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Exploring the potential of fish oil (Omega-3 and Omega-6 Polyunsaturated Fats) as metabolic mediators for targeted cancer therapy

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Abstract

Cancer mortality and incidence are both sharply increasing on a global scale. GLOBOCAN estimates that in 2020, there were around 10.0 million cancer-related deaths and nearly 19.3 million new cancer diagnoses, making cancer the top cause of death globally and a significant impediment to improving life expectancy. Cancer cannot be completely cured, though. However, supplements containing polyunsaturated fatty acids with marine origins, such as EPA and DHA, are frequently taken. Fish oil (above 3 grams per day) and EPA/DHA (above 1 and above 0.8 grams per day) have been shown to have good clinical effects, indicating that they may have the potential to be an effective adjuvant to chemotherapy and may alleviate some of the harmful consequences of cancer. This review is aimed at examining the importance of Omega-3 PUFAs as metabolic mediators and their impact on cancer.

Keywords: DHA (docosahexaenoic acid); ALA (alpha-linolenic acid); EPA (eicosapentaenoic acid); PUFAs (polyunsaturated fatty acids); NF-KB (Nuclear Factor Kappa light chain enhancer of activated B cells).

1. Introduction

Fish oil serves as one of the most utilized dietary supplements. It contains eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are ω-3 fatty acids needed for preventing and perhaps treating a variety of diseases. It originates from a variety of fish species. The building blocks of all lipids are fatty acids, which have 12–24 carbon atoms and make up the majority of dietary and bodily fats as well as membrane lipids. The lipids in membranes contain a substantial portion of fatty acids. During digestion, the small intestine produces and absorbs free fatty acids (FFAs). FFA are converted into triacylglycerols in the intestinal mucosa cells, and chylomicrons then carry these triacylglycerols through lymphatic capillaries to the bloodstream. According to Arid and Christian (2005), fatty acids are transported in the bloodstream either by binding to albumin or as part of lipoproteins. Protein carriers function in aiding the movement of fatty acid across the plasma membrane, which are then transported intracellularly by Fatty acid binding proteins. The acyl-CoA activation of fatty acids is essential prior to its delivery to mitochondria or peroxisomes where it undergoes B-oxidation to yield cellular energy currency and heat or transported to the ergastoplasm where it will be esterified into other groups of lipids. Acyl-CoA or specific FFA can interact with gene controlling protein or are transformed into eicosanoids, which are signaling molecules. These include polyunsaturated acids (PUFAs) containing more than one double bond with a methyl group existing between each of the double bond, saturated fatty acid and unsaturated fatty acid with one double bond linking the carbon atoms.

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The ω 6 and ω3 series, or polyunsaturated fatty acids containing two or more cis double bond, are the two different categories of PUFAs. Although these fatty acid families have broad spectrum of metabolic activities and cannot be converted, the body can process them further by increasing the number of carbon atoms and desaturation via dehydrogenation (Arid and Christian 2005). Even though animal cells lack these desaturases, animals can modify the ALA and LA they consume from food because they have the 6(FAD2) and 5(FAD1) desaturases and elongases (Arid and Christian 2005). PUFAs exhibit amphipathic characteristics, or hydrophobic heads and hydrophilic tails. In addition to other unsaturated fatty acid properties, these organic compounds have structural composition with outstanding physiological importance which include permeability of the cellular membrane maintenance, modulating inflammatory actions, lowering the risk of heart rhythm issues, improving the activities of vascular endothelial cells, preventing the accumulation of blood clotting machineries, and lowering of production of triacylglyceridein triglyceride-producing cells

2. Metabolism of ω-3 polyunsaturated fatty acids (PUFAs)

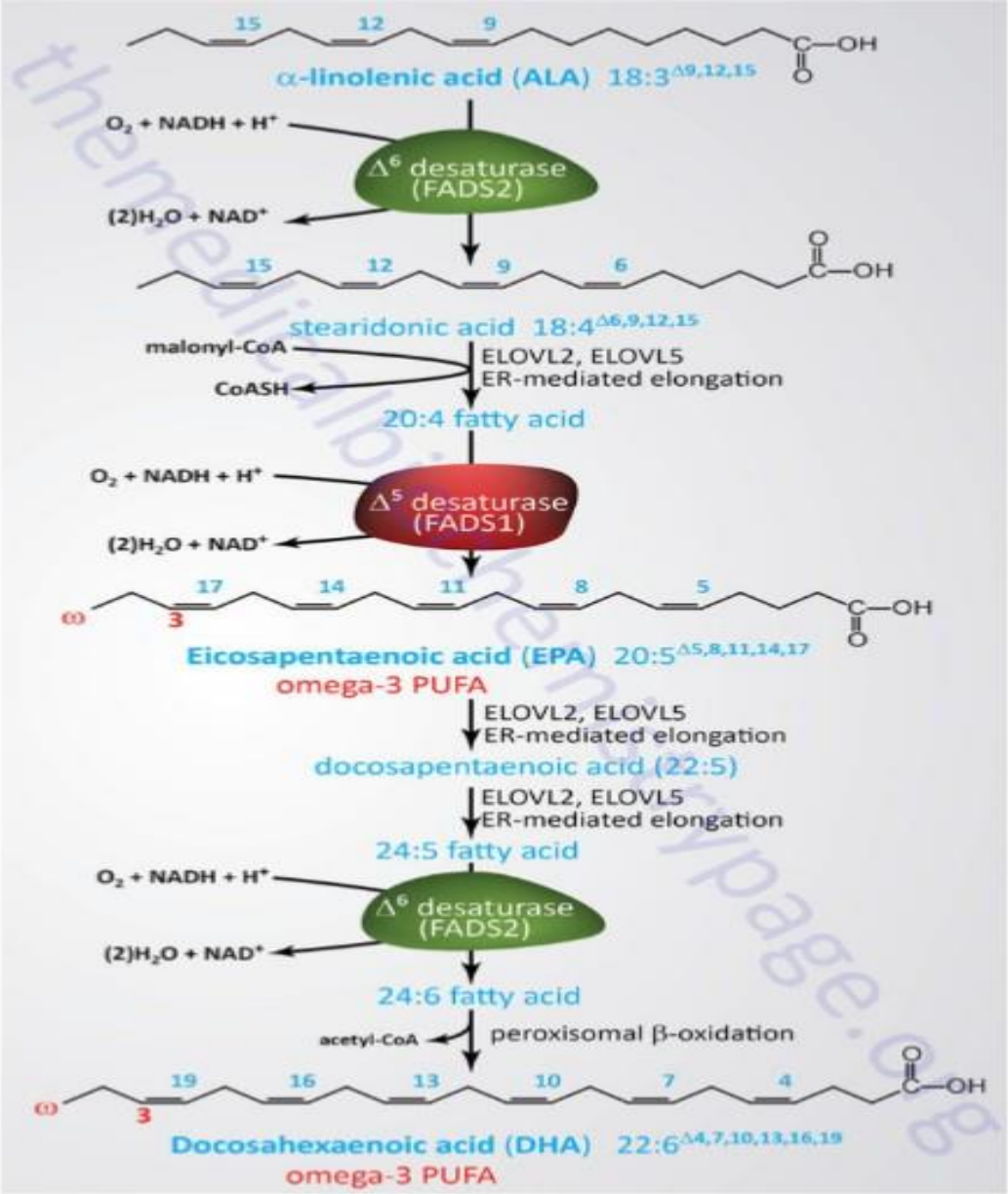

Figure 1 Synthesis of omega-3 PUFA(The Medical Biochemistry Page, Updated December 2022).

The polyunsaturated fatty acids consist of α-Linolenic acid(ALA), stearidonic acid, eicosapentaenoic acid(EPA) and docosahexaenoic acid(DHA). DHA alongside with EPA are contained in algae, fish(trout, salmon and tuna) and in fish oil supplements.ALA is only present in plants (such as walnuts and They lack the required enzymes for an 18-carbon chain fatty acid with 15 double bonds. The metabolic reaction of ALA mainly takes place in the liver, while it also happens in other organs (Hughes and Dhiman 2002). α-linolenic acid (ALA) can be transformed into eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) by the sequential, alternate desaturation and elongation (extension of the carbon chain) actions of microsomal endoplasmic reticulum 5-desaturase and 6-elongase. The enzyme D15-desaturase desaturates omega-6 fatty acid [18:2(n-6)] to produce linolenic acid. The rate-limiting enzyme D6-desaturase first converts linolenic acid [18:4(n-3)] into stearidonic acid. Eicosatetraenoic acid can then be produced by extending stearidonic acid [20:4(n-3)].D5-fatty acid desaturase performs additional desaturation to produce EPA [20:5(n-3)], which is thought to be superior to α-linolenic acid since it does not need the action of the regulating-step D6-desaturase enzyme. D6-Desaturase then converts EPA into DHA [22:6(n-3)] by a restricted process of peroxisomal -oxidation. Docosapentanoic acid (DPA3) is also utilized in this process. Hormones, nutritional condition, and feedback inhibition by end products are only a few of the variables that might affect the enzymes' (D6- and D5-desaturases) activity (Philip 2012). Additionally, DHA, EPA, and DPA can be produced by a process called retro-conversion that only necessitates a little amount of peroxisomal oxidation.

3. Role of omega -3 PUFAS on cancer

3.1. NF-KB downregulation

An ancient protein complex, Nuclear Factor-Kappa B (NF-kB), belonging to a family of activating transcription factors that controls a broad category of genes needed for several biological activities. It can be found in almost all animal cells. In the cytoplasm of inactive cells, NF-kB is usually found in p65 and p50 as a dimer of different structure that is connected to IkB which exhibit an inhibitory action. IkB kinase (IKK) complex phosphorylates IkB and the process is initiated or triggered by proinflammatory stimuli. This causes IkB to be ubiquitinated and broken down by proteasomes, which causes NF-KB to translocate to the nucleus. Cancer, autoimmune disorders, viral infections, and malignancy have all been linked to inadequate control of this transcription factor. In cultured endothelial cells, it has been discovered that EPA and DHA block the formation of cycloxygenase-2 (COX-2), cell signaling protein(TNF-alpha), pro-inflammatory cytokines, as well as inducible nitric oxide (NO) synthase. These NF-KB inhibitory action of (n-3) PUFA is apparently connected to reduced IkB phosphorylation and NF-KB induction. Fish oil supplementation also lowers NF-KBinduction in lab mice (Xi *et al.,* 2001). According to Vanden *et al.* (2003), ligand-bound PPAR physically interacts with NF-KB to stop it from moving to the nucleus. (ω-3) PUFA may be useful in altering the formation of cancer by preventing the overexpression of NF-kB target genes.

3.2. Production of pro resolution mediators

The ω-3 PUFAs(EPA and DHA), which are found in fishes containing fats in considerable amounts that are used in dietary supplements, have been related to a number of health benefits. Prior research has demonstrated the protective effects of high daily dosages of essential omega-3 PUFAs (milligrams to grams) on cancer, a number of inflammatory illnesses, and human health in general (Simopoulos, 2002). Inflammation, which raises the risk of getting cancer, supports all phases of carcinogenesis. Acute inflammation must completely subside and be followed by a return to equilibrium for tissues to be considered healthy. Lipid mediators with anti-inflammatory effects can act as agonists and exert their protective effects in a variety of ways. They enhance leukocyte (neutrophil) and granulocyte permeation, promote monocyte non-inflammatory penetration, foster mucosal antimicrobial defense, and increase phagocyte exocytosis from the inflammatory site to the lymphatic system (Serhan *et al.,* 2008). The body converts EPA, DPA, or DHA into resolvens, lipoxins, and protectins, three structurally different pro-inlammatory mediators. Resolvins of the E(E1/E2) and D(D1-4) classes are obtained from EPA and DHA that have two forms with structural distinctions. Human vascular endothelial cells can produce resolvin E1 in vitro when aspirin is present in a reduced oxygen containing vicinity. When these cellular entities emit 18R-hydroxyeicosapentanoic acid (18R-HEPE), activated human neutrophil 5-lipoxygenase swiftly alters it (Serhan *et al.,* 2000). EPA undergoes a transformation that results in the production of 18R-hydroperoxyeicosapentaenoic acid (18R-HPEPE). Human neutrophils can then convert 18-HEPE into resolvin E1 and resolvin E2 from EPA, which are changed into 18-HEPE by micro-organism and human cytochrome P450 enzymes (Serhan *et al.,* 2000). Resolvin E1 is formed in peoplewith good state of health, it is elevated in the blood plasma of individualusing EPA alongside with or without aspirin, but Resolvin E2 has a potent anti-inflammatory effect because it decreases zymosan-initiated neutrophil infiltration (Tjonahen 2006). A collection of Resolvin D1 to D4 containing 17S-hydroxyl groups are produced in vivo from endogenous DHA (Serhan *et al.,* 2002). Strongly anti-inflammatory, these resolvins. A process involving lipoxygenase converts DHA into an intermediate that contains 17S-hydroperoxide to

produce protectin (Hongv *et al.,* 2003). This intermediate is spontaneously transformed by human white blood cells into a 16,17-epoxide, via enzymatic action to produce a 10,17-dihydroxy anti-inflammatory molecule. Protectin D1 inhibits the mobility of T-cell intracellularly and increases T-cell mortality, according to Sharma et al.'s findings from 2003.

3.3. COX-2 suppression

Cancer cells usually have high levels of cycloxygenase-2 expression. The development of cancer and inflammatory diseases has been linked to the inflammatory-inducible enzyme cycloxygenase-2 (COX-2). Sharma *et al*. (2003) speculate that it could also promote angiogenesis, tumor tissue invasion, and resistance to apoptosis. Phospholipase A2 releases arachidonic acid (AA) from the phospholipids in cellular membranes. This AA is next transformed by COX2 into prostaglandin (PGH2), which is then further modified by prostaglandin synthase into specific prostaglandins like PGE2. In contrast to eicosanoids made from arachidonic acid, Needleman *et al*. (1979) found that DHA/EPA lowers or modifies COX 2 products, resulting in compounds that have a tendency to drive inflammation and proliferation less. PGE2 stimulates the downstream EP receptor, increasing cellular proliferation, encouraging angiogenesis, and inhibiting apoptosis. The COX2 gene promoter on chromosome 1 is responsible for encoding the NF-kB response element, according to Chandrasekharan and Simmons (2004). N-3 PUFAs decrease NF-KB, culminating to a decrease COX 2 manifestation which result in the growth of metastatic cancers. COX 2 produces proliferative eicosanoids.

3.4. Effect on mitosis

A cancer cell must divide often in order to increase in size. It must go through the mitotic process, which is the division of a single cell into two identical daughters, in order to do this. Multiple mitotic protein kinases must collaborate in order to start mitosis (Larry and Alan, 1991). A crucial regulator of cell cycle advancement and specialization is the enzyme kinase C member of serine/threonine phosphate group adding enzymes. According to Silvia *et al.* (2018), PKC regulates mitotic development via centrosome-controlled movement and assemblage of mitotic spindle fiber. The conclusion drawn from this study supports the idea that PKC might make a good target for cancer remedy. According to Larry *et a*l.(1991), studies have indicated that a continuous sequence of ω-3 fatty acids, which are found in various fish oil in high concentrations, offer protective advantages against a variety of prevalent malignancies. Laboratory and population-based research have unveiled that the dissolution of layer of nucleus during mitosis and mitotic on-set depend on Protein kinase -II activation at the G2 phase. According to Craven and DeRubertis (1988); Rose and Connolly (1999), LA/AA either boosts PKC directly inside the cell or indirectly by acting on the cell membranes, whereas EPA/DHA decreases PKC activity. In the oncogenes Cancer cells frequently have active Ras and AP-1, which starts the mitotic process. The n-3 FA inhibits the activation of the ras and AP-1 oncogenes, according to research by Collett *et al.* (2001) and Liu *et al.* (2001).

3.5. Angiogenesis suppression

For a tumor to grow and spread, angiogenesis, which is controlled by chemical signals in the body and results in endothelial cellular mobility, multiplication, specialization and lines the inner walls of blood vessels, is crucial. High concentration of ω-3 in fish oil has the potential to inhibit tumor angiogenesis and reduce tumor invasiveness. Studies have shown that whereas the ω-3 products of LOX and COX fails to promote growth of blood vessels in cancerous tissues, the n-6 products do. The eicosanoid metabolic pathway and a reduction of hormonal induction in protein kinase C are two examples of metabolisms that could be changed to accomplish this.

3.6. Upregulating apoptotic pathway

Intentional cell death is known as apoptosis. It is used to remove cells that have been irreparably damaged, and if it is interfered with in any manner, it can result in unchecked cell division and the subsequent growth of tumors. The transcription factor NF-KB has been demonstrated to be associated with apoptosis and to perform either a pro- or anti-apoptotic role depending on the kind of cell in which it is expressed. According to Alessio *et al.* (2004) and Chen *et al*. (2007), NF-kB happens to be most significant transcription factor involved in survival because it increases the transcription of proteins that stop apoptosis, such Bcl-2. According to Wang et al.'s research, cells with inactive NF-kB are more vulnerable to apoptosis in response to stimuli other than the pro-inflammatory cytokine TNF-. Kern *et al.* (2006) found that COX-2 inhibition in hepatocellular cancer also stimulates mitochondrial and death receptor-mediated apoptotic signaling. Cao *et al.* (2002) claim that COX-2 reduces cancer cells' production of nitric oxide (NO), a sign of pro-apoptosis, after prostaglandin (PGE2).Because of their capacity to prevent NF-KB and COX-2 activation, EPA and DHA can reduce the negative effects of their apoptosis-suppressing effects. The protein group (Bcl-2), which has both pro-apoptotic and anti-apoptotic members, is responsible for controlling the mitochondrial apoptosis process. When present, the anti-apoptotic proteins (Bcl-2 and Bcl-XL) halt apoptotic process. Studies by Chiu and Wan (1999) and Narayanan *et al.* (2001) claim that DHA enhances the genetic synthesis of Ribonucleic acid and regulatory

protein(transcription factors) that trigger programmed cell death while suppressing the transcription of Bcl-2 family genes.

4. Conclusion

Fish oil is considered to have a variety of advantages due to its high amount of ω -3 fatty acids. Numerous diseases can be prevented and possibly treated with the help of the (ω-3) PUFA group of physiologically active fatty acids. Linolenic acid, the most fundamental class of this family, can be changed into a more physiologically active and extremely long-chain (n-3) PUFA(EPA and DHA) through a number of desaturation and elongation pathways. Both epidemiological and experimental research have shown that ω-3 fatty acids that are prevalent in fish oils and also associated with lower risk of getting cancer, have preventive effects. The interaction of PUFA biology with nuclear receptor proteins is one of its most fascinating features. So it makes sense to assume that eating of food rich in ω-3 fatty acids may lengthen the lives of cancer patients, also improve the quality of their lives by reducing or preventing the proliferation of cancer cells with deleterious effect. This would make consuming of food rich in omega-3 fatty acids an efficient tumor treatment method. There is an imperative need for our daily meal to contain a whole grain, vegetables, fruits, small amount of meat, fat-contained fishes and may be ω-3 supplements. The aforementioned food source will help to increase the ω-3 bodily requirement that may help to ameliorate the health burden caused by cancer.

Compliance with ethical standards

Disclosure of conflict of interest

There is no conflict of interest.

Contribution of authors

All authors contributed immensely to this review article. Isaac S. MOMOH made substantial contributions to conception, design and drafting of the manuscript; Micheal O. IBRAHIM and Victoria S. EMMANUEL participated in acquisition of data and drafting of the manuscript. Emieseimokumo NUMONDE and Peter A. AKOMOLAFE revised the article critically for important intellectual content and gave a final approval of the version to be submitted.

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