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Omega-3 Fatty Acids and Health. A Literature Review

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ABSTRACT

Introduction and Purpose: Omega-3 polyunsaturated fatty acids (PUFAs) are essential nutrients primarily obtained from marine sources. These compounds, particularly EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid), play a critical role in modulating inflammation, supporting cardiovascular and neurological health, and potentially preventing certain cancers. Despite extensive research, mixed clinical results highlight the need for comprehensive analyses. This study aims to synthesize findings on omega-3's effects on cardiovascular health, neurocognitive development, inflammation, and bioavailability challenges, with a particular focus on research published between 2012 and 2024.

Methodology: The review is based on the thorough analysis of the materials selected from "PubMed" and "Google Scholar" scientific databases from 2012 to 2024 using the following key words: dietary supplements, DHA, EPA, omega-3 fatty acids. These key words were chosen based on their relevance to the matter of an article.

Conclusions: Omega-3 fatty acids demonstrate notable benefits in reducing inflammation, improving lipid profiles, enhancing cognitive function, and lowering the risk of cardiovascular events. However, results regarding the efficacy of omega 3 in the prevention and treatment of chronic disease are inconsistent, due to differences in dosage, bioavailability and study design.
Keywords: dietary supplements, DHA, EPA, omega-3 fatty acids

1. Introduction and Purpose

Fats are the most concentrated source of energy in human food (1). In food fats, depending on the number of double bonds, fatty acids are divided into (1, 2): SFA - Saturated Fatty Acids, MUFA - Monounsaturated Fatty Acids, PUFA - Polyunsaturated Fatty Acids. Polyenoic fatty acids contain more than one double bond and depending on the position of the first one (counting from the methyl end) they are divided into them into two groups (1, 3, 4):
- n-3 or ω-3, which is the α-linolenic acid (ALA) family (the first double bond at the 3rd carbon atom);
- n-6 or ω-6, the so-called linoleic acid (LA) family (the first double bond at the 6th carbon atom).

The parent fatty acids of the ω-3 (α-linolenic - C18:3) and ω-6 (linoleic acid - C18:2) families are not synthesized in the human body due to the lack of desaturases introducing a double bond in the molecule of the acid at the 3rd and 6th carbon, so they must be supplied with food (1, 5-8). Among polyenoic fatty acids, LC PUFAs - Long Chain Polyunsaturated Fatty Acids - are the most important. Their sources are plants (1, 9), fish (especially cold-water fish waters), marine animals (clams, oysters, shrimp) (1, 10), but also plant products such as nuts (especially English walnuts), sesame seeds (1, 11), flaxseed and vegetable oils such as soybean and canola (1, 12). Long-chain forms such as eicosapentaenoic acid (EPA, C20:5ω3) and docosahexaenoic acid (DHA, C22:6ω3) play a fundamental role in cellular structure: they are essential components of cell membranes, especially in nerve tissue and the retina, where DHA is the predominant fatty acid in neuronal and synaptic phospholipids. In addition, they play a role in

modulating inflammation and membrane fluidity, affecting various physiological functions to maintain homeostasis and health of the human body (13). Given their wide range of actions, omega-3 fatty acids have been extensively studied for their effects on cardiovascular health, neurological development, immune function and potential anti-cancer properties.

In recent decades, omega-3 supplementation and dietary guidelines have been promoted, especially in populations with low seafood consumption, which may lead to omega-3 deficiencies. Despite these recommendations, clinical studies yield mixed results regarding the effectiveness of omega-3s in preventing chronic diseases. This literature review synthesizes findings from studies on omega-3 and health, mostly focusing on cardiovascular health, neurocognitive benefits, anti-inflammatory effects, bioavailability from various sources, and emerging evidence on cancer prevention.

2. The state of knowledge

2.1. Cardiovascular Health

Cardiovascular diseases are among the most common causes of death worldwide. Chronic inflammation is believed to be the primary cause of cardiovascular diseases. Pro-inflammatory cytokines and oxidative stress play an important role in the inflammatory process. This causes damage to vascular endothelial cells, leading to reduced vascular elasticity and the formation of atherosclerotic plaques. Rupture of such plaques can result in heart attack or stroke (14). Chronic inflammation is also associated with autoimmune diseases, such as rheumatoid arthritis or thyroid disease, which increase the risk of cardiovascular disease (14). Swanson et al. (2012) (15) highlighted that EPA and DHA have anti-inflammatory properties, reduce oxidative stress, and improve cellular function through changes in gene expression. Moreover Bouwens et al. (2009) (16) demonstrated on a sample of human blood that supplementation with EPA and DHA altered the expression of as many as 1,040 genes. The study observed reduced expression of genes involved in pathways related to inflammation and atherosclerosis, such as hypoxia signaling, scavenger receptor activity, nuclear transcription factor kB signaling, adipogenesis, and eicosanoid synthesis. The consumption of EPA and DHA reduces levels of inflammatory markers (CRP, IL-6, IL-1), which correlate with an increased likelihood of cardiovascular events (16).

Ebrahimi et al. (2009) (17) confirmed that supplementation with the aforementioned omega-3 fatty acids significantly reduces the titer of antibodies against heat shock protein 27 (Hsp27). This is significant because this protein is overexpressed in cardiac muscle cells after the return of blood flow following ischemia and may have cardioprotective effects. Hsp27 acts as a

chaperone, stabilizing protein structures, preventing their aggregation, and participating in protective processes against apoptosis and cellular damage. Although there is evidence that Hsp27 may support the protection of cardiac muscle during ischemia and reperfusion, studies on the role of antibodies directed against this protein are limited. Further research is needed to fully understand the mechanisms through which Hsp27 antibodies may influence reperfusion outcomes and heart function after ischemic episodes.

Swanson et al. (2012) (15) reported conflicting results regarding the use of EPA and DHA in relation to major coronary events and their use after myocardial infarction. However, EPA and DHA supplementation was associated with a reduced risk of recurrent coronary events and sudden cardiac death after acute myocardial infarction, as well as with a reduction in the number of heart failure events.

In addiction Yokoyama et al. (2007) (18) compared the effectiveness of EPA supplementation combined with a statin to statin therapy alone. After an average follow-up period of 4.6 years, it was observed that major coronary events occurred in 262 patients (2.8%) in the EPA group, compared to 324 patients (3.5%) in the control group, representing a 19% relative risk reduction ($p=0.011$). In both groups, LDL cholesterol levels decreased by 25% from a baseline level of 4.7 mmol/L. The EPA group showed a significant reduction in the incidence of unstable angina and nonfatal coronary events, while the rates of sudden cardiac death and coronary death were similar in both groups. Among patients with a history of coronary artery disease, EPA use reduced the risk of major coronary events by 19% (158 cases [8.7%] in the EPA group vs. 197 [10.7%] in the control group; $p=0.048$). Conversely, among individuals without a history of the disease, the risk of major coronary events decreased by 18%, although this result was not statistically significant (104 cases [1.4%] in the EPA group vs. 127 [1.7%] in the control group; $p=0.132$). Swanson et al. (2012) noted that when interpreting the results, the specificity of the Japanese population must be considered, as their higher fish consumption compared to most other nations means that patients already had relatively high baseline levels of EPA and DHA at the beginning of the study (15).

What is more Oikawa et al. (2009) (19) compared patients with impaired glucose metabolism to those with normal glycemia. Patients with impaired glucose metabolism had a significantly higher high-risk (HR) ratio: 1.71 in the non-EPA group and 1.63 in the EPA group. Following treatment of glucose metabolism disorders, patients with EPA supplementation showed a significantly lower HR for major coronary events of 0.78 compared to patients with glucose metabolism disorders who did not receive EPA, demonstrating that EPA significantly inhibits major coronary events (15, 19).

Another study by Kromhout et al. (2010) (20), analyzed the impact of use EPA and DHA on cardiovascular events after myocardial infarction in 4,837 patients. A major cardiovascular event occurred in 671 patients (13.9%). A post-hoc analysis of data from these patients with diabetes showed that rates of fatal coronary heart disease and arrhythmia-related events were lower in the EPA and DHA group compared to the placebo group. Conversely, Rauch et al. (2010) (21) found no significant difference in sudden cardiac death or overall mortality between the EPA and DHA supplementation group and the control group among patients treated after myocardial infarction.

Two similar studies Dawczynski et al. (2010) and Cawood et al. (2010) (22, 23) concluded that both EPA and DHA improve plaque stability, reduce endothelial activation, and improve vascular permeability, thereby reducing the risk of cardiovascular events. Moreover, they found that EPA supplementation is associated with a significantly higher amount of EPA in carotid atherosclerotic plaque, which may lead to reduced plaque inflammation and increased stability. One of the symptoms of atherosclerosis is peripheral arterial disease (PAD), characterized by plaque buildup in the leg arteries, which can ultimately lead to complete artery blockage. Data analyses on PAD by Swanson et al. (2012) showed that EPA and DHA supplementation improves endothelial function in PAD patients by reducing plasma soluble thrombomodulin levels and improving flow-mediated dilation in the brachial artery from 6.7% to 10.0%. PAD patients who received EPA supplementation had significantly lower HRs for major coronary events than those who did not take EPA (15).

Furthermore, Swanson et al. (2012) noted that omega-3 fatty acids enhance platelet reactivity to subtherapeutic antithrombotic therapies, including aspirin. In patients with stable coronary artery disease taking low doses of aspirin, EPA and DHA supplementation was found to be as effective as increasing the aspirin dose to 325 mg/day in achieving antithrombotic benefits. Studies also showed that taking EPA and DHA reduces the P2Y12 receptor reactivity index (a marker of clopidogrel resistance) (15, 24).

The publication by Swanson et al. (2012) highlights the role of EPA and DHA in reducing triglycerides, improving lipid profiles, and decreasing inflammation. The authors note that despite mixed results, there is sufficient evidence to support the role of omega-3 in heart health (15).

Visioli and Agostoni (2022) (25) in their study noted that years of research on docosahexaenoic (DHA) and eicosapentaenoic (EPA) acids have left many aspects of their effects inconclusive or insufficiently studied. Particular attention has been paid to methodological problems, as most of the studies reviewed did not include measurements of omega-3 fatty acid concentrations

before and after supplementation. The authors pointed out that the Omega-3 Index (the percentage of EPA and DHA in erythrocytes) is a significant predictor of cardiovascular disease risk. Higher values (>8%) are associated with a 30% lower risk of cardiovascular death compared to lower values (<4%). Moreover, many studies used insufficient doses of omega-3 fatty acids or failed to account for the bioactivity of the preparations, complicating the interpretation of results (25, 26).

High doses of EPA have demonstrated heart-protective advantages, prompting the Food and Drug Administration (FDA) to authorize its use in 2019 for managing hypertriglyceridemia (27). At the same time, while DHA's impacts are notable, additional studies are needed (25). The authors also expressed worries regarding the efficacy of secondary prevention. Although initial clinical trials, such as GISSI-Prevenzione and JELIS, showed positive effects of omega-3 in heart protection, newer studies do not confirm clear benefits in secondary prevention of cardiovascular diseases. The reasons for this could be changes in treatment standards, including the widespread use of statins and other medications that may mask the effects of omega-3 (25, 18, 28).

The review also pointed out the controversies surrounding the antiarrhythmic effects. Initial research indicated that omega-3 fatty acids might possess antiarrhythmic properties; however, recent meta-analyses reveal a heightened risk of atrial fibrillation in individuals consuming elevated amounts of omega-3, especially in high-risk populations.

Visioli and Agostoni (2022) underscore the necessity for additional research, especially regarding the assessment of EPA and DHA levels and their variations in different clinical contexts. The article points out the difficulties in understanding omega-3 research findings and emphasizes the importance of effectively incorporating them into evidence-based nutritional therapy. These results have great importance for future studies and medical uses (25).

Weylandt et al. (2015) (29) analyzed studies on the efficacy of polyunsaturated omega-3 fatty acids (PUFAs) within cardiology. The GISSI-Prevenzione study (28) carried out in the 1990s, involving 11,324 post-myocardial infarction patients, showed a significant reduction in mortality risk (including cardiovascular causes) with a 1g/day dose of omega-3 PUFAs. These findings formed the basis for recognizing omega-3 as effective in secondary cardiovascular prevention.

Weylandt et al. (2015) in their analysis also emphasized the possibility of achieving an antiarrhythmic effect, as preclinical studies (in vitro and in vivo) indicated that omega-3 PUFAs could block proarrhythmic effects of adrenaline, calcium, and other factors. However, clinical

studies, such as the double-blind study by Leaf et al. (2005) (30), did not show clear antiarrhythmic benefits, which could have been due to low patient compliance.

In ORIGIN Study (2012) (12,536 patients with dysglycemia), omega-3 PUFA supplementation did not show a significant impact on the reduction of cardiovascular events (31).

The authors of the analysis mention several potential factors influencing the ambiguity of the results. First, Weylandt et al. (2015) point to interactions with cholesterol-lowering drugs, as in the GISSI-P study, only 5% of patients used statins, whereas in ORIGIN, about 50% did. Statins may hypothetically modify the effects of omega-3 PUFAs. Dietary changes are also significant: the increase in omega-3 intake in the population over the decades may have raised baseline omega-3 levels in the study participants. The last reason mentioned by the authors for the ambiguous results is the lack of standardization in measurements: insufficient data on omega-3 PUFA levels in tissues (e.g., omega-3 index in erythrocytes) makes it difficult to compare results between studies (28, 29, 31).

Weylandt et al. (2015) also describe the mechanisms of action, which are based on the fact that EPA and DHA are precursors of bioactive lipid mediators such as:

- 17(R),18(S)-EETeTr, which has chronotropic effects and protects cardiomyocytes,
- 18-HEPE, which inhibits the pro-inflammatory action of macrophages and counteracts heart remodeling in the case of overload.

Although numerous studies have confirmed the protective effects of omega-3 PUFAs in secondary prevention, especially in the context of arrhythmias and cardiovascular deaths (28), newer, large studies do not provide clear evidence of their effectiveness in primary cardiovascular prevention. Further studies are needed, with better standardization of measurements, consideration of potential interactions with drugs, and dietary changes (29, 32).

Nichols et al. (2014) (33) conducted a review of the symposium results, which presented the latest findings on the health benefits, sources, products, and bioavailability of long-chain omega-3 fatty acids (LC omega-3).

Von Schacky et al. (2014) (34) presented the Omega-3 Index (O3I) as a cardiovascular health biomarker. The authors highlighted the lack of clear results from large clinical studies on the impact of EPA and DHA on reducing cardiovascular events, emphasizing the need for studies targeting individuals with low baseline omega-3 levels.

Howe et al. (2014) (35) discussed the potential use of O3I as a risk marker for obesity and other metabolic disorders. Low DHA levels in women were identified as a risk factor for increased adiposity, suggesting the need to include DHA as part of therapies supporting obesity treatment.

Carvalho et al. (2018) (13) showed a roles of fatty acids (FAs) in prokaryotic and eukaryotic organisms. It covered biosynthesis processes, modulation of membrane properties, energy storage, and signaling functions. The authors claim that omega-3 polyunsaturated fatty acids, such DHA and EPA, are essential for the cardiovascular system, brain, and retina. In addition to lowering plasma triglyceride levels and preventing atherosclerosis, they also help lessen the risk of arrhythmia. Polyunsaturated fatty acids are essential for preserving homeostasis in the body. By increasing the erythrocyte membrane's flexibility, they lower the risk of problems related to diabetic microcirculation. Low amounts of polyunsaturated fatty acids in erythrocyte membranes have been linked to decreased flexibility and elevated tissue hypoxia, both of which exacerbate the problems of diabetes.

2.2. Neurocognitive and Developmental Benefits

The hallmarks of Alzheimer's disease (AD) include cognitive decline, memory loss, and a diminished ability to live independently. Currently, some 26.6 million people suffer with this degenerative and crippling neurological disorder; by 2050, that number is expected to rise to 106.2 million (15, 36, 37).

According to Swanson et al. (2012) (15), DHA is essential for the healthy operation of the nervous system and is found in phospholipids found in neuronal membranes. Serum levels of DHA and EPA cholesterol esters were significantly lower in AD patients than in the control group, according to a case-control research, which may indicate a connection between the development of the disease and their deficit (15, 38). Swanson et al. (2012) found that a diet high in omega-3-containing foods, like nuts, vegetables, and fish, was linked to a decreased prevalence of AD (15, 39). A mouse model demonstrated that a diet supplemented with DHA reduced amyloid plaques by 40.3%, particularly in the parietal cortex and hippocampus (15, 40). Additionally, EPA and DHA supplementation decreased inflammatory markers such TNF-α, IL-1B, and IL-6 in AD patients (15, 41).

The authors do point out that there is conflicting evidence about omega-3's effects on cognitive function. In one study, there were no discernible changes in cognitive deterioration between the DHA and EPA supplement group and the placebo group. However, in patients with very mild cognitive symptoms, supplementation slowed the deterioration of MMSE scores (15, 36). Conversely, another study using the ADAS-Cog scale showed no cognitive benefits after 18 months of DHA supplementation (15, 42).

Omega-3, especially DHA and EPA, may play a role in the pathophysiology of AD through neuroprotective, anti-inflammatory, and weight-supporting actions. However, conflicting

results regarding their effects on cognitive performance suggest that more research is necessary to fully comprehend the mechanisms of action and determine which patient populations might most benefit from supplementation (15).

Stonehouse (2014) (43) investigated the effects of LC omega-3 on cognitive function across a range of age groups. The authors stressed the need for standardization of biomarkers, such as the proportion of DHA in erythrocytes, and the limitations in research designs in order to accurately determine the relationship between omega-3 intake and improved neurological function.

Carvalho et al. (2018) (13) explained the connection between changing the properties of eukaryotic cell membranes and brain functioning. According to the article, eukaryotic cell membranes—including those of neurons – are essential for processes including molecular transport and intercellular signaling.

The lipid composition of membranes, particularly the content of unsaturated fatty acids such as PUFAs (including DHA), affects membrane fluidity, the formation of lipid microdomains, and protein-membrane interactions. These features are important for neurotransmission processes and the dynamic organization of synapses (13).

A literature review by Swanson et al. (2012) also focuses on the importance of omega-3 fatty acids (EPA and DHA) in fetal development and their beneficial effects during pregnancy. It emphasized that past guidelines for pregnant women's nutrition focused on adequate calories and protein intake, but now attention is also given to essential fatty acids. Taking supplements during pregnancy provides several benefits for the developing fetus, including fostering the development of the brain and retina, since EPA and DHA are necessary for cell membrane function. During the third trimester, when it quickly accumulates in embryonic tissues, notably in the brain and retina, DHA is highly important for improving cognitive and visual capacities (15).

Study by Judge et al. (2007) (44) discovered that children of pregnant women who took DHA supplements performed better on tests of problem-solving at 9 months of age ($P = 0.017$). Additional research verified that children who took EPA and DHA supplements at the age of 2.5 years had better visuomotor coordination scores than those in the placebo group ($P = 0.008$). Supplementing with EPA and DHA was linked to a longer pregnancy duration and a lower risk of preterm delivery, according to Swanson et al. (2012) (15). This mechanism is attributed to reduced production of pro-inflammatory prostaglandins E2 and F2α, which limits uterine inflammation (15). One study showed a 51% reduction in the risk of preterm birth (<34th week of pregnancy) ($P = 0.03$) and a higher newborn birth weight (by an average of 68 g, $P = 0.003$)

in the DHA-supplemented group (15, 45). Additionally, taking EPA and DHA supplements while pregnant and nursing may lower the child's risk of developing allergies. Studies have shown that fish oil supplementation lowers inflammatory markers, associated with reduced rates of food allergies and atopic eczema ($P < 0.05$) (15, 46). The 2010 U.S. Department of Health and Human Services dietary guidelines recommend that pregnant and breastfeeding women consume 8–12 ounces (about 300–900 mg of EPA and DHA daily) of fish per week (15, 47). Unfortunately, most women in the U.S. and Canada do not meet these guidelines, which may lead to omega-3 deficiencies in the fetus (15, 44).

The authors emphasize the clinical significance of EPA and DHA intake, arguing that it supports fetal development, reduces the risk of pregnancy complications associated with preterm birth, and has long-term effects on child health (48). Furthermore, this supplement may lessen the likelihood that children will develop inflammatory illnesses and allergies (15).

2.3. Inflammation and Immune Response

Weylandt et al. (2015) (29) go into great detail about how omega-3 polyunsaturated fatty acids (PUFAs) control inflammatory processes and how they might be used to treat inflammatory diseases. Omega-3 polyunsaturated fatty acids (PUFAs) have anti-inflammatory effects by competitively inhibiting enzymes such as lipoxygenase (LOX) and cyclooxygenase (COX). Furthermore, because omega-6 polyunsaturated fatty acids (PUFAs) are precursors to pro-inflammatory mediators like prostaglandins and leukotrienes, it is still unknown how significant they are for inflammatory conditions like Crohn's disease, ulcerative colitis (IBD), and non-alcoholic steatohepatitis (NASH). This particularly applies to arachidonic acid. Often, omega-3 polyunsaturated fatty acids have too little or no impact on the occurrence of relapses or the progression of the illness to justify strong recommendations. Variations in dosages, methods, and the diversity of study populations can all lead to ambiguity in research (29). Weylandt et al. (2015) also go over the subject of new lipid mediator classes. They emphasize that the discovery of resolvins (E and D), which are derivatives of EPA and DHA, has revolutionized research on omega-3 PUFAs. Pro-resolving mediators like 17-HDHA and 18-HEPE are powerful resolvens that help resolve inflammatory processes. This field of research provides new information on how to treat chronic inflammatory diseases. Future treatments may rely on the direct use of these medications, leading to more targeted and effective interventions (29, 49-52).

The data showing that PUFAs are substrates for the synthesis of specialized lipid mediators, such as resolvins and protectins, which have anti-inflammatory and pro-resolving effects, were confirmed by Carvalho et al. (13) (2018).

2.4. Bioavailability and New Sources

Nichols et al. (2014) described the issue of omega-3 bioavailability and highlighted that New Zealand green-lipped mussels (Perna canaliculus) have proven to be a rich source of omega-3 phospholipids with unique anti-inflammatory properties (33, 53). At the same time, an analysis of farmed fish, such as Atlantic salmon and barramundi, revealed a decrease in omega-3 content due to the replacement of fish oil with poultry oil in feeds. Higher concentrations of these advantageous substances may be restored by adding plant-based omega-3 oils to aquaculture diets (33, 54-56). The topic of omega-3 supplement quality was also addressed, including Antarctic krill oils, which are gaining popularity due to the better bioavailability of phospholipids. The necessity of keeping an eye on persistent organic pollutants (POPs) in supplements was highlighted, as food safety laws become more stringent (33, 57). The article also discussed the development of alternative sources of long-chain (LC) omega-3, including transgenic plants like Camelina sativa enriched with DHA. This approach can alleviate the pressure on the fish market while also promoting sustainable development and guaranteeing consumers a consistent supply of omega-3 fatty acids (33, 58, 59). Additionally, research findings are provided about the utilization of food waste as a carbon source for bacteria that produce lipids rich in omega-3. One promising technique for the sustainable synthesis of omega-3 oils is the use of bread crumbs in static fermentation (33, 60). The paper highlights how omega-3 research is multidisciplinary, involving sustainability, aquaculture, biotechnology, and public health. Emerging innovations, such as plant-based DHA sources and the use of waste for lipid production, could significantly impact the global omega-3 market. At the same time, further clinical research, biomarker standardization, and increasing public awareness of the benefits of omega-3 are necessary (33).

2.5. Potential Cancer Prevention and Cellular Mechanisms

Weylandt et al. (2015) describe the mechanisms of action of omega-3 fatty acids (PUFAs) in the context of their potential anti-cancer properties. A number of in vitro studies and animal models(61, 62) suggest that omega-3 PUFAs may prevent tumor development and support anti-cancer therapy. Omega-3 PUFAs have been shown to alter a number of molecular pathways, impacting angiogenesis, invasion, differentiation, cell proliferation, and survival (29). The authors outline four main mechanisms of action of omega-3 PUFAs related to their anti-cancer efficacy. The first is integration into cell membranes: increased omega-3 PUFA content in cell membranes leads to changes in the lipid microenvironment (rafts), which play a key role in the pathophysiology of inflammatory conditions (29).

Based on experimental data from animal models, supplementation with omega-3, particularly ethyl esters of EPA and DHA, reduced symptoms of colitis in mice (models induced by DSS or Citrobacter infection). However, in some models, especially with high doses of omega-3 fatty acids or in the context of infections, worsening of inflammation was observed, suggesting the possibility of varying effects depending on the dose, disease type, and immune environment. In the Fat-1 mouse model, characterized by endogenous elevation of omega-3 PUFA levels, consistent anti-inflammatory effects were observed, including a reduction in colon adenomas and mitigation of DSS- or D-GalN/LPS-induced inflammation. These data
draw attention to the possible advantages of preserving healthy levels of omega-3 PUFA in tissues (29, 63–67).

However, controversies have not been avoided in clinical studies, as findings related to modifies the activity of receptors, channels, and enzymes. For example, docosahexaenoic acid (DHA) reduces the proliferation of cancer cells by changing the structure of the EGFR receptor, which results in its degradation and suppression of the EGFR-Ras-ERK1/2 pathway (29, 68). Another mechanism involves lipid peroxidation: the high susceptibility of omega-3 PUFAs to oxidation induces changes in the oxidative status of cells, affecting molecular pathways associated with proliferation, apoptosis, and inflammation.

The third route is metabolic conversion, in which omega-3 polyunsaturated fatty acids are converted into bioactive mediators with potent anti-inflammatory and pro-resolving properties, such as protectins and resolvins. Interactions with receptors such as PPARγ and GPR120 activate specific molecular pathways (27, 69, 70).

Epigenomic modulation is the fourth mechanism. Omega-3 polyunsaturated fatty acids (PUFAs) can alter the epigenetic regulation of genes critical to the growth and survival of cancer cells. They accomplish this through altering histones, modulating miRNA expression, and influencing DNA methylation (29). Weylandt et al. (2015) (29) emphasize specific applications for colorectal cancer (CRC) and prostate cancer. Studies conducted both in vitro and in vivo (71, 72, 73) have shown that DHA and EPA can raise apoptosis, stop the proliferation of cancer cells, and make cells more sensitive to chemotherapeutics like 5-fluorouracil. Additionally, omega-3 polyunsaturated fatty acids (PUFAs) affect colorectal cancer stem cells (CCSC) by encouraging differentiation and decreasing their potential to form malignancies. Prostate cancer results are less certain. Omega-3 PUFAs have been shown to have preventive effects, particularly in advanced stages of cancer, however other studies suggest no significant benefits or even potential risks (29).

Despite conflicting results from epidemiological and interventional studies, omega-3 polyunsaturated fatty acids have considerable anti-cancer potential. To verify their efficacy in cancer prevention and treatment, more meticulously planned clinical trials are required (29).

3. Conclusion

The research on omega-3 fatty acids offers compelling evidence of their numerous health benefits, albeit certain limitations and contradictions. Across cardiovascular, cognitive, and inflammatory health, EPA and DHA demonstrate significant potential, especially when individualized approaches are applied, such as using the Omega-3 Index for cardiovascular prediction. Neurocognitive benefits are also consistently supported, with particular emphasis on DHA's role in early brain development and potential protective effects against cognitive decline.

Although omega-3's anti-inflammatory and cancer-preventive qualities seem encouraging, further research is necessary, especially in the areas of bioavailability and sustainable sources. The use of algae-derived omega-3s and other plant-based sources could address ecological concerns and provide viable options for supplementation. Moving forward, research should focus on optimizing omega-3 bioavailability, exploring targeted benefits of EPA versus DHA, and clarifying their mechanisms at the cellular level to refine clinical applications.

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