International Journal of Nutritional Sciences

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Mini Review

Polyunsaturated Fatty Acids and their Role in the Diet of Cancer Patients: An Overview

Frattaruolo L[1], Aiello F[1], Carullo G[1], Fiorillo M[1], Brindisi M[1], Cappello MS[2], Pilco G[1] and Cappello AR[1]*

[1]Department of Pharmacy, Health and Nutritional Sciences, University of Calabria, Italy

[2]CNR, Institute of Science of Food Production (ISPA), Lecce, Italy

***Corresponding author:** Cappello AR, Department of Pharmacy, Health and NutritionalSciences, University of Calabria, Edificio Poli Funzionale, Via P. Bucci, 87040 Arcavacata di Rende, Cosenza, Italy

Received: June 25, 2018; **Accepted:** August 13, 2018; **Published:** August 20, 2018

Abstract

Polyunsaturated Fatty Acids (PUFAs) are a class of natural compounds with interesting biochemical effects on human health. Indeed, in addition to their beneficial effects in brain and cardiovascular disorders, ω-3 LC-PUFA supplementation can exert antineoplastic activity by triggering cell death in human cancer cells, either alone or in combination with conventional therapies. The aim of this review is, by analyzing the recent scientific literature, to highlight the molecular mechanisms of Omega-3Polyunsaturated Fatty Acids (ω-3 PUFAs) in antineoplastic events, and the effects of supplementing diets with them during chemotherapy regimens. This analysis may provide specific information to carry out future pre-clinical and clinical studies aimed at a better use of omega-3polyunsaturated fatty acids in cancer therapy.

Keywords: Polyunsaturated fatty acids; Anti tumor activity; Cancer therapy; Diet in chemotherapy regimen

Introduction

Polyunsaturated fatty acids, also known as PUFAs, are molecules chemically characterized by a long carbon chain, starting with a Carboxyl Group (COOH) followed by a series of carbon atoms and ending with a methyl group (CH_3), held together by simples and at least two double bonds. The nomenclature of fatty acids involves assigning a Greek letter to each carbon atom according to its distance from the carboxylic end, and the terminal carbon atom is indicated with the last letter in the Greek alphabet, i.e. omega (ω). PUFAs can be classified as "omega-6" or "omega-3" on the basis of the position of the first double bond with respect to the methyl terminal portion. A secondary classification, important from a biochemical point of view, could be made to distinguish short- and long-chain polyunsaturated fatty acids. Short-chain PUFAs, Alpha-Linolenic Acid (ALA, 18:3 n-3) and Linoleic Acid (LA, 18:2 n-6), are defined as Essential (EFAs) because animals are unable to synthesize them ex-novo, so they must be obtained *via* the diet. The cell desaturation systems are in fact unable to introduce double bonds into the proximity of the methyl terminal, and these systems are just able to extend the fatty acid chain and to increase the number of unsaturations on it. The cellular desaturation/elongation pathway is thus responsible for the conversion of ALA into ω-3 long-chain PUFAs, such as Eicosa Pentaenoic Acid (EPA, 20:5 n-3) and Docosa Hexaenoic Acid (DHA, 22:6 n-3), and LA into ω-6 long-chain PUFAs, such as Arachidonic Acid (AA, 20:4 n-6) (Figure 1) [1]. The conversion efficiency in humans, however, is not high [2]. And consumption of long-chain ω-6 and ω-3 PUFAs containing food help keep them at optimal levels for cellular functions. ω-6 and ω-3 PUFAs are, indeed, essential components of the plasma membrane and precursors of eicosanoids, such as prostaglandins, thromboxanes and leukotrienes. All of them derive from ω-6 and ω-3 fatty acid metabolism through reactions catalyzed by the enzymes cyclooxygenase and lipoxygenase, and is important mediators of many physiological and pathological functions.

Oily fish, such as salmon, herring, mackerel, anchovies and sardines, as well as other fish and seafood are the main sources of long-chain ω-3 PUFAs, while eggs and lean red meat provide smaller amounts. Moreover, an interesting vegetarian source of DHA is marine algae, responsible for making fish a rich source of long-chain ω-3 PUFAs. On the other hand, cereals and vegetable oils provide high levels of ALA but are poor sources of long-chain ω-3 PUFAs [3,4].

ω-3Pufas in human health

Polyunsaturated fatty acids are essential molecules in human health. They are involved in various biological pathways and are beginning to play a significantrole in the treatment of several diseases [5-8]. For example, it is well known that a ω-3 PUFA-based diet is a good way of treating the hyper lipidemia associated with junk food consumption, which is rich in saturated fatty acids, responsible for atherosclerotic plaque formation, particularly around heart tissue. Various food supplements and nutraceuticals are based on ω-3 PUFAs and are used to promote positive cardiovascular health. Substantial (2 g/day) intakes of ω-3 PUFAs efficiently reduce plasma Triacylglycerol (TG) concentrations. This is the most relevant effect of ω-3 PUFAs on plasma lipids and has been explained by different mechanisms such as decreased TG synthesis due to reduced substrate availability subsequent to lipogenesis inhibition and β-oxidation stimulation and a shift in lipid synthesis toward phospholipids rather than TG [5]. Moreover, DHA is a constituent of retinal tissue and ω-3 PUFAs have shown cytoprotective and cytotherapeutic actions, contributing to several anti-angiogenic and neuroprotective mechanisms within the retina [6]. DHA also contributes to the formation of phospholipids in brain tissue, and several studies and clinical trials in healthy individuals indicate that long-chain ω-3 Poly Unsaturated Fatty Acid (ω-3 LC-PUFAs) intake may be associated with increased functional activation of the prefrontal cortex in children, and greater gray matter volume and white matter integrity during aging. However, its effects on cognition are not clear and, at the moment there is

Citation: Frattaruolo L, Aiello F, Carullo G, Fiorillo M, Brindisi M, Pilco G , et al. Polyunsaturated Fatty Acids and their Role in the Diet of Cancer Patients: An Overview. Int J Nutr Sci. 2018; 3(2): 1024.

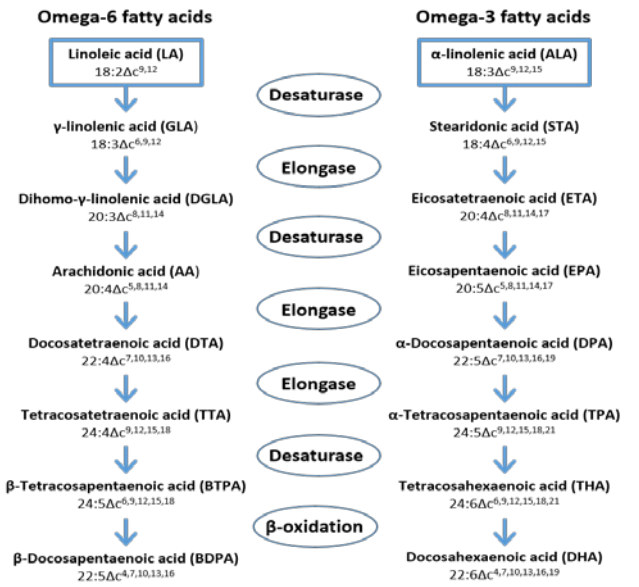

Figure 1: Biosynthesis of long-chain PUFAs, through elongation/desaturation system.

only limited evidence to support the hypothesis that ω-3 LC-PUFA supplementation is beneficial in brain disorders, such as Alzheimer's disease, attention deficit/hyperactivity disorder, major depressive disorder and schizophrenia [7].

A report by a FAO/WHO expert panel supported the hypothesis that high PUFA intake is a 'probable' beneficial factor for diabetes; although further experimental data demonstrated that the relations between fatty acid intake and markers of type 2 diabetes risk may depend on the dietary sources of the fatty acids [8].

Fatty acids, moreover, are versatile molecules which can be conjugated to various substrates with the aim of improving the biological activity of the substrate itself and, in this field, several examples are present in literature. For example, unsaturated fatty acids have been conjugated with hormones for androgen-requiring therapy [9]. Or with flavonoids to improve antioxidant capacity [10,11].

ω-3PUFA antitumor activity

In vitro and *in vivo* studies have highlighted ω-3 PUFAs' antitumor activity. These molecules are indeed able to induce cancer cell death by intrinsic and extrinsic apoptotic pathways. Over the years, various studies have been carried out, aiming to identify the molecular mechanism by which ω-3 PUFAs perform their activity. The results have shown that these molecules are characterized by a complex action mode and that their anti tumoral effect seems to be the consequence of different coexistent mechanisms, such as lipid raft alterations, PPARγ alterations and oxidative stress induction (Figure 2).

Alteration of Lipid Rafts Composition and Function

ω-3 PUFAs are incorporated into phospholipids of biological membranes. The presence of ω-3 PUFAs in the plasma membrane changes its chemical-physical properties such as permeability, fluidity and the activity of proteins associated with it. For example, ω-3 PUFAs are able to alter specific micro domains of the lipid membrane, termed lipid rafts. These domains are characterized by high cholesterol and sphingolipid content and include proteins that mediate different signal-transduction processes, such as those involved in the proliferative stimulus and cell survival. Several studies performed on T-cells and different tumor cell lines have shown that the incorporation of ω-3 PUFAs into membranes leads to an imbalance in phospholipid composition and in the amount of cholesterol in lipid rafts. This structural alteration evolves towards displacement of several raft-associated onco-proteins, including Epidermal Growth Factor Receptor (EGFR), protein a superficial di membrane c-erbB-2 (c-erbB-2), heat shock protein 90 (Hsp90), protein-chinasi B (Akt), and proto-oncogene tyrosine-protein kinase (Src), over expressed or functionally alternated in several tumor cell lines and responsible for uncontrolled tumor proliferation [12-16].

Pparγ activation and gene expression regulation

ω-3 PUFAs are able to interact with the family of Peroxisome Proliferator-Activated Receptors (PPARs), several studies having shown that ω-3 PUFAs are able to activate the PPARγ receptor. PPARs bind to a specific DNA sequence termed Peroxisome Proliferator Response Element (PPRE). Most known target genes of PPARγ regulate lipid metabolism and transport, but some of its targets are cancer-related genes, involved in different ways in cellular growth and survival. *In vitro* and *in vivo* studies, performed on breast and prostatic cancer and lymphocytic leukemia models, have demonstrated that PPARγ targets related to the anticancer effect of ω-3 PUFAs include the promoters of protein tumor suppressor p^{53}, Fas ligand and syndecan 1, which are involved in cell cycle arrest and in the triggering of extrinsic and intrinsic apoptotic processes [17-20].

Lipid Peroxidation and Oxidative Stress

The antineoplastic activity of ω-3 PUFAs has also been associated with their ability to stimulate ROS production at cellular level and to induce oxidative stress [21,22]. This seems to be due to the susceptibility to peroxidation processes of ω-3 PUFAs incorporated in plasma and mitochondrial membranes; thus, the highly reactive products generated by these oxidative mechanisms are able to react with biological macromolecules and to form DNA adducts [23]. Further studies have shown that the ability of these molecules to increase Reactive Oxygen Species (ROS) levels is responsible for sensitizingcancer cells to the activity of different anticancer agents, in combined treatments [24]; the pro-oxidant nature at the base of this latter synergistic activity has been confirmed by investigations in which loss of activity has been evidenced after administration of antioxidant agents [25].

Enzymatic Oxydation Metabolites

At cellular level, ω-3 PUFAs may undergo oxidative metabolism catalyzed by Cyclooxygenase (COX) and Lipoxygenase (LOX) enzymes. ω-3 PUFAs compete with ω-6 PUFAs, such as arachidonic acid, as substrates for the two enzymes, and the products that are obtained from the metabolism of these two classes of PUFAs are very different from a biological potential point of view.

EPA can be hydroxylated by 15-Lipoxygenase (15-LOX) and

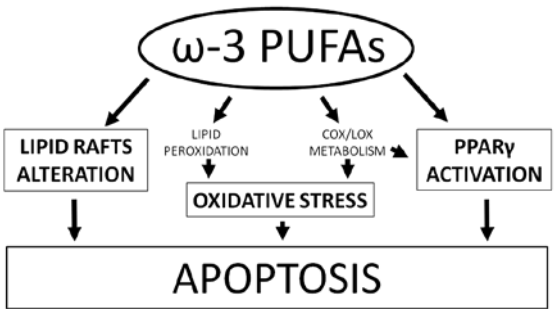

Figure 2: Mechanisms underlying the antitumor effect of ω-3 PUFAs.

Acetylated Cyclooxygenase-2 (acetylated-COX-2) to form 18(R/S)-HEPA, Precursors of E-Series Resolvins (RvE). DHA, similarly, is hydroxylated to form 17S-HDHAand 17R-HDHA, Precursors of D-Series Resolvins (RvD) and protectins. The involvement of resolvins and protectins in the antitumor action of ω-3 PUFAs is unclear. Conversely, these mediators play anti-inflammatory and pro-resolving roles, leading to cellular protection [26]. However, the oxidative metabolism of ω-3 PUFAs is different in cancer cells than in normal cells and this may explain the different effects (cytoprotective-cytotoxic) of these compounds in different cell types. Recent studies have in fact shown that the toxic action of DHA on neuroblastoma cells is due to its conversion to 17-hydroperoxydocosahexaenoic acid (17HpDHA) by 15-LOX activity. This molecule, strongly cytotoxic *via* pro-oxidant mechanisms, is an intermediate in the synthesis of resolvins and protectins, and is quickly metabolized in healthy cells. In neuroblastoma cells, the production of resolvins and protectins is blocked and this is reflected in 17HpDHA accumulation and cytotoxicity [27].

Another bioactive metabolite involved in the antitumor activity of ω-3 PUFAs is Prostaglandin E3 (PGE3), generated from EPA by COX-2. It has shown anti-proliferative, pro-apoptotic and anti-angiogenic activity on human lung cancer cells, through alteration of Epidermal Growth Factor Receptor (EGFR) and Mitogen-Activated Protein Kinases (MAPK) pathways [28].

ω-3PUFA Supplementation in Chemotherapy: Clinical Trials

In cancer, there is a close relationship between malnutrition and disease itself. It is known that undernourished individuals report decreased quality of life, and present increased risks of therapy failure and sideeffects, besides a higher mortality rate [29].

Several recent clinical trials have shown improved chemotherapy tolerability and patient outcomes associated with adjuvant ω-3 PUFA supplementation [28-30].

A clinical study has shown that addition of DHA to chemotherapy is devoid of adverse side effects and may improve the outcome of metastatic breast cancer patients. For example, patients with high incorporation of supplemented DHA experienced longer time to disease progression (8.7 months *vs* 3.5 months) and significantly longer survival (median survival time: 34 months *vs* 18 months) compared to patients with lower incorporation of supplemented DHA [28]. These results suggest that DHA has the potential to specifically chemo sensitive tumors.

Additionally, lung cancer patients receiving platinum-based chemotherapy with fish oil supplementation received more chemotherapy cycles and showed significantly higher tumor response rates (60% *vs* 25.8%), clinical benefits (80% *vs* 42%) and one-year survival rates (60.0% *vs* 38.7%), compared to the control group, proving that ω-3 PUFA supplementation can increase the efficacy of chemotherapy without affecting the toxicity profile [29].

A randomized clinical trial demonstrated that dietary supplementation of ω-3 PUFAs in patients with advanced cervical cancer may help to reduce the inflammatory status, enhancing tumor response to radiation therapy [30].

Moreover, it has been reported that fish oil supplementation (2g/day) for the first 9 weeks of chemotherapy contributes to a delay in tumor progression in colorectal cancer patients, with a significantly longer time to tumor progression in the supplemented chemotherapy group [593 days (±211.5) vs 330 days (±135.1)] [31].

Chemotherapy is commonly associated both with nutritional impact symptoms, which may alter the intake of important nutrients, and with chemotherapy-induced toxicities, leading to lower quality of life, worse outcomes and interruption of prescribed treatment.

Recent clinical trials have shown that ω-3 PUFA supplementation, during chemotherapy, can reduce nutritional impact symptoms such as nausea, vomiting and appetite loss, increasing nutrient consumption and decreasing lean body mass depletion and loss of weight [32-41]. This improvement in nutritional status may be related to the better chemotherapy tolerability and overall patient outcomes, demonstrated in clinical trials. Furthermore, ω-3 PUFA supplementation was reported to significantly reduce the pro-inflammatory status induced by chemotherapy, and other therapy-related toxicities, such as anemia, thrombocytopenia and neuropathy, in colorectal [37,38], lung [39,40], and breast [28,42], cancer patients. Moreover, ω-3 PUFA adjuvant therapy ameliorates methotrexate-induced hepatotoxicity in children and adolescents with acute lymphoblastic leukemia [43].

Conclusion

According to *in vitro* and *in vivo* pre-clinical studies, ω-3 PUFAs are characterized by interesting antitumor activity, due to their ability to interfere with different pathways in cancer cells, through direct action or cell metabolism derivatives. Clinical trials have confirmed the usefulness of ω-3 PUFA nutritional supplementation to improve chemotherapy efficiency and tolerability. Therefore, today, despite the widespread belief that a good nutritional state improves tolerability to chemotherapy, there is not much experimental evidence that closely links feeding with response to chemotherapy treatments; further investigations will be needed to firmly establish this correlation.

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Int J Nutr Sci - Volume 3 Issue 2 - 2018
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Citation: Frattaruolo L, Aiello F, Carullo G, Fiorillo M, Brindisi M, Pilco G , et al. Polyunsaturated Fatty Acids and their Role in the Diet of Cancer Patients: An Overview. Int J Nutr Sci. 2018; 3(2): 1024.