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MINI REVIEW

# Immunomodulatory effect of fish oil and its polyunsaturated fatty acid components

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**Abstract**

Trends in purchasing functional foods and pharmaceutical products as immune boosters in Indonesia have begun to increase due to the current COVID-19 pandemic situation. One of them is fish oil, which is known as the oil with the highest polyunsaturated fatty acids (PUFA) content compared to other oils, especially eicosapentaenoic acids (EPA) and docosahexaenoic acids (DHA) are well-known to have many health benefits. EPA and DHA also act as immunomodulators to maintain the immune system. It is shown by the presence of anti-inflammatory, vasodilating, anti-arrhythmic, and anti-aggregation effects. Journal articles and national reports published from 2011 to 2021 from several databases, such as Google Scholar, Scopus, and PubMed were collected to obtain abstract and original articles related to the immunomodulatory effects of EPA, DHA, and fish oil. This study highlights the immunomodulatory function of EPA and DHA in fish oil, and several studies of EPA and DHA *in vitro*, *in vivo*, and in human study. The potential health benefits of fish oil are explored, especially to evaluate the immunomodulatory effect of fish oil.

## 1. Introduction

As a result of the current COVID-19 pandemic situation, the purchasing of functional foods and pharmaceutical products in Indonesia has increased since those are believed to have many health benefits; especially, as immune boosters. Statistics show that the import net weight for medicinal and pharmaceutical commodities had increased from 21,072,615 kg per year in 2019 to 23,714,179 kg per year in 2020 (Central Bureau of Statistics, 2020). One of those pharmaceutical products which experienced that demand is fish oil since its import weight reached 10,056 million kg in 2017 (Central Bureau of Statistics, 2017).

The most abundant fatty acids in fish oils are omega-3 polyunsaturated fatty acids, especially EPA and DHA (Ojagh and Hasani, 2018). EPA and DHA have important roles in managing and preventing many diseases, such as cardiovascular disease, cognitive disorder, hypertriglyceridemia, cancer, diabetes, and acquired immunodeficiency syndrome (AIDS) (Durmus, 2019). Moreover, EPA and DHA act as immunomodulators to maintain the immune system, which shows anti-inflammatory, vasodilatation, anti-arrhythmic, and anti-aggregation effects.

As immunomodulators, EPA and DHA work to regulate immune response, so that the body can reduce the risk of chronic inflammatory disease (Dari *et al.*, 2017; Gutiérrez *et al.*, 2019; Mendivil, 2021). Furthermore, a study which had conducted by Zhao and Wang (2018) mentioned that omega-3 supplementation has proven to decrease the production of the pro-inflammatory cytokine, such as Interleukin-6 (IL-6),

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Tumor Necrosis Factor (TNF)-α, and C-reactive protein, while increasing the production of antibodies, such as immunoglobulin A (IgA) and immunoglobulin G (IgG).

This review highlighted the research published in the last ten years on the immunomodulatory function of EPA and DHA. A brief explanation of EPA and DHA will be explained at the beginning of this review, continuing with several studies of EPA and DHA, such as *in vitro, in vivo*, and human studies. Several health benefits of fish oils are reviewed, along with the immunomodulatory effect.

## 2. Methodology

Journal articles and national reports related to the immunomodulatory effects of EPA, DHA, and fish oils were collected by using Google Scholars, Scopus, as well as PubMed. The keywords used to obtain the information were EPA, DHA, and immune. The research articles and reports included in this review were published from 2011 to 2021. More than 17,000 articles were found in Google Scholars, while 126 and 84 research articles were found in Scopus and PubMed respectively. However, approximately 50 articles that were the most relevant were selected and included in this review.

## 3. Polyunsaturated fatty acids component in fish oil

Fish are animals that contain high fat; especially, unsaturated fatty acids. The composition of fatty acids in fish consists of 75% PUFA and 25% saturated fatty acids (SFA) (Andhikawati *et al.*, 2020). Fish oil is one of the fish processing products often produced in the industry. Fish oil is obtained by extracting the fatty components in fish body tissues to produce oil (Mulyawan *et al.*, 2018).

One of the main nutritional content of fish oil is PUFA, specifically omega-3 and omega-6 fatty acids. Omega-3 fatty acids include linolenic acid (C18:3, w-3), eicosapentaenoic acid or EPA (C20:5, w-3), and docosahexaenoic acid or DHA (C22:6, w-3). Meanwhile, omega-6 includes linoleic acid (C18:2, w-6) and arachidonic acid or ARA (C20:4, w-6) (Pandiangan, 2016). Several types of fish are known for their rich content of omega-3 fatty acids, such as sardines, tuna, mackerel, milkfish, flying fish, and catfish (Andhikawati *et al.*, 2020).

The main fatty acid component in fish oil is EPA and DHA (Arbi *et al.*, 2016). The content of EPA and DHA in fish oil is quite high and varied, ranging from 14-19% for EPA and 5-8% for DHA (Pratama *et al.*, 2011). Furthermore, several types of fish, such as lemuru has a high EPA content, while in tuna, the DHA content tends to be higher. Lemuru fish oil (*Sardinella lemuru*) contains 14.36% of EPA and 4.6% of DHA (Suseno *et al.*, 2014). Meanwhile, sardine fish oil (*Sardinella sp.)* which is obtained through the twice purification process, has higher EPA and DHA content with 15.62% EPA and 16.31% DHA (Dari *et al.*, 2017). In addition, in tuna fish oil (*Thunnus thynnus*), the DHA content is higher than EPA, with 36.3% of DHA and 4.7% of EPA (Visentainer *et al.*, 2007). The DHA content in mackerel fish oil (*Rastrelliger kanagurta*) also tends to be higher than its EPA, with 28.5% of DHA and 5.2% of EPA. Moreover, in mackerel tuna fish oil (*Euthynnus affinis*), the content of EPA and DHA is reported to be almost the same, with 3% EPA and 5% DHA (Mohanty *et al.*, 2016). The differences in the composition of fatty acids in fish oil can be influenced by several factors, including differences in species, season, type of water, salinity, and feed given (Pratama *et al.*, 2011; Suseno *et al.*, 2019).

## 4. EPA and DHA immunomodulatory effects *in vitro*

Table 1 shows some *in vitro* research related to the immunomodulatory effect of EPA and DHA. EPA and DHA have been known to have many health benefits, especially in maintaining the body's immunity. An *in vitro* study on peripheral blood mononuclear cells (PMBC) from Alzheimer's patients which was conducted by Serini *et al.* (2012) mentioned the effect of EPA and DHA on the modification of proliferation and cytokine secretive response. The addition of EPA and DHA to these cells has been shown to significantly reduce the release of cytokines in Alzheimer's patients. The combination of these two omega-3 components shows that EPA can reduce the IL-6/IL-10 ratio, while DHA can reduce the high IL-1/IL-10 ratio.

Another *in vitro* study also conducted on PMBC cells which was conducted by Jaudszus *et al.* (2013) stated that EPA and DHA can selectively reduce the percentage of T helper (Th) cells which express cytokines. This study was conducted to determine the inflammatory aspects of EPA and DHA components on Th cells. The results suggest that a combination of EPA and DHA can increase interleukin 10 (IL-10) without affecting tumor necrosis factor-alpha (TNF-α) and IL-6, which are pro-inflammatory cytokines. In general, EPA and DHA do not affect immune cell function in an inhibitory manner but through a pro-resolving response.

Several other studies have also shown the positive effect of adding EPA and DHA on various cells related to their inflammatory aspects. It is mentioned that EPA and DHA can modulate immune function and the level of gene expression related to inflammation, such as lowering the level of gene expression of cytokines, IL-1β, MCP1, and TNF-α (Allam-Ndoul *et al.*, 2016),

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Table 1. *In vitro* studies of fish oil, EPA, and DHA on the immune function

| No. | Purpose of the Study | Remarks | References |
|---|---|---|---|
| 1 | To evaluate the effect of DHA on the treatment of chronic inflammation and cancer. | DHA in the form of ω-liposomes has been shown to have strong antioxidant and anti-inflammatory effects, as shown in the inhibition of ROS, NO, MCP1, and TNF-α production, as well as inhibition of NFκB activation in activated immune cells. In addition, ω-liposomes also induce the inhibition of tumor cell proliferation. | Alaarg *et al.* (2016) |
| 2 | To evaluate the effect of EPA, DHA, and a mixture of EPA and DHA on the gene expression levels involved in inflammation in THP-1 macrophages. | EPA and DHA have been shown to modulate the gene expression levels related to inflammation, such as lowering the gene expression levels of cytokines, IL1B, and MCP1, as well as TNF-α. However, the use of EPA appears to be more effective in modulating the gene expression levels of inflammation, when compared to DHA or a combination of EPA and DHA. A dose-dependent effect was observed, with higher concentrations (50 M) being more effective than lower concentrations (10 M). | Allam-Ndoul *et al.* (2016) |
| 3 | To comparatively assess several inflammatory aspects of EPA and DHA on T helper cells (Th) and human monocytes. | EPA and DHA selectively reduce the percentage of Th cells expressing cytokines. In monocytes, EPA and DHA increased IL-10 without affecting TNF-α and IL-6. EPA and DHA generally do not affect immune cell function in an inhibitory manner but rather by a pro-resolving effect. | Jaudszus *et al.* (2013) |
| 4 | To assess the *in vitro* effects of EPA and DHA on phagocytosis and oxidative burst occurring in monocytes. | EPA and DHA have important roles in modulating monocyte immune function *in vitro*. This is indicated by a significant increase in phagocytic activity in monocytes with the addition of EPA with a concentration of 25-100 μM and the addition of DHA with a concentration of 100 μM. | Lecchi *et al.* (2011) |
| 5 | To compare the effect of different concentrations of EPA and DHA on immune response in renal macrophages isolated from yellow Corvina fish. | This study showed that EPA and DHA had significant effects on fish macrophage viability, lipid peroxidation, phagocytosis, oxidative burst, as well as eicosanoid and cytokine production, which could comprehensively modulate the immune response of fish macrophages. | Li *et al.* (2013) |
| 6 | To determine whether polyphenols and PUFAs (EPA and DHA) have a synergistic anti-inflammatory effect on murine macrophages *in vitro*. | The combination of polyphenol and EPA has a potential anti-inflammatory effect on LPS-stimulated RAW 264.7 macrophages, by lowering NO levels, lowering mRNA levels of proinflammatory and oxidative stress genes, and influencing the phosphorylation of proteins involved in the activation of NF -kB and AP-1 proinflammatory pathways. | Pallarès *et al.* (2012) |
| 7 | To assess the comparative effect of EPA and DHA on rat neutrophil function *in vitro*. | EPA and DHA can modulate various mouse neutrophil functions. These fatty acids exhibit different effects on cytokine production, phagocytosis, and neutrophil fungicidal activity. EPA and DHA have similar effects on ROS production, although at different concentrations. This difference is because EPA and DHA can change the composition of the fatty acid phospholipid membrane, as well as change the binding affinity of the ligand-receptor. DHA can increase the phagocytic capacity and fungicidal activity of neutrophils. EPA and DHA can increase the release of TNF- α in unstimulated cells. DHA can increase IL-1b production in LPS-stimulated cells. | Paschoal *et al.* (2013) |
| 8 | To evaluate the effect of *in vitro* treatment using pure EPA and DHA on the proliferation and secretive response of PBMC cytokines from Alzheimer's patients stimulated with PHA *in vitro*. | The addition of EPA and DHA significantly decreased cytokine release, with the effect of DHA being higher than EPA. DHA can reduce the high IL-1/IL-10 ratio, while EPA can reduce the IL-6/IL-10 ratio. DHA appears to be more potent in inhibiting single inflammatory cytokines, the pro-inflammatory profile of PBMC in Alzheimer's patients is better restored by EPA. | Serini *et al.* (2012) |
| 9 | To evaluate different concentrations of EPA and DHA on MMP-9 protein levels secreted from PBMC and human T cell migration through the fibronectin barrier | EPA and DHA have a role in inhibiting the migration of active immune cells into the central nervous system, and significantly reduce MMP-9 protein levels and MMP-9 activity. | Shinto *et al.* (2011) |
| 10 | To determine the effect of arachidonic acid (AA), EPA, and DHA on mast cell phenotype, mast cell degranulation, and cytokine production. | AA, EPA, and DHA can modulate mast cell phenotypes differently. AA can increase the production of pro-inflammatory mediators, by increasing the degranulation and secretion of TNF-α and $PGD_2$. While EPA and DHA can suppress the secretion of $PGD_2$, IL-13, and IL-4 as well as the formation of ROS effectively. | van den Elsen *et al.* (2013[a]) |

increasing phagocytic activity in monocytes (Lecchi *et al.*, 2011), and effectively suppress the secretion of prostaglandin $D_2$ ($PGD_2$), IL-13, IL-4, and ROS formation (van den Elsen *et al.*, 2013a). Moreover, EPA and DHA have also been shown to significantly reduce matrix metalloproteinase 9 (MMP-9) protein levels and MMP-9 activity (Shinto *et al.*, 2011), and show significant effects on macrophages viability, lipid peroxidation, oxidative burst, production of eicosanoids and cytokines which can modulate macrophages immune response (Li *et al.,* 2013).

In addition to the combination of EPA and DHA, several previous studies mentioned the effect of adding EPA or DHA, which also shows a positive response to the inflammatory aspect. Furthermore, the addition of DHA in the form of ω-liposomes is known to exhibit antioxidant and anti-inflammatory effects. It is shown in the inhibition of the production of reactive oxygen species (ROS), nitric oxide (NO), monocyte chemoattractant protein-1 (MCP1), and TNF-α, as well as the inhibition of nuclear factor-κB (NF-κB) activation in activated immune cells. Inhibition of tumor cell proliferation can also be induced with DHA in the form of ω-liposomes (Alaarg *et al.*, 2016). Meanwhile, the addition of EPA also shows an anti-inflammatory effect on macrophages by reducing NO levels, pro-inflammatory gene mRNA, and oxidative stress. EPA is also known to affect the phosphorylation of proteins that are involved in the activation of NF-κB and activating protein-1 (AP-1) pro-inflammatory pathways (Pallarès *et al.*, 2012).

## 5. EPA and DHA immunomodulatory effects *in vivo*

Table 2 shows some *in vivo* research related to the immunomodulatory effect of EPA, DHA, and fish oil. As mentioned before, EPA and DHA have many health benefits, especially for their immunomodulatory effects. A mice study which was conducted *in vivo* by Soni *et al.* (2017) showed positive results of protective effects in the spleen for the group which was treated with EPA and DHA. It is mentioned that EPA and DHA can lower splenic inflammation in high-fat-fed mice by reducing the pro-inflammatory immune response, such as NF-kB levels, which plays a critical role in inducing the pro-inflammatory cells and cytokines, T-cell receptor signaling pathway, and T-cell differentiation and co-stimulation.

Those results were supported by research which was conducted by Céspedes *et al.* (2020), which evaluates the role of EPA and DHA on prolonged liver partial ischemic damage in rats. This research shows that the subjects who are induced by liver partial ischemic showed increasing levels of TNF-α and IL-1β, which are pro-inflammatory cytokines. On the other hand, opposite findings are shown in subjects who are induced by liver partial ischemic added with EPA and DHA treatment, that there are decreasing levels of TNF-α and IL-1β and even indicated increasing levels of IL-10, which is an anti-inflammatory cytokine.

Some earlier studies also showed the immunomodulatory effects of EPA and DHA *in vivo*. It is found that EPA supplementation in rats can lower the pro-inflammatory indicators, such as CD4+, CD8+, NF-kB (Bie *et al.*, 2020), TNF-α (Figueras *et al.*, 2011; Di Biase *et al.*, 2013), IL-6 (Figueras *et al.*, 2011), IL-1β (Di Biase *et al.*, 2013), MMP-9, MMP-2, and MCP-1 (Kanai *et al.*, 2011). Moreover, EPA treatment can modulate the immune system by increasing spleen and thymus index, spleen cell proliferation, phagocytosis activity of macrophages, and natural killer (NK) cell activity (Bie *et al.*, 2020). In addition, the immunomodulatory activity of DHA is shown in a mice study which was conducted by Han *et al.* (2018). The results indicate the enhancement of thymus and spleen index, proliferation and activity of macrophage, and splenocytes (spleen cells) proliferation in the group given higher DHA.

EPA and DHA are known for relieving allergy reactions by lowering allergy-related antibodies; such as IgE, IgG1, IgG2a, and MMCP-1 (Van den Elsen *et al.*, 2013b). Fish oil modulates inflammatory indicators by decreasing pro-inflammatory mediators such as MMP-2, MMP-12, and CD86 (Kugo *et al.*, 2017).

## 6. EPA and DHA immunomodulatory effects on human subjects

Table 3 shows some research related to the immunomodulatory effect of EPA, DHA, and fish oil in human subjects. EPA and DHA contribute to the production of cytokines in the body, which can help to prevent inflammation in the human body (Waitzberg and Torrinhas, 2009). A study which was conducted by Gray *et al.* (2012) on sixteen young males who had been given 3 g/day fish oil supplementation (1,3 g EPA and 0,3 g DHA) has shown positive results. After being given fish oil supplementation for six weeks, the subjects increased the PBMC, interleukin-2 (IL-2) production, and natural killer (NK) cells cytotoxic activity in the recovery period after exercise. It shows that fish oil supplementation which is rich in EPA and DHA can improve both innate and acquired aspects of the immune system. Furthermore, another study on male elite paddlers as subjects shows similar results. The subjects were given 6 g fish oil capsules each day for 4 weeks, containing 2.4 g EPA and 1.2 g DHA. The result of this study shows that fish oil supplementations for 4 weeks can significantly

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Table 2. *In vivo* studies of fish oil, EPA, and DHA on the immune function

| No. | Purpose of the Study | Remarks | References |
|---|---|---|---|
| 1 | To study the relationship between antitumor and immunomodulatory activity of EPA *in vivo*, to evaluate the effect of EPA on the splenocyte proliferation, NK-cell activity, phagocytic activity of macrophages, and immune-related enzymes in serum or liver. | Thymus index, phagocytic activity, the proliferative capacity of splenocytes, and NK cell activity increased in the EPA-administered groups in a dose-dependent manner. EPA can also lower CD4+ and CD8+ levels as well as peroxidation levels. EPA has been shown to have anti-tumor activity. | Bie *et al.* (2020) |
| 2 | To evaluate the role of EPA and DHA in partially ischemic liver damage (IR group) and its effect on the survival ability of the mice model. | ALT and AST levels increased significantly in the IR group. However, this condition can be inhibited by the presence of omega 3 for 48 hours. The cytokine levels in tissue namely TNF-a and IL-1b were found to increase in the IR group for 20-48 hours, IL-10 also increased in the omega 3-IR group. However, the comparison between the IR and control groups did not show any significant difference. | Céspedes *et al.* (2020) |
| 3 | To determine the effect of EPA administration in protecting myelin of cuprizone-induced (CPZ) non-inbred Wistar rat's brain from damage. | In the CPZ treatment, rats that were given EPA experienced less weight loss than the PBS group. In the EPA group, the myelin component also had a higher trend than in the PBS group. However, splenocytes in the group of EPA-21/CPZ-9 mice produced more nitrite than PBS-21/CPZ-9. | Di Biase *et al.* (2013) |
| 4 | To determine the long-term effect of EPA treatment on substrate utilization and inflammatory status in diabetic rats. | EPA consumption can increase GLUT4 expression in skeletal muscle, and reduce TNF-a by 49% and IL-6 by 75% in skeletal muscle. In adipose tissue, EPA can also decrease IL-6 gene expression as well as TNF-a expression compared to control, but this result was not statistically significant. | Figueras *et al.* (2011) |
| 5 | To evaluate the effect of EPA administration on the prevention of arterial media calcification (AMC), as well as the effect of EPA on decreasing the expression of genes that play a role in osteogenesis and MMP-9 in the calcified aorta. | EPA can reduce AMC in the abdominal aorta and iliac arteries. RT-PCR analysis showed a decrease in the expression of osteogenic genes such as ALP, indicating an inhibition of the osteogenesis process in rats with AMC. EPA can also significantly reduce macrophage infiltration, both in the abdominal aorta and iliac arteries. Western blot analysis also showed that subjects in the EPA group had reduced MMP-9 expression and activity, but did not show a significant difference in MMP-2 reduction and activity compared to controls. EPA can decrease the MCP-1 mRNA expression. This indicates the possibility of reduction of macrophage infiltration through inhibition of MCP-1 expression in the aorta. Therefore, it was concluded that EPA could reduce AMC in warfarin-induced rats. | Kanai *et al.* (2011) |
| 6 | To determine the effect of fish oil in softening the aortic wall caused by nicotine administration in mice. | Fish oil modulates inflammatory indicators by decreasing pro-inflammatory mediators; such as MMP-2, MMP-12, and CD86. | Kugo *et al.* (2017) |
| 7 | To evaluate the effects and mechanisms of pure EPA and DHA on the immune response in the spleen through gene expression. | EPA and DHA can lower splenic inflammation in high-fat-fed mice by reducing the pro-inflammatory immune response, such as NF-kB levels, T-cell receptor signaling pathway, and T-cell differentiation and co-stimulation. | Soni *et al.* (2017) |
| 8 | To study the contribution of regulatory T cells (Treg) in the prevention of food allergies, in this case, whey protein allergy, using long chain PUFA omega-3. | Scores of anaphylaxis symptoms in mice fed with a fish oil diet tended to decrease. The levels of IgE, IgG1, IgG2a as well as serum MMCP-1 decreased after administration of fish oil. In addition, the concentration of IL-10 increased, while the TGF-b levels decreased. The fish oil has a protective effect against allergic reactions and this effect can be transferred through splenocyte donors. | van den Elsen *et al.* (2013) |
| 9 | To determine the immunomodulatory activity of DHA *in vivo.* | The thymus and spleen index, macrophage proliferation and activity, splenocyte proliferation as well as cytokines increased after the administration of DHA in the diet. | Han *et al.* (2018) |

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Table 3. Studies of the effect of fish oil, EPA, and DHA on the immune function in human subjects

| No. | Purpose of the Study | Remarks | References |
|---|---|---|---|
| 1 | To evaluate the effect of fish oil supplementation on immune response in subjects undergoing endurance training. | In subjects who were given fish oil supplementation, there was an increase in EPA levels in the blood. After 3 hours of exercise, PBMC IL-2 and NK cell activity in the intervention group was higher than in the control group. However, there was no significant effect on PBMC IL-4, IFN-γ production, plasma IL-6, cortisol concentration, and neutrophil activity. | Gray *et al.* (2012) |
| 2 | to evaluate the effect of low-dose fish oil supplementation on improving blood neutrophil function in cancer patients undergoing chemotherapy after the tumor removal surgery. | In the group which was given fish oil supplementation, there was an increase in body weight (average of 1.7 kg), EPA and DHA, polymorphonuclear cells (PMNC) in the blood by 30%, phagocytic function by 15%, superoxide anion production by 28%, whereas the arachidonic acid (AA) decreased. While in the control group, there was an average weight loss of 2.5 kg. In addition, there is a decrease in the function and number of PMNCs in the blood and a decrease in the production of $H_2O_2$. Lysosomal volume in the intervention group was also found to be higher than in the control group after 8 weeks of supplementation. | Bonatto *et al.* (2012) |
| 3 | To study the effect of omega-3 fatty acids on the changes in immune and inflammatory responses in Surgical Intensive Care Unit (SICU) patients. | The results showed a decrease in IL-1, IL-8, and IFN-γ on day 4 post-surgery, and a decrease in IL-1, IL-8, IFN-γ, IL-6, and TNF-α on day 7 post-surgery in the intervention group. There was a decrease in liver dysfunction and infection rates, but not statistically significant. | Han *et al.* (2012) |
| 4 | To evaluate the effect of omega-3 addition in parenteral nutrition to reduce inflammation and increase the immune system in patients after esophageal cancer surgery. | The results showed a decrease in serum procalcitonin (PCT) levels in both groups after 5 days of parenteral nutrition. In the intervention group, there was a significant decrease in PCT levels and a significant increase in the CD4+/CD8+ ratio on day 6 post-surgery. | Long *et al.* (2013) |
| 5 | To evaluate the effects of EPA and enriched fish oil on nutritional and immunological parameters of treatment naïve breast cancer patients. | In the intervention group, there was a significant increase in plasma phospholipid EPA and DHA. In addition, the percentage of peripheral blood CD4+ T lymphocytes and serum hsCRP levels can be maintained normally. In the control group, there was a significant increase in serum hsCRP levels. As for anthropometric parameters, the two groups did not show any difference. The serum proinflammatory cytokine and prostaglandin $E_2$ levels were not changed. | Paixão *et al.* (2017) |
| 6 | To evaluate the effects of fish oil supplementation (2 g of fish oil containing 600 mg of EPA and DHA for 9 weeks) on the inflammatory markers and nutritional status in colorectal cancer patients undergoing chemotherapy. | The results showed that there was a decrease in body weight and BMI in the control group, but no change in the intervention group. Patients supplemented with fish oil showed a clinically significant decrease in the CRP/ albumin ratio. However, other pro-inflammatory indicators such as IL and TNF did not show a significant decrease. | Silva *et al.* (2012) |
| 7 | To evaluate the effect of intense physical exercise and fish oil supplementation on the production of cytokines and T helper (Th) in elite paddlers. | The results showed a decrease in the production of TNF-α and IL-1β in the supplemented group. However, IL-6 and IL-10 production was found to be increased in the supplemented group. The supplemented group also experienced a significant decrease in IFN-γ production, whereas IL-4 production was not affected. FO supplementation reduced Th1 and Th1/Th2 ratio at the end of the study although it was not significant. In the control group given a placebo, there was an increase in TNF-α production, but no change in IL-1β secretion. In addition, there was no significant change in the production of IFN-γ and IL-4 in the control group. | Delfan *et al.* (2015) |
| 8 | To study the effect of omega-3 supplementation on nutritional status, immune profile, and inflammation in gastric cancer patients during antineoplastic pre-treatment. | In the control group, there was an increase in CRP, and several anthropometric parameters, such as arm muscle area and arm muscle circumference. While in the intervention group, there was an increase in body weight as well as maintenance of the nutritional and immune profiles. | Feijó *et al.* (2019) |
| 9 | To evaluate the effect of fish oil supplementation on nutritional parameters and inflammatory nutritional risk in patients with hematological malignancies during initial chemotherapy. | The results showed an increase in the proportion of EPA and DHA in blood plasma in the intervention group. In addition, there was a decrease in CRP and a greater CRP/albumin ratio when compared to the control group. Overall, survival was also seen to be higher in the group given fish oil supplements. | Chagas *et al.* (2017) |

decrease the production of pro-inflammatory cytokines, such as TNF- α. The supplementation group also shows decreased production of interferon (IFN)-γ, while the production of IL-4 does not affect much at this supplementation. The production of anti-inflammatory cytokines, IL-10, has been shown to increase significantly. In addition, this study shows that fish oil supplementations decrease the ratio of Th1 to Th2 and IL -1 β, although not statistically significant (Delfan *et al.*, 2015).

Several studies which were conducted on cancer patients as subjects also show similar results. The subjects who had been given oral fish oil supplementation containing EPA and DHA showed an improvement in immune parameters. Fish oil supplementation has been shown to increase the number of polymorphonuclear cells (PMNC), phagocytosis, and superoxide production during cancer chemotherapy (Bonatto *et al.*, 2012). Moreover, the fish oil supplementation group has also shown a significant decrease in C-reactive protein (CRP), CRP/albumin ratio, and IL-6. Furthermore, the percentages of peripheral blood CD4+ T lymphocytes are maintained in cancer patients who are given fish oil supplementation (Chagas *et al.*, 2017; Feijó *et al.*, 2019; Paixão *et al.*, 2017; Silva *et al.*, 2012).

Another study was conducted in post-operative patients who received either a central venous catheter or peripheral catheter for 7 days of fish oil as a lipid emulsion in parenteral nutrition. The result shows that patients who have been given fish oil supplementation in their parenteral nutrition have lower serum procalcitonin (PCT) levels and higher $CD^{4+}/CD^{8+}$ ratio than the control group. Moreover, IL-1, IL-8, IFN-γ, IL-6, and TNF-α were decreased significantly in patients with fish oil supplementation (Han *et al.*, 2012; Long *et al.*, 2013).

## 7. Potential of fish oil as immunomodulator

Fish oil is known to contain high levels of PUFA. In fact, its content is the highest compared to other types of oils (Arbi *et al.*, 2016). In comparison, sardine oil and shark oil have PUFA content of 20-30% and 19.11% (Andriyani *et al.*, 2017; Noor *et al.*, 2021). Meanwhile, other types of oil, such as coconut oils and olive oils only have PUFA content of 1.60% and 7% (Lioe *et al.*, 2018; Rohimah and Astuti, 2017). It proves that fish oil has more potential to be used in the nutrition sector because of its dominant PUFA content.

There are many health benefits of fish oil. Durmus (2019) recommended the consumption of fish oil as much as 2 capsules per day for disease prevention therapy. In addition, regular consumption of fish oil is known to improve brain intelligence and has a good influence on pregnant women, especially in helping the growth development, and endurance of the fetus (Andhikawati *et al.*, 2020; Suseno *et al.*, 2019). Based on previous studies, EPA and DHA in fish oil are also known to have potential as immunomodulators by showing anti-inflammatory, vasodilating, antiarrhythmic, and anti-aggregation effects. As an immunomodulator, the content in fish oil will regulate the body's immune response. Thus, it can reduce the risk of chronic inflammatory diseases (Dari *et al.*, 2017; Gutiérrez *et al.*, 2019; Mendivil, 2021).

The high production of capture fisheries in Indonesia contributes to 7.19% of the total production of world fish catches (Kusdiantoro *et al.*, 2019). It shows that the ingredients for fish oil production are easy to find in Indonesia. Furthermore, various types of fish, from marine fish to cultured fish with high EPA and DHA content, such as salmon, sardines, mackerel, catfish, milkfish, and herring can be used as ingredients for fish oil production (Andhikawati *et al.*, 2020; Susanto and Fahmi, 2012). Even, other results of the fish processing process are in the form of crude fish oil and fish viscera, which can also be used as a good raw material for fish oil production since their nutritional content is no less good than fish body parts (Al-Hilphy *et al.*, 2020). It will also affect the price of commercial fish oil in the future which can be more affordable. Therefore, with the various advantages of fish oil, both in terms of benefits, content, and production, fish oil has enormous potential to be used as an immunomodulator in the form of commercial nutritional supplements for the wider community.

## 8. Conclusion

EPA and DHA in fish oil serve as immunomodulators that are beneficial for improving immunity and supporting the immune system by protecting other organ systems from inflammation. EPA and DHA modulate the immune system by increasing the activity of immune cells such as monocytes, splenocytes, macrophages, and NK cells. These w-3 PUFA also suppress the production of pro-inflammatory cytokines such as IL-1b, IL-6, and TNF-a. They also act as anti-inflammatory substances by reducing ROS, NO, MCP1, TNF-a production, and NF-kB activation. Fish oil could alleviate allergy by reducing the level of IgE and MMCP-1. Fish oil containing EPA and DHA can be consumed as nutraceuticals or food supplements that increase the immune system both in healthy subjects or patients with certain diseases such as tumors, cancer, and diabetes.

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**Conflict of interest**

The authors declare no conflict of interest.

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