response – a Narrative Review

Natalia Paulina Bielecka-Kowalska * and Natalia Lewkowicz *

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Review

How Fish and Shark-Derived Oils Affect Antiviral Immune Response - A Narrative Review

Natalia Bielecka-Kowalska * and Natalia Lewkowicz

Department of Periodontology and Oral Diseases, Medical University, Łodz, Poland
* Correspondence: natalia.bielecka-kowalska@umed.lodz.pl

Abstract: Background/Objectives: For years, research has been conducted on the relationship between anti-inflammatory diets and the incidence and risk of various diseases. In recent years, much attention has been paid to the beneficial effects of fish oil (FO) or shark liver oil (SLO) consumption, which is increasingly being used clinically. Health benefits of FO have been associated mainly with omega-3 polyunsaturated fatty acids (n-3 PUFAs), but also alkylglycerols (AKGs) and squalene. n-3 PUFAs, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the main components of FO, have been shown interfere with host immunity, but also various stages of viral infection, particularly viral entry and replication. **Methods**: In this narrative review we tried to answer the question on the role of n-3 PUFAs, AKGs and squalene in modulation of antiviral response based on the available literature from 2001 to 2023, starting from in vitro and ex vivo studies through animal studies coming up to the human studies. **Conclusions**: In general, DHA and EPA have an inhibitory effect on the activation of both innate and adaptive immune cells, while squalene and AKGs were shown to enhance antimicrobial and antitumor immune response.

Keywords: omega-3 polyunsaturated fatty acids (n-3 PUFAs); DHA; EPA; fish oil (FO), shark liver oil (SLO); inflammation; dietary supplements; virus infection; antiviral

1. Introduction

Viral pandemics are becoming a real clinical challenge due to the nature of these infections, especially respiratory viral infections (RVI). Prevention and treatment are therefore of paramount importance in controlling the spread and course of the disease. Nutrition and supplementation to strengthen the efficacy of immune system is an important and debated element.[1]

Western diet is high in saturated fat, sugar, refined carbohydrates, protein and salt, and low in fibre and fruits. [1,2] In addition, food is subjected to many industrial processes, which is why it is called ultra-processed food (UPF). Dietary habits are related to prevalence of metabolic syndrome and non-communicable chronic diseases. Individuals with unhealthy dietary patterns have been found to have higher levels of exogenous advanced glycation end products (AGEs). The deficiency of n-3 fatty acids and the accumulation of excessive amounts of saturated fatty acids (SFAs) as a result of a Western diet can affect the health of the gastrointestinal tract (including the mucosal barrier) and the brain, while at the same time acting as a pro-inflammatory signal in the periphery [3]alters lipoprotein profile which, in turn, can adversely affect the course of viral infections.[4,5] Other adverse effects of the Western diet, such as learning and memory deficits, depressive disorders and neurodegenerative diseases, are well documented in the literature. [6,7]

Fish oil (FO) is mainly a source of n-3 polyunsaturated fatty acids (PUFAs), but it additionally contains alkylglycerols (AKGs), squalene, minerals, vitamins A and D. Shark liver oil (SLO) contains both AKGs and squalene. [8,9] The components of fish oils have a wide range of applications in the pharmaceutical and cosmetic industries. For example, squalene is used as a drug carrier, detoxifier, skin moisturiser and emollient. This has made it important to the nutraceutical and pharmaceutical industries. [10]Many studies have shown that fish products are promising candidates for many health benefits. The health benefits of FO and SLO supplementation have been studied for years. FO and SLO has the potential to modify the immune response and can also be used in therapy of various

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inflammatory diseases. Specifically, benefits were demonstrated in promoting wound healing, inflammatory diseases such as asthma, gastrointestinal disorders, cancer and skin diseases, including preventing cardiovascular diseases, chronic and metabolic diseases such as diabetes, obesity, osteoporosis, arthritis, neurological degeneration and bone fractures. SLO and FO are very popular in traditional medicine. [3,11,12]

In contrast, relatively little is known about the potential effects of FO and SLO on the anti-viral immune reaction. Although, there is an emerging literature investigating the relationship between FO and SLO intake and antiviral response, it mainly focuses on n-3 PUFAs. Systematic reviews focusing on the other components of FO and SLO are lacking. Understanding how this supplementation affects immune response is important for the development and implementation of dietary strategies to protect health. Therefore, the aim of this review was to determine how FO and SLO supplementation influences the antiviral immune response.

2. Materials and Methods

The literature search was conducted using several databases, including Pub Med and Pub Med Central, Cochrane Library, Google Scholar, Web of Science and Elsevier. The electronic literature search included articles in the English language that were published between 2001 and 2023. Forty articles were included. The search strategy was a combination of MeSH and keywords: “fish oil(s)"; "shark liver oil";” n-3 PUFA”, “DHA”, “EPA”, “"virus" or "antiviral".

3. N-3 PUFAs and Immune Response In Vitro and In Vivo

N-3 PUFAs, EPA and DHA are considered essential and must be obtained from the diet. Once ingested, EPA and DHA enter the bloodstream relatively quickly, are incorporated into the phospholipids of cell membranes and subsequently inhibit the activation of key transcription factors, such as nuclear factor κB (NFκB), which increase the expression of pro-inflammatory cytokine genes by cells involved in the inflammatory process.[3,6,13,14] EPA and DHA present at the site of inflammation are enzymatically converted into specialised pro-resolving mediators (SPMs), namely resolvins, protectins and maresins. SPMs are biologically active compounds formed by the action of COX, LOX and cytochrome P450 on EPA and DHA. These molecules exert potent anti-inflammatory effects and limit free radical formation by helping to regenerate and repair tissues. SPMs can inhibit the synthesis of pro-inflammatory cytokines. Among others, inhibitory effects on IL-1, IL-6 and IL-8 have been demonstrated. EPA-derived resolvins (E-series resolvins), DHA-derived resolvins (D-series resolvins) and DHA-derived proteins have anti-inflammatory effects. They reduce leukocyte infiltration into damaged tissue[15]. DHA-derived mediators stimulate macrophage uptake of apoptotic neutrophils, have antimicrobial effects and regulate resolution of inflammation. [13,14,16]

The effect of n-3 PUFAs on NK function is not well understood. NK cells are the innate lymphocytes. They do not require prior contact with antigen to be activated. They mediate immune response against tumour cells and virus-infected cells. The effect of FO on NK cell cytotoxic activity is not well understood and study results are conflicting. Supplementation with n-3 PUFAs in one of the studies resulted in a significant reduction in circulating NK cell levels (CD16+ CD56+) and their activity.[17] In another study, supplementation with EPA-rich oil had no effect on the number of circulating NK cells. [18] FO supplementation was found to increase IL-2 production by peripheral blood mononuclear cells (PBMCs) and cytotoxic activity of NK cells in the functional compartment after exercise. [19] Another study showed that moderate amounts of EPA can reduce NK cell activity in healthy individuals, mainly in people over 55 years of age. [20,21] This effect was completely reversed 4 weeks after discontinuation of supplementation.

n-3 PUFAs also affect macrophage function, promoting polarisation of M2 phenotype. M2 macrophages produced maresin-1 and lower amounts of leukotriene B4 and prostaglandin than M1.[20,22]

The effects of n-3 PUFAs on adaptive immune response is well documented. Mainly, inhibition of polarisation of CD4+ T cells into Th1 and Th17 cells was demonstrated. The mechanism of this phenomenon was probably based on modification of the IL-6/gp130/STAT3 pathway. [23] Another

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study showed that both EPA and DHA (to a lesser extent than EPA) dose-dependently reduced intracellular levels of immunostimulatory cytokines in Th cells: IL-2, TNF-, IL-4 with unchanged IFN. [24] n-3 PUFA supplementation reduces plasma IL-17 levels in children with asthma, consistent with reduced differentiation of CD4+ T cells into Th17 cells. [25] Fan et al. demonstrated that FO supplementation (4 g N-3 PUFA/d) for 6 weeks in healthy subjects increased the levels of EPA in the membrane phospholipids of CD4+ T cells and rearranged the membrane lipids and increased their fluidity. This study suggests that only higher doses of exogenous N-3 PUFA strongly enhance the anti-proliferative potential of exogenous n-3 PUFA in human primary CD4+ cells. [26,27] The differentiation of CD4+ T cells into Th17 and their activation is likely to be attenuated by n-3 PUFAs. In animal models, there are conflicting data on the effects of n-3 PUFAs on B-cell activation. EPA and DHA increased IgM production by B-cells without changing in IgA, IgG or IgD production by B-cells. [25] N-3 PUFAs also improved humoral immunity by influencing B cell development in the bone marrow, B cell activation and antibody production in response to antigen.[23]

4. N-3 PUFAs and Antiviral Immune Response

Several mechanisms have been proposed to explain mediation of antiviral activity of n-3 PUFAs. In general, the antiviral properties focus on targeting of infected cell membranes, free radical production and formation of cytotoxic lipid peroxides or bioactive immunomodulatory metabolites. [3,14] However, some studies identified more direct mechanisms protecting from viruses. n-3 PUFAs by modulating lipid rafts may inhibit angiotensin-converting enzyme 2 (ACE2)-induced of SARS-CoV-2 infection reducing viral entry. [19] EPA and ALA showed the highest efficacy in inhibiting the binding of viral myeloid protein receptor-binding domain (RBD) to the ACE2 receptor. In addition, ALA and EPA could also inhibit viral binding, membrane fusion and entry, inhibit the activity of transmembrane protease serine protease-2 (TMPRSS2) protease and cathepsin L, which facilitate the attachment and entry of SARS-CoV-2, but did not affect their expression at the protein level. [24] n-3 PUFAs were shown to directly inhibit of influenza virus replication. [16] Another studies demonstrated that DHA derivatives, DHA-derived D1-protectin isomer (PDX; 10S,17S-dihydroxy-4Z,7Z,11E,13Z,15E,19Z-docosahexaenoic acid) and D1-protectin (PD1; 10S,17R,-dihydroxy-4Z,7Z,11E,13E,15Z,19Z-docosahexaenoic acid) can inhibit influenza virus replication. It was probably an effect of inhibition of the nuclear export of influenza virus mRNA. [23,28]

The relevance of n-3 PUFA supplementation was studied in HIV-infected patients. According to a systematic review and meta-analysis by Morvaridzadeh et al. n-3 PUFA supplementation in HIV-infected patients resulted in a significant reduction in serum CRP levels compared to controls. However, no significant effect was shown for the levels of IL-6 and TNF-α. [16,21]

Interesting information on the effect of SPMs on viral diseases comes from studies in animal models. Morita et al. studied the effect of D1-protectin on the course of influenza caused by H5N1 virus in mice. In this study, they found that D1-protectin suppressed influenza virus replication and its administration improved survival and disease course.[29] Another study demonstrated that DHA-derived SPM supplementation resulted in the increase of antibody levels. [20] This led to greater immunity against the H1N1 influenza virus. In addition, it has been reported that DHA pre-treatment of Zika virus-infected SH-SY5Y cells increased cell viability, reduces the number of apoptotic cells, increased the proliferative capacity of infected cells, significantly reduced viral load and decreased the secretion of the pro-inflammatory IL-6 and monocyte chemoattractant protein-1, thereby suppressing the pro-inflammatory response induced by Zika virus.[14]

There are only a few studies on the effectiveness of n-3 PUFAs in patients with COVID-19. A study by MA and colleagues demonstrated the benefits of habitual FO use, reducing the risk of SARS-CoV-2 infection, COVID-19-related hospitalisation and death in this group.[18] According to an expert statement from the European Society for Parenteral and Enteral Nutrition, their use may improve oxygenation in patients with COVID-19, but this is not well documented. However, there are concerns about n-3 PUFAs, with evidence pointing to a counterintuitive increase in oxidative stress and inflammation due to increased susceptibility of cell membranes to damage. It is important to remember that PUFAs are highly susceptible to non-enzymatic oxidation and can be oxidised by

 doi:10.20944/preprints202411.0164.v1

ROS to alpha and beta-multisaturated lipid aldehydes. The molecules formed by the ROS-mediated oxidation of omega-6 and omega-3 fatty acids can act as bioactive molecules under physiological and/or pathological conditions. In summary, they can have both a pro-inflammatory and an anti-inflammatory effect on a variety of cells. Under normal conditions, these aldehydes are detoxified. However, under severe oxidative stress, they can induce mitochondrial dysfunction leading to apoptosis. [21] Oxidised phospholipids may be biomarkers for atherosclerosis and other pathologies. [17,18,20] N-3 PUFA supplementation in COVID-19 patients influenced the competing roles of lipid mediators, suggesting a pathological lipid mediator "storm" in severe COVID pneumonia. Patients with mild COVID-19 had higher plasma SPM levels (especially protectin conjugate in tissue regeneration 1 (PCTR1) PCTR3, maresin conjugates in tissue regeneration 3 (MCTRs3). [30]

There is some evidence in the literature to suggest that DHA supplementation during pregnancy may reduce the incidence of respiratory tract infections in children.[31] Other studies have shown a lower incidence of bronchiolitis in a group of children on omega-3 PUFA supplementation.[31,32] A study by Thienprasert et al showed that consuming n-3 PUFAs was associated with fewer episodes and shorter duration of upper respiratory tract infections (Tables 1 and 2).[19]

 doi:10.20944/preprints202411.0164.v1

Table 1. Effects of supplementing with N-3 PUFAs - Human studies. [17,24,26,33].

Study, Year	Population	Subjects	Supplementation	Duration of intervention	Results
Thies, 2001	healthy subjects aged 55–75 years.	n= 46	-Individuals in these groups consumed 2 g ALA, 770 mg GLA, 680 mg AA, 720 mg DHA or 1 g EPA plus DHA (720 mg EPA + 280 mg DHA) per day, respectively. The total fat intake from the capsules was 4 g/d.	12 eeks	-The daily supplementation of healthy older individuals with 700 mg of GLA, AA, or DHA, or 1 g of EPA plus DHA, resulted in a notable alteration in the fatty acid composition of plasma phospholipids. These changes were discernible after a period of four weeks. -The administration of fish oil resulted in a notable decline (mean reduction: 48%) in natural killer (NK) cell activity, which was fully reversed four weeks following the cessation of supplementation. -In contrast, a 12-week course of fish oil supplementation resulted in a significant reduction in natural killer (NK) cell activity.
Miles, 2006	healthy adult men aged between 18 and 42 years.	n= 93	-Four intervention groups: placebo, low epa (epa:1.35 ; dha: 0.3g/d) , moderate epa (epa: 2.7g/d ; dha: 0.6g/d) or high epa(epa: 4.05 g/d ; dha: 0.9 g/d) (n // 25/group). -The subjects consumed nine 1-g capsules daily. -Pronova biocare (lysaker, nor- way).	12 weeks	- EPA incorporation into the phospholipids of mononuclear cells was linear and dose-dependent. - EPA did not affect the proportion of T lymphocytes, helper T lymphocytes, cytotoxic T lymphocytes, B lymphocytes or natural killer cells in the circulation. The proliferation and function of T lymphocytes and natural killer cells was shown to be slightly altered in healthy young men. -There was no change in the production of the cytokines interleukin-2, interferon and interleukin-10. However, interleukin-4 production increased with increasing EPA supplementation. Natural killer cell activity was only slightly modified by the different therapies.
Mukaro,2008	• healthy subjects aged 23 to 63 years.	n=42	-Portions of fortified food provided 125 mg EPA + DHA, / consumption of eight	6 months	-The good news is that the levels of n-3 PUFAs in erythrocytes were higher in the cohort, while the absolute numbers of leukocytes and lymphocytes were lower.

 doi:10.20944/preprints202411.0164.v1

			servings per day, which equated to 1 g n-3 PUFA/day. -Maritex, Aarhus, Denmark.		-The good news is that there were no changes observed with regard to neutrophils, monocytes (CD3+), CD4+, CD8+ or CD19+ lymphocytes. -However, there was one little hiccup. The number of NK cells (CD3-CD16+CD56+) was a little lower in those who were taking n-3 supplements than in the control group. What's more, the drop in NK cell numbers was directly linked to the amount of eicosapentaenoic or docosahexaenoic acid present in the erythrocytes. -We didn't see a strong link between lymphoproliferation and the production of IFN-gamma and IL-2, but we did notice that lymphotoxin production increased with higher n-3 LCPUFA content in the cell membrane. -Similarly, we didn't see any changes in neutrophil chemotaxis, chemokinesis, bactericidal activity or adherence with changes in n-3 LCPUFA levels in red blood cells.
Fan, 2018	• healthy 60 to 87 years.	n=12	-All subjects consumed eight 1 g capsules, resulting in 4 g n-3 PUFA (approximately 2-4 g EPA + 1-6 g DHA) per day for 6 weeks. -Swanson Health Products	6/12 weeks	-The daily supplementation of 4 g n-3 PUFA resulted in a significant enrichment of EPA in CD4+ T-cell membrane phospholipids after 3 and 6 weeks. However, no significant enrichment of other n-3 PUFA was observed in total phospholipids or neutral lipid fractions. -FO uplementation changed the order of T cell membranes. Fan et al. Page 9 -Dietary n-3 PUFA supplementation does not alter metabolic and proliferative phenotypes of human CD4+ T cells

Table 2. FO and SLO supplementation and infections .[19,34].

 doi:10.20944/preprints202411.0164.v1

Study	Country, Yea	Population	Subjects	Supplementation	Duration of Intervention	Type of study	Results
Brunvoll	Norway, 2020-2021	adults (aged 18-75 years), not taking daily vitamin D supplements.	N= 34 601	5 mL/day of cod liver oil (10 µg of vitamin D, n=17 278) or placebo (n=17 323)	six months	Quadruple blinded, randomised placebo controlled trial.	Supplementation with cod liver oil in the winter did not reduce the incidence of SARS-CoV-2 infection, serious COVID-19, or other acute respiratory infections compared with placebo
Thienprasert	Thailand 2009	children (aged 9 to 12 years)	N=180	consumed milk containing placebo (soybean) oil (n = 86) or fish oil (n = 94) 200 mg eicosapentaenoic acid plus 1 g docosahexaenoic acid daily.	on 5 days per week for 6 months	randomized, double-blind, placebo-controlled intervention trial	The FO group had fewer episodes (p = .014) and shorter duration (p = .024) of disease (mainly upper respiratory tract) than the placebo group

 doi:10.20944/preprints202411.0164.v1

5. Squalene

Squalene is a natural lipophilic biomolecule. Squalene is a polyunsaturated triterpene that acts as a precursor to sterols and other bioactive terpenoids. Structurally similar to β-carotene, it is made up of six isoprene units. It is organic found in SLO, wheat germ, rice bran and olive oil. It is a potent adjuvant for influenza vaccines. It improves vaccine immunogenicity, even in immunocompromised patients. Antigen presentation and induction of inflammatory response enhanced by AKGs and squalene. [35] Squalene is thought to have an anti-inflammatory effect by reducing the excessive activation of neutrophils and monocytes and by increasing the activity of anti-inflammatory enzymes. Terpenoids appear to be antiviral agents. They activate membrane mechanisms and inhibit viral DNA synthesis. It has demonstrated anticancer activity due to its chemopreventive potential against cancer and antioxidant activity by directly scavenging reactive oxygen species (ROS). Nutritional squalene has anti-inflammatory effects by preventing an increase in cytokine levels. [9,36,37] Hillaireau et al. investigated the antiviral efficacy of squalenylated didanosine (ddI) and dideoxycytidine (ddC, zalcitabine) nanoparticles against HIV and the effect of squalenylation on nucleoside reverse transcriptase inhibitor (NRTI) absorption and biodistribution after oral administration to rats. The conjugation of nucleoside analogues with squalene leads to amphiphilic prodrugs that are capable of self-assembly. Squalenolysis is a promising method. Researchers showed that squalenylated prodrugs of NRTIs can enhance absorption and biodistribution, resulting in increased antiviral efficacy against HIV-infected cells.[38,39]

A clinical trial by Ebrahimi et al investigated the efficacy of squalene microemulsion in the treatment of COVID-19. The results showed that it had a significant effect on improving symptoms in intensive care patients. It reduced fever and cough during the treatment period and improved radiological parameters.[39]

6. Alkylglycerols

SLO is rich in AKGs in the form of monoalkyl-diacylglycerols (TG(O)). Marine sources of AKGs, such as the liver oil of certain species of sharks or elasmobranchs, contain high levels of these compounds. Literature suggests AKGs may be effective in improving haematopoiesis, reducing radiotherapy-induced injury , reducing tumour growth or improving vaccine efficacy. They are precursors of ether phospholipids involved in structuring and functioning the membranes of certain cells. They are found in white blood cells, macrophages, bone marrow lipids and milk.[39,40]

They are immunologically active substances that have been proposed primarily for their anti-tumour and anti-proliferative activities. Naturally occurring AKGs are a mixture of several AKGs that differ in the length and unsaturation of the alkyl chain. It is likely that the incorporation of AKGs into cell membrane phospholipids has the effect of modifying their physical properties, such as membrane fluidity and antioxidant status. They may also be able to alter cell signalling through the phospholipase pathway. [39,41]

7. Conclusions

There is limited evidence that the administration of FO and SLO as prevention or treatment of viral infections has potential benefits. However, multiple effects of FO and SLO induced in host immunity together may contribute to their clinical applicability (Table 5).

Potential beneficial mechanisms induced by FO include ability to inhibit viral entry, replication and prevention of inflammatory storm. However, there are many limitations of lipid mediators, i.e. low oral bioavailability and short half-life. FO and SLO, due to their rich composition, may have a multidirectional effect in anti-infective prevention. Supplementation with FO/SLO as an important element of a well-balanced diet is a safe and effective way to support optimal immune function, thereby reducing the risk and consequences of infection.

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