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THERAPEUTIC POTENTIAL OF OMEGA FATTY ACIDS IN BREAST CANCER. REVIEW

POTENCIAL TERAPÉUTICO DE ÁCIDOS GRASOS OMEGA EN CÁNCER DE MAMA. REVISIÓN

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ABSTRACT

Background: Breast cancer is the second cause of death in women in developed and undeveloped countries, including Colombia. A high percentage of these tumors is estrogen dependent, for which the hormonal treatment is the most used therapy in breast cancer. Currently, the first line treatment for breast tumor in postmenopausal women is the letrozole, an aromatase enzyme inhibitor that avoids the transformation of androgens to estrogens. Since letrozole produced adverse effects on patients, there is a requirement for new alternative treatments. Furthermore, omega fatty acids (ω-FA), essential as they are obtained from the normal diet or from dietary supplements, have demonstrated nutraceutical potential because of their anti-inflammatory or pro-inflammatory activity. Nonetheless, there is controversy in *in vitro*, *in vivo* and epidemiologic reports regarding their preventive or inducing activities of carcinogenesis in animals and humans, depending on the structure of the ω-FA. **Objectives**: This review aims to show the main *in vitro*, *in vivo* and epidemiologic evidences of the chemotherapeutic potential of ω-3 and ω-6 FA in different types of neoplasm, particularly in breast cancer, in individual or combined treatments with diverse antineoplastics. **Methods**: PubMed and Science Direct databases revealed the most representative studies, published during the last two decades, about ω-3 and ω-6 FA, breast cancer and the principal therapeutic strategies for this neoplasm. Findings were presented in separated topics to provide an overview of ω-FA and their potential in treatments for breast cancer. **Results**: Patients treated with estrogens and progesterone derivate have shown predisposition to develop breast cancer after two years of continued therapy. Furthermore, ω-FA with known nutraceutical potential have demonstrated their potential as adjuvants in the treatment against different neoplasms, like hepatic and colon cancer. **Conclusions**: Current therapies for breast cancer and their low efficacy in the long term led to explore new alternative treatments with ω-FA. These essential fatty acids in daily consumption could enhance the antineoplastic agent effect. Nevertheless, metabolism of the ω-FA must be considered for this use.

Keywords: Unsaturated fatty acids, hormonal treatment, fish oils, anti-inflammatory agents.

RESUMEN

Antecedentes: el cáncer de mama es la segunda causa de muerte de mujeres en países desarrollados y no desarrollados, incluido Colombia. La mayoría de estos tumores son dependientes de estrógeno por esa razón, la terapia más utilizada es la hormonal. Actualmente, el tratamiento de primera línea en mujeres posmenopáusicas es el letrozol, inhibidor de la enzima aromatasa, que evita la conversión de

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andrógenos en estrógenos. El letrozol causa efectos adversos en las pacientes, lo cual motiva la búsqueda de nuevas alternativas que disminuyan estos efectos. Los ácidos grasos omega, esenciales en la dieta regular o suplementaria, han mostrado su potencial nutracéutico ambivalente, como antiinflamatorios o proinflamatorios. Debido a esto, existe controversia en distintos reportes a nivel *in vitro*, *in vivo* y epidemiológicos sobre la actividad preventiva o quimioterapéutica de los ω-3 y ω-6 AGOs. **Objetivos**: el aporte de este artículo, es mostrar las principales evidencias *in vitro*, *in vivo* y epidemiológicas del potencial quimioterapéutico de los AGOs en tratamientos individuales y combinados con antineoplásicos, en distintos tipos de cánceres, particularmente en el cáncer de mama. **Métodos**: se revisaron las bases de datos PubMed y Science Direct y se seleccionaron los estudios más representativos de las dos últimas décadas sobre ω-3 y ω-6 AGOs y las principales estrategias usadas en el cáncer de mama. Los hallazgos se presentan en temas separados, primero una visión general de los AGOs y luego su potencial bioactivo en tratamientos contra el cáncer de mama. **Resultados**: la mayoría de los estudios en pacientes con cáncer de mama, tratadas con estrógenos y derivados de progesterona, han mostrado predisposición a desarrollar cáncer de mama después de dos años de terapia continua. De otro lado, los AGOs han demostrado su potencial como adyuvantes en el tratamiento en diferentes cánceres como el de colon y hepático. **Conclusiones**: las terapias actuales para el cáncer de mama y su baja eficacia a largo plazo exigen explorar nuevas alternativas de terapias, que incluyen los AGOs podrían potenciar fármacos, no obstante, es necesario tener en cuenta, el metabolismo de los AGOs, para uso.

Palabras clave: Ácidos grasos insaturados, tratamiento hormonal, aceites de pescado, antiinflamatorios.

INTRODUCTION

This work analyzed the most relevant publications on the results of the evaluation of the preventive or therapeutic potentials of omega fatty acids (ω-FA), such as, omega-3 (ω-3), omega-6 (ω- 6) and omega-9 (ω-9) and some of its derivatives in the control of cancer, particularly of breast carcinoma. The used key words related to the topic were, among others, breast tumor cell lines, viability, cell cycle and apoptosis, and the most recent information was reviewed in PubMed and ScienceDirect databases, through the digital platform of Universidad Nacional de Colombia, in the period 2012-2018.

From the articles to which we had access, we also reviewed older references that supported the *in vitro*, *in vivo* or epidemiological evidences of the biological effects of the ω-FA in animal and human cellular models. In addition, some treatments used in combination with these ω-FA in cancer patients were reviewed to contextualize the state of the art for breast cancer and its potential alternative therapies to reduce the side effects of conventional hormonal treatments.

Polyunsaturated fatty acids (PUFAs) are large hydrocarbon molecules with different number of unsaturated bonds. The presence of the first double bond in the position 3, 6 or 9 from the terminal -CH3 group of the hydrocarbon chain classifies them as fatty acids (FA) of the omega series and are of special interest for their benefits in health. Further, they are named as ω-3, ω-6 and ω-9, and their main characteristics are described in Table 1.

ω-3 FA, as *cis*-5,8,11,14,17-eicosapentaenoic (EPA, C20:5) and *cis*-4,7,10,13,16,19-docosahexaenoic (DHA, C22:6) acids are important at dietary level and are found in cold-water fishes. Similarly, *cis*-9,12,15-octadecatrienoic acid (α-linolenic, ALA, 18:3), found in linseed, colza and nuts, is also important in certain diets (Figure 1). In some genetically modified plants the ω-3 *cis*-6,9,12,15-stearidonic acid (SDA, C18:4), besides from producing EPA from SDA (1,2), can be synthesized.

Table 1. Classification of ω-3, ω-6 and ω-9 fatty acids according to the number of carbon atoms and to the number of unsaturated bonds.

Omega fatty acid (ω)	Common name	Initials	IUPAC name	# of carbon atoms/ #unsaturation	Chemical formula
ω-3	Docosahexaenoic acid	DHA	*cis*-4,7,10,13,16,19-Docosahexaenoic acid	C22:6	$C_{22}H_{32}O_2$
ω-3	Eicosapentaenoic acid	EPA	*cis*-5,8,11,14,17-Eicosapentaenoic acid	C20:5	$C_{20}H_{30}O_2$
ω-6	Arachidonic acid	AA	*cis*-5,8,11,14-Eicosatetraenoic acid	C20:4	$C_{20}H_{32}O_2$
ω-3	α-Linolenic acid	ALA	*cis*-9,12,15-Octadecatrienoic acid	C18:3	$C_{18}H_{30}O_2$
ω-6	Linoleic acid	LA	*cis*-9,12-Octadecadienoic acid	C18:2	$C_{18}H_{32}O_2$
ω-9	Oleic acid	OA	*cis*-9-Octadecenoic acid	C18:1	$C_{18}H_{34}O_2$

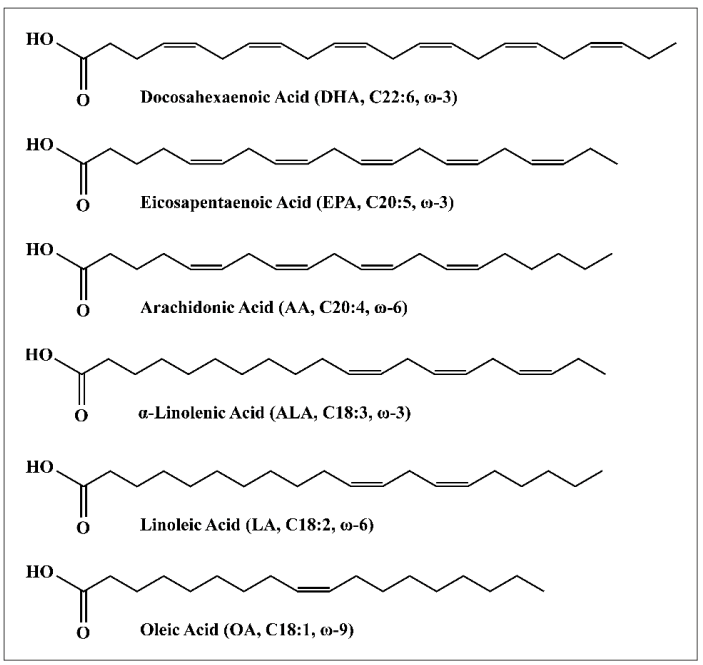

Figure 1. Chemical structure of ω-3, ω-6 and ω-9 fatty acids. DHA: docosahexaenoic acid, EPA: eicosapentaenoic acid, AA: arachidonic acid, ALA: α-linolenic acid, LA: linoleic acid, OA: oleic acid.

Moreover, the ω-9 acid, monounsaturated 9-octadecanoic or oleic (OA, C18:1), present in foods of the Mediterranean diet, such as olive oil (80-85%), avocado (70-75%), grape (15-20%) and pork meat (38%) (3), has demonstrated its preventive potential in human breast (4-6) and early colorectal carcinogenesis (7-9), and in animals it avoids the development of colon cancer (10-12). Furthermore, in breast tumor cell lines MDA-MB-231, it stimulated cell migration by AA metabolism (13), further to avoiding the development of colon cancer in animals (Figure 2). The OA has been used as a treatment for the prevention of cancer development, but there are no studies that reveal its potential as a chemotherapeutic agent.

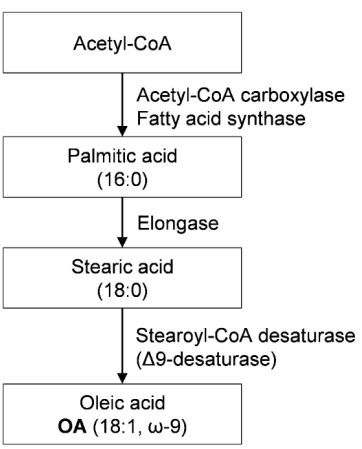

Figure 2. Metabolic pathway of the ω-9 fatty acid, oleic acid (OA). Adapted from (14).

Despite PUFAs are essential cell components, there are more studies for ω-3 FA concerning their biological activities than for ω-6 FA regarding their benefic potential. For instance, some epidemiologic evidences associate the low incidence of different types of cancer with the fish oil consumption (15,16), and studies performed with animals show the antitumor potential of DHA (16-18). Furthermore, DHA and lauric acid (SLA, saturated) have demonstrated to activate the TLR_4 receptor of T lymphocytes (18) and the inflammatory response (19). Additionally, tumor progression was promoted in 20% of all neoplasms (20, 21).

In animal models, the inhibition of TLRs activation caused by ω-3 acids and anti-inflammatory phytochemicals is well documented (22-24). Also, it has been demonstrated that reactive oxygen species (ROS) induce the SLA dimerization and the TLR_4 recruitment in the lipid rafts of the plasmatic membrane (25). Additionally, expression of cytokines, chemokines and growing factors, activation of the TLR_4, stimulation of the progression and metastasis of tumor and stromal cells and dependent promoters of the enzyme cyclooxygenase-2 (COX-2) were evidenced (25). Moreover, COX-2 enzyme, the most studied in the metabolic pathways of ω-3 and ω-6 FA, is considered a therapeutic target and is also expressed from inducible gene (25).

Likewise, saturated fatty acids activate the TLR_2 and TLR_4 receptors, which increases the risk of developing tumors while it has been demonstrated that ω-3 acids inactivate TLRs, reducing the risk of developing cancer (26-30). Despite some genic variants of TLR_4 have reduced the risk of suffering from prostate, gastric, colorectal cancer and lymphoma (26-31), other polymorphic receptors, as TLR_6-TLR_1-TLR_{10}, increase the risk of suffering from prostate cancer (32) or of developing prostate tumors (33-35), as TLR_2 polymorphisms.

ω-3 fatty acids

The ω-3 DHA and EPA acids with recognized and diverse biological activities (36) are synthesized in the peroxisomes by sequential enzymatic reactions. Furthermore, β-oxidation from ALA acid (37) produced intermediaries as *cis,cis*-9,12-octadecadienoic or linoleic acid (LA C18:2) with low efficiency, which are very common metabolites in occidental diets (38).

At intracellular compartments, ω-3 EPA and DHA acids produce potent anti-inflammatory molecules, as resolvins and protectins, while ω-6 *cis*-5,8,11,14-eicosatetraenoic or arachidonic acid (AA, C20:4) produces powerful pro-inflammatory molecules, such as prostaglandins and leukotrienes catalyzed by metabolic pathways of common enzymes of ω-3 and ω-6 FA (39-42) (Figure 3).

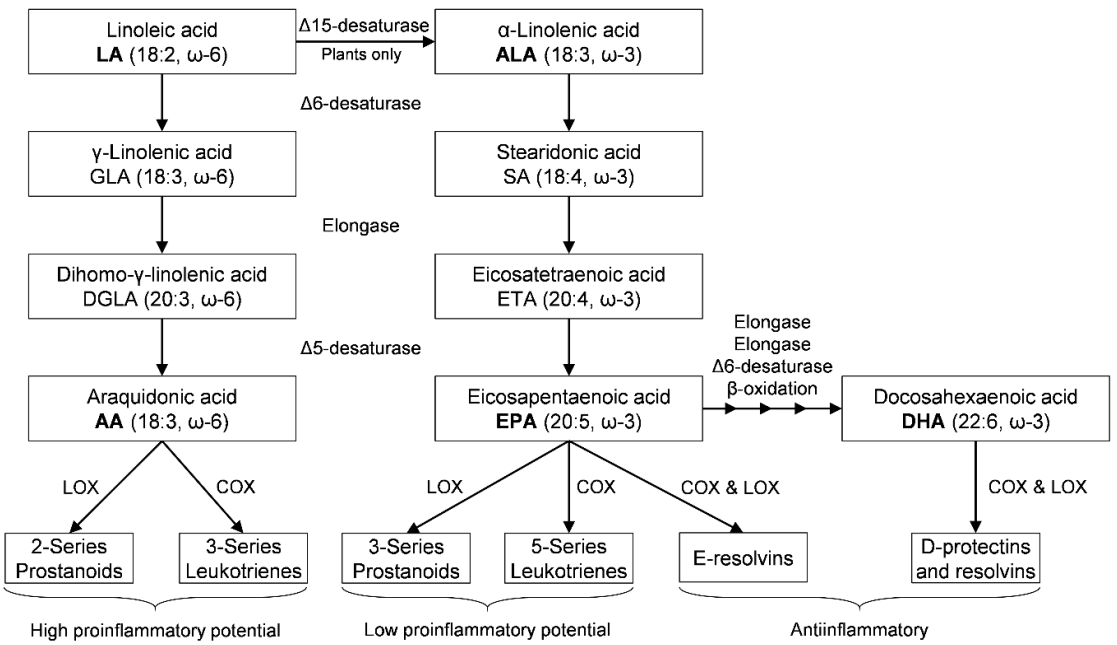

Figure 3. Metabolic pathways of ω-3 and ω-6. Adapted from (46, 47).

In vivo studies show that in animals supplemented with EPA and DHA in the form of free acids, or fish or algae oil, in the transgenic mouse (*fat-1*) model, which expresses the desaturase of *Caenorhabditis elegans* and wherein great quantities of ω-3 from ω-6 acids are produced, it has been promising to eliminate some confounding factors, characteristic in these studies. These results could explain the significant differences with the responses found for animals supplemented with a specific diet (43). Moreover, such studies have shown that DHA is the largest ω-3 acid found in biological systems (44) that exhibits antitumor activity (45).

Dietary high doses of ω-3 FA have been studied in most animal models, in which the clinical development of cancer is simulated (49-51). The results obtained are then compared with studies of human populations (52), and there are slight associations between the development of the illness and the FA consumption (48). Notwithstanding, the extrapolation of these studies is generally based on incomplete descriptions of the experimental conditions, dosimeter or purity of the ω-3 acids used in the evaluated diets (53).

In animal models with colon cancer or intestinal mucosa inflammation (54, 55), ω-3 acids inhibited the neoangiogenesis and the IL-8 production in HUVEC cells stimulated by IL-1β (55). These ω-3 FA induced the α-TNF factor by the UVB radiation on HaCaT keratinocyte cells (56) or reduced the NF-κB factor produced in the inflammatory process or during the growth of human tumors (57).

In animal models transfected with hepatoma cells, ω-3 FA stimulated the expression of *c-myc* and TGF-α mutated genes, decreased the levels of NF-κB and the tumor development (58). In rat embryo cells, EPA avoided the invasion and tumor metastasis by TNF-α induced metalloprotein 9 (MMP-9) (59), and in breast cells inhibited the EGFR signaling (60, 61) and reduced the tumor growth in ovary cells by TGF-β1 and other cell signaling modulators (62).

In humans, DHA and EPA consumption from marine sources has shown therapeutic benefits in health (63, 64) as there is robust evidence of common and specific functions of ω-3 PUFAs in tumor cells of different tissues (54, 65-67). In colon cancer cells and melanoma, these ω-3 FA cause antineoplastic effects by incorporation in cellular membranes, phospholipid concentration and changes in the functions of some membrane proteins (55) through the β-catenin protein (68, 69).

Additionally, ω-3 FA regulate the production of pro-inflammatory eicosanoids derived from ω-6 AA acid and the production of pro-inflammatory regulators as cytokines and reactive oxygen species (ROS) (70). For instance, EPA reduces the expression of cytokines in patients with advanced tumors, and the diet high in ω-3 FA improves the carcinogenesis induced by UVB radiation (71-74). In pancreatic AR42J tumor cells, ω-3 FA inhibit the expression of IL-1β and IL-6 cytokines (75), and fish oil reduces IL-8 expression in the colonic mucosa of rats with carcinogenesis induced by 1,2-dimethylhydrazine. Additionally, it increases the expression of tumor necrosis factor TGF-β (76, 77).

Despite controversial results of the effects of PUFAs in humans, an observational study showed a correlation between high levels of DHA in plasma of Caucasian patients (78) and the low incidence of neuroblastoma and Hodgkin lymphoma (79, 80). The high correlation between the serum levels of ω-3 FA and their cancer incidence was shown in 11 different types of cancer compared in 20 cohorts of patients in 10 studies (80). On the contrary, other study showed low association between fish intake and the risk of carcinogenesis (81).

Some benefic effects of the combination EPA/DHA have been demonstrated in the suppression of colon sporadic polyposis in patients with high risk of suffering colorectal cancer (82). Huang et al (1996) (83), showed that fish oil intake reduces the colonic epithelium proliferation in patients with high risk of developing a second tumor (84). Other report showed that in patients with familial adenomatous polyps and EPA treated, the number of such polyps and their diameter was reduced (84). Moreover, fish intake was associated with the decrease of hepatomas development (85).

ω-6 fatty acids

Some evidences show that the precursor of ω-6 *cis*, *cis*-9,12-octadecadienoic or linoleic acid (LA, C18:2), abundant in seeds and plant oils, stimulates the proliferation of human breast (BT-474) and lung (A-549) cancer cell lines. It also promotes tumorigenesis and colon and prostate cells growth (61, 86-90), and high doses of LA inhibited the colon tumor line Caco-2 proliferation (48).

In addition, conjugated linoleic acids (CLAs), produced by biohydrogenation in bacteria from the gastrointestinal tract (91-93), show the antitumor effect in breast, MCF-7 (94-96); colon, HT-29, DLD-1 and Caco-2 (97, 98); prostate, PC-3 and DU-145 (96, 98-100), and gastric SGC-7901 (101) human cell lines, among others. In animal models, the LA daily intake protects from carcinogenesis (102) and some of its derivatives, like prostaglandin PE_2, produced by the inducible COX-2 enzyme, promote the development of cancer (88, 103-106).

Arachidonic acid (AA), the most abundant of the ω-6 FA, is associated with adverse and benefic effects in human health. In this regard, studies on animals and humans have correlated their high intake with elevated incidence of breast, prostate and colon cancer. In addition, the consumption rate of ω-6/ω-3 is considered as a risk prognostic factor for carcinogenesis (107-111). There is controversial evidence of cancer development caused by AA derivatives, such as prostaglandins and leukotrienes, and also, some reports, antitumor effect of other metabolites, like γ-linoleic (GLA) and dihomo-γ-linolenic (DGLA) acids (48, 85, 112-122) (Figure 3). From GLA and DGLA and the COX-2 enzyme can be produced prostaglandins PE_1 and PE_2, respectively, and free radicals that might cause adverse effects (85, 104-111, 113).

Evidence showed that ω-6 dietary FA can modify the composition of cell membranes and have anti-proliferative effects by the expression of proteins in the cell cycle progression or the apoptosis induction. For instance, GLA alters the triacylglycerol content in the cellular membrane of the WRC256 rat tumor model (120). Further, GLA also increases the triglycerides and polyenoic acids, and decreases the monoenoic acids in human neuroblastoma cell line (101, 112).

Additionally, GLA causes metabolism changes and mitochondrial structure alterations. Moreover, it induces apoptosis and cytochrome c release in rat sarcoma cells LLC-WRC25 (120). CLAs stopped the cells in phase G1 by the p21 inhibitor and the decrease of cyclins A and D in prostate and colon tumor cell lines, DU-145 (117) and HT-29 (99) , respectively. It also promoted apoptosis in colon (Caco-2 and HT-29), prostate (PC-39), gastric (SGC-7901) and hepatic (dRLH-84) cancer cell lines (97-101, 124-126).

Furthermore, prostaglandins PE_1, PE_2 and AA production can be stimulated by lipid peroxidation of ω-6 FA mediated by COX-2. While PE_2 derived-DGLA is a proinflammatory cancer inductor, PE_1 inhibits the *in vitro* growth of HeLa cells (113, 127) and cellular invasion, it stimulates the differentiation and diminishes the metalloproteins MMP-2 and MMP-9 levels in murine melanoma metastatic cells B16-F10 (106). In addition, in rats treated with cisplatin/PE_1 combination decreases tumors and renal cytotoxicity (128).

AA reduces the dependent proliferation of the dose in colon tumor cell line Caco-2 with overexpression of the COX enzyme (48, 51), effect that can be partially countered with a COX inhibitor (127), and in some tumor lines, it can be potentiated by GLA (127, 129). Furthermore, free radicals derived from ω-6 FA can inhibit HeLa cells proliferation, which can be reverted by vitamin E (113), similarly to partial growth reduction of human neuroblastoma cell lines treated with GLA/antioxidants (112). Moreover, increase of lipoperoxidation species and ROS can inhibit rat sarcoma cells LLC-WRC256 proliferation (120, 130).

The Table 2 summarizes the main evidences *in vitro* and *in vivo* of biological effects of ω-3 and ω-6 FA, related with the seven cancer biomarkers: the influence in growth factors, the insensibility to inhibitor signals of growth, the evasion of apoptosis and inflammation, decrease of replicative potential of tumors, invasion and metastasis of tumor tissue and the angiogenesis.

Table 2. Evidences *in vitro* and *in vivo* of the biological effects of PUFAs (ω-3 and ω-6) on cellular markers of cancer. Taken from (47).

Studies in ω-3 PUFAs/Hallmarks	*In vitro* evidences	*In vivo* evidences
ω-3 PUFAs and growth signals	↓ EGFR in lipid rafts and ↓ growth in EPA and DHA treated breast cancer cell lines MDA-MB-231. ω-3 PUFAs inhibit protein kinases PKC-β2, Ras and NF-κB. DHA modulates chaperones Hsp and steroidal receptors in human tumor cell lines. NO ↑ tumor cells invasiveness and ↑ PGE_2 in the progression and growth of the tumor. ↓ NO in EPA and DHA dose-dependent macrophage cell lines. ↓ Cell density compared to LA treated cells in EPA or DHA treated human colon cancer cell line Caco-2. **References**: (131-142)	COX-2 overexpression in 90% of tumors and colonic adenomas. COX-2 overregulation in growth signals, prostaglandins, angiogenesis, apoptosis and cell-cell interaction. ω-3 PUFAs ↓ COX-2 and PGE_2 levels. In xenotransplants of a prostate cancer rat model. ↓ COX-2 and PGE_2 levels. ↓ Growth rate and tumor volume and PSA levels in serum. In colon carcinogenesis: hyper-proliferation by PKC-β2 blocking. In rats fed with fish oil, induction of autocrine growth factors, cancer promotion and epithelial hyper-proliferation. **References**: (143-151)
ω-3 PUFAs and tumor insensitivity to growth inhibition signals	EPA ↓ cellular proliferation in cell lines HRT-18, HT-29 and Caco-2. DHA ↓ cellular proliferation in SIC transformed cell line. EPA and DHA ↓ proliferation of cell line HT -29 and other cell lines. **References:** (142, 146, 152-155)	**In breast cancer murine model.** DHA ↓breast tumors and overregulates 60% of the suppressor gene of BRCA1 tumor. **Reference:** (156)
ω-3 PUFAs and evasion of apoptosis tumor	ω-3 PUFAs ↑ apoptosis in cell line HT-29. DHA induces dose and cytochrome c release dependent apoptosis in tumor cells. DHA modulates the expression of the PPAR receptor and induces Syndecan-1- mediated apoptosis. EPA and DHA deregulate pro-apoptotic proteins Bcl-2 and Bcl-xL and ↑ the levels of Bak and Bcl-xS proteins. ↑ NF$\kappa\beta$ in murine macrophages, ω-3 PUFAs strengthen tumor survival and ↓apoptosis. ↓ COX-2 expression restores apoptosis. **References:** (79, 153, 154, 157-172)	**Colon carcinogenesis rat models, ω-3 PUFAs** ↑ Apoptosis via COX-2. Repress anti-apoptotic Bcl-2. In normal conditions, Bad displaces BAX from Bcl-2 and induces death. Phosphorylated Bad inhibits Bax and Bcl-2 and affects cell survival. **Prostate tumors in *knockout* mice in PTEN supplemented with ω-3 PUFAs.** ↓ Phosphorylated Bad and ↑apoptosis in ω-6 PUFA-supplemented mice. ↓ Tumor growth, slow histopathologic progression and ↑survival rates. **References:** (144, 163, 172-177)
ω-3 PUFAs and limitation of the replication potential of the tumor	AA promotes tumor growth via PKC activation, mitosis stimulator. In colonocytes and JB-6 rat epidermal cells. ω-3 PUFAs promote growth via Ras and ↓ AP1. AA metabolites stimulate mitosis. EPA-derived metabolites ↓ growth in human breast cancer cell lines. **References:** (178-181)	**ω-3 PUFAs in colon cancer animal models.** ↓ Tumor growth. **In rat colon, ω-3 PUFAs** ↓ Ras expression in the membrane. ↓ Adducts formation in DNA. ↑ DNA repair. ↓Colon cancer beginning. **References:** (22, 182-191)
Dietary fatty acids in inflammation and tumorigenesis	Anticancer effects of ω-3 PUFAs can be independent from COX. DHA is not a COX substrate and suppresses the expression of pro-inflammatory TLR genes. **References:** (123, 192)	**Epidemiology**: association between saturated fat intake and ↑ risk of suffering some cancers. Inverse association between fish oil intake and colon cancer. **Clinic with ω-3 PUFAs in fish oil** ↓ Intestinal hyper-proliferation in patients with colorectal cancer risk. Colon cancer prevention in ω-3 PUFAs-treated animals. EPA, low specificity substrate of COX and competitive inhibitor of AA, displaces AA in membrane lipids. ↓ Substrate availability for COX. **References:** (50, 52, 53, 80, 81, 123, 192-202)

ω-3 PUFAs and angiogenesis	ω-3 PUFAs ↓ angiogenesis, ↓VEGF, ↑ proliferation, migration and formation in endothelial cells. ↓expression in VEGF-1 (FIK-1). ↓ Formation of human umbilical cord and migration of endothelial cell. EPA ↓ proliferation of the bovine carotid artery cell. EPA inhibited the binding of PDGF and its receptor. ↓ Expression of c-fos mRNA. EPA and DHA ↓ VEGF, COX-2 and PGE_2 levels in colon cancer cell line (HT-29). Synergism in ω-3 PUFAs inhibition and inhibitors of COX-2 in cell lines growth. NO ↑ survival, proliferation and ↓ apoptosis. NO and COX-2 regulate VEGF-mediated angiogenesis. DHA ↓ NO production and ↑ the iNOS expression. DHA overregulates NO and NF-κB in human colon cancer cell lines. EPA ↓ production of MMP-2 and 9 in human endothelial cells. DHA ↓ the β-catenin in colon cancer cells. **References:** (54, 137, 141, 203-214)	DHA supplement prior to tumor injection ↓ formation and prevents xenotransplant in neuroblastoma rats. In animals, DHA supplements at high and low doses. DHA inhibits BxPC-3 pancreatic cancer cells in *nude* mice. ↑ DHA in combination with curcumin. ↓ Tumor volume and ↓ VEGF mRNA levels in EPA -supplemented fibro-sarcoma Fischer 344 rats. ↓ VEGF, COX-2 and PGE_2 expression in *nude* mice transplanted with colorectal carcinoma cells and supplemented with ω-3 PUFAs. ↓ Micro-vascularization and VEGF levels in *nude* mice tumors transplanted with breast carcinoma and fed with high levels of EPA and DHA. ↓ PDGF migration of vascular smooth muscle cell by EPA and DHA supplement. ↓Tumor growth and micro-vascularization in colon cancer cells HT-29 in *nude* mice. **References:** (185, 207, 215-220)
ω-3 PUFAs in tumor tissue invasion and metastasis	DHA ↓ adhesion and transmigration of monocyte by TNFα. NO ↑tumor growth and angiogenesis. EPA and DHA ↓ NO production and ↓ tumor migration. DHA modulates the cell-cell adhesion via overregulation of Rho GTPase. ↓ Reorganization of cytoskeleton and ↓ICAM-1 and VCAM-1 expression. **References:** (44, 139-141, 221-224)	**Gastric cancer animal models via COX-2 treated with ω-3 PUFAs.** ↓ Cell-cell and cell-matrix interaction. ↓ COX-2 progression, metastasis and inhibition. ↓Invasiveness in animal xenotransplant. ↓ Tumor growth and invasion. ↓ COX-2 and PGE_2 levels. **In xenotransplant in colon cancer model:** ↓Tumor that overexpresses COX-2 by ω-3 PUFAs supplementation. ↓ Metastasis in murine colorectal cancer models. EPA and DHA ↓ lung metastasis and type IV collagenase 2-kDA activity. **References:** (163, 184, 225-228)

↓ and ↑ mean decrease and increase of activity, respectively.

Breast cancer

Despite the increase in survival rate of patients with early diagnose and hormonal therapy, in United Kingdom, breast cancer (BC) in women has high incidence and represents the 31% of all cases of cancer, causing around 12,000 deaths/year (229).

A total of 50-70% of invasive tumors are originated in breast ducts. Considering specific gene expression, these tumors are classified in four types: a) *Luminal A* showed low proliferation and low histological grade, representing 50-60% of total BC (ER^+, $HER2^-$); b) *Luminal B* representing to 10-20% of the most aggressive cancers, exhibited high histological grade and poor prognostic; c) *Triple negative tumors* (ER; PR; HER-2) and *d) $HER2^+$ tumors* that do not express the estrogenic receptor (ER^-) nor the progesterone receptors (PR^-) (230), but include lobular carcinomas and is equivalent to 10-20% of all BC (231).

Postmenopausal women suffer the 75% cases of all BC, and about 80% of them express the estrogenic receptor (ER). The most used therapy in BC until some time ago was the antiestrogen Tamoxifem (TAM), which produces resistance in breast tumor cells in long-term use (232). Thus, in the last decades the use of inhibitors of the aromatase enzyme (AI), letrozole and anastrazol (233, 234) as first line therapies for BC has incremented, since they block the estradiol production from testosterone and they significantly contribute to the survival of patients. Currently, there are not known cases of resistance of breast tumor cells to the AI therapy.

Controversy exists on the influence of estrogen in breast carcinogenesis of postmenopausal women. Registered data in *Cochrane Database of Systematic Reviews* (2012) revealed that the risk of suffering BC did not increase in postmenopausal women that had used estrogen replacement therapy. Nonetheless, patients do show predisposition to develop BC after continued estrogen and derivatives of progesterone therapy (106). Moreover, in these tumors, cells express the ER and exhibit higher histologic grade; however, such risk disappears, after two years of hormonal replacement therapy (235).

Therapeutic strategies for breast cancer

Beatson published in 1896 the first evidence regarding the association between hormones and BC (236). Since then, different targets have been used to inhibit estrogen activity or biosynthesis and to reduce cell proliferation (237), particularly blocking the G_1/S transition of cell cycle (238).

Receptors ERα and Erβ expressed in the plasmatic membrane of the normal breast tissue are binding sites of the drug that reduce the transcription of estrogen-regulated genes, (128,239,240). Nevertheless, in the tumor tissue, estrogens are produced mainly by the sulphatase enzyme (STS) pathway. In both normal and tumor tissues, the great expression of the ERα-controlled STS (241) is associated to poor prognostic of tumors (242). Hormonal therapy in BC ($ER\alpha^+$) shows the expression of different STS isoforms, estrogen signaling inhibition and increased progression of the tumor in patients (241). This alternative pathway provides a benefic potential on TAM and AIs therapies in premenopausal and postmenopausal women with BC (ER^+).

The estrogen dependent BC has allowed developing therapeutic strategies. For instance, different inhibitors of its synthesis such as ER selective modulators, pure antagonists (243), inhibitors of intracellular signaling pathways (235) and AIs (244). The ER selective modulator TAM, used since 1973 as a hormonal therapy in BC (ER^+) treatment in postmenopausal women (245-248), blocks the union of the estrogen to the ERα and inhibits cell proliferation.

Combination TAM/doxorubicin or taxanes (249, 250) achieves the disease-free survival patients (251), after 10 years of treatment; nevertheless, it can cause adverse effects such as endometrial cancer development, thromboembolism risk increase and acquired tumor resistance (252, 253). In *in vitro* studies, the fulvestrant, ER selective inhibitor, lacking agonist activity in murine models (239, 254, 255), induces degradation via ubiquitin-proteasome of the ER dimers (256).

Most therapies against BC aim to block the biosynthesis of estrogen responsible of initiation, promotion and progression of the tumor (257) since the hydroxyestrogens (258-260) are inductors of the ER signaling pathways, the epidermal growth factor (EGFR) and the phosphatidylinositol-3-kinase (PIK-3) (261-271). Moreover, estrogen pathways are considered therapeutic targets of selective inhibition (272) via cytochrome P-450 aromatase enzyme (125) which is expressed in different issues as the ovarian, adipose, muscular, hepatic and mammary (273, 274).

Cytochrome P-450 aromatase enzyme catalyzes the aromatization of the androgen in the final stage of the biosynthesis of estrogen (275-277), a key regulator in the hormonal therapy. In postmenopausal women, the adrenal glandule produces androstenedione (278) main source of estrogens (279) and increases the aromatase enzyme expression of a malignant tumor to synthetize more estrogen (245, 280-282) because the polymorphisms of this enzyme affects the pathophysiology of the disease (249).

The first generation AIs (aminoglutethimide) (283) with low selectivity (284) and adverse effects, such as the inhibition of the biosynthesis of cortisol, aldosterone and the thyroid hormone (285) and the induction of hepatic enzymes (261, 286). The second generation nonsteroidal AIs (fadrozole) improve their effect compared to the first-generation AIs (287) but not when compared to TAM (288, 289) and the formestane steroidal inhibitor. And the third-generation inhibitors (letrozole and anastrazol) block the estrogen production without affecting the steroidogenic pathways (216).

The letrozole (4-[(4-cyanophenyl)-(1,2,4-triazol-1-yl)methyl]benzonitrile) was modeling designed to join the active site of aromatase (290,291). *In vitro* and *in vivo* tests demonstrated that it is 10-30 times stronger and selective than anastrazol (292) and other AIs (121, 170, 285, 293-295). The bioactive potential of letrozole was evaluated in aromatase transfected cell lines CHO-K1 and MCF-7-Ca, in normal adipose human fibroblasts and in human carcinoma cell

line JEG-3 (292). Moreover, the design of letrozole was based in its action mechanism (296) and its similitude with the structure of imidazole, triazole, cyanobenzyl and the heme group of the aromatase, which partially mimicries the skeleton of the androstenedione (290).

The therapeutic concentrations of letrozole in patients are achieved at 2-6 weeks of treatment without drug accumulation (248), 42 hours of midlife after oral administration, rapid absorption and 60% albumin-conjugated antineoplastic (297). Further, the selectivity of letrozole in BC treatment on postmenopausal women completely inhibits the peripheral aromatase tissues (287, 292, 298-300). It does not affect the plasmatic levels of 17-OH progesterone, thyroid stimulant, luteinizing, follicle-stimulating, androstenedione, and urinary excretion hormones (298, 301, 302). In early BC patients, clinical benefits of AI treatment were demonstrated on extended adjuvant, TAM adjuvant (303, 304) or TAM neoadjuvant (305). In postmenopausal women, the latter treatment also inhibited aromatase, reduced the estrogen concentration (285) and significantly decreased the sulfate estrone enzyme in invasive cancer patients (306).

Antitumor effect of letrozole was also demonstrated in several animal models (292, 296, 307). In adult rats, it completely reduced estrogen dependent and induced by 9,10-dymethylbenzo-α-anthracene breast tumors (303). In MCF-7 cells of transplanted athymic rats, there was higher inhibition of tumor growth dependent of the letrozole dose (170, 279, 285, 295) respect to anastrazol, and it showed higher effectivity than fulvestrant and TAM in the transplanted cells. Moreover, TAM was agonist of letrozole in estrogen synthesis inhibition (308).

Letrozole/TAM combination was more effective as first line treatment in MCF-7-Ca cell line, but they did not respond to the second line treatment with TAM or fulvestrant (309, 310). In contrast, TAM pretreated tumors were more sensible to letrozole and it was more effective than TAM or exemestane in third line treatments (311). In transgenic female rats with aromatase overexpression, letrozole decreased pre-neoplastic lesions and reduced the incidence of spontaneous breast tumors (301, 302).

Combined therapies of omega fatty acids and antineoplastics

The ω-3 FA in enriched diets enhance the effect of the treatment with other treatments in tumor cells (194). They highlight tumor growth inhibition of antineoplastic agents as doxorubicin (195) and mitomycin C in animal models (197). Furthermore, they also potentiate TAM in xenotransplantation of estrogen dependent tumor cells (198).

Combinations of DHA with doxorubicin, irinotecan, cisplatin, melphalan and vincristine showed synergism in the neuroblastoma cell survival (157, 158), and the DHA/epirubicin, cyclophosphamide and 5-fluoracil combination caused tumor reduction and increased survival of BC patients. They showed high incorporation of DHA in erythrocyte membranes and high levels on serum (199). The rate of DHA consumption of patients is reflected in single differences of the metabolism, enzymatic activity, normal diet, age and sex of individuals (157, 192, 200).

Furthermore, two years of therapy with ω-3 FA/celecoxib combination showed synergism with COX enzyme inhibitor, avoiding the occurrence of new adenomas (312). DHA/sulindac sulfate combination reduced the tumor growth through the apoptotic receptor (DR5) in the colon xenotransplant (313) and DHA/clioquinol treatment showed PPARα dependent synergy, diminished the NF-κB and survival molecules Bcl-2, Akt and p65 production in tumor cells (314) and enhanced the anti-proliferative effect of curcumin in BC cells (315).

Moreover, the combination of ω-6 FA or their metabolites also increased the efficacy of some antineoplastics. For instance, the GLA/paclitaxel or docetaxel treatment synergically inhibited cell growth in human BC cell lines MDA-MB-231, T47D, SK-Br3 and MCF-7 (316) and DGLA/vincristine combination significantly increased death in vincristine resistant cells (KBC-hR-8–5) respect to individual treatments (104). DGLA derivatives also increased the cytotoxicity of 5-fluoracil in HCA-7 (colony 29) colon tumor line by apoptosis induction via caspase-9 (105) and in rats the cisplatin/PE_1 treatment enhanced the reduction of renal cytotoxicity (128).

Furthermore, 12-Hydroxyeicosatetraenoic acid [12(S)-HETE], AA derivative, showed pleiotropism in tumor cells as it stimulated the angiogenesis, metastasis and the induction of platelet aggregation (9, 317-320). 12(S)-HETE

is mitogenic of endothelial cells and combined with BMD122 inhibited the lipoxygenase (12-LOX) and initiated cell repair inducible by serum (321). Additionally, 12(S)-HETE showed cardio-protector effect after the opioid non-steroidal anti-inflammatory treatment (322).

Finally, there is evidence of other chemotherapies synergism in lipid pathways. For instance, in human CCRF-CEM and Jurkat acute lymphoblastic resistant to synthetic retinoid, N-(4-hydroxyphenyl) retinamide (4-HPR, fenretinide) is exhibited a distinctive endogenous sphingolipid profile correlated with the inhibition of dihydroceramide desaturase. In this cellular model, it acquired resistance to 4-HPR is selective and continues in the absence of sphingolipid profile alteration (323). In other reports, using several paired wild-type and drug-resistant (doxorubicin-selected) cancer cell lines, including breast, ovary, cervical, and colon, was studied the role of the glucosylceramide synthase (GCS) gene in doxorubicin resistance. Results showed significantly suppressed doxorubicin-up-regulated GCS expression , which explains that ceramide contributes to cellular resistance to doxorubicin (324). Additionally, in myeloid leukemia human KBM-5 cells, decursin, an analog of coumarin, induces apoptosis via regulation of COX-2 and survivin. Moreover, decursin can activate caspase family members and triggers PARP cleavage. Further, decursin in synergy with COX-2 inhibitor, celecoxib, can activate apoptosis in KBM-5 cells (325).

Evidences *in vitro* in BC derived cell lines of different DHA /antineoplastic agents treatment combinations (Table 3).

Table 3. Some *in vitro* evidences of the effect of DHA in combination with other antineoplastics.

Drug	Cell lines	Enhancer	Activity	References
Arsenic trioxide	MDA-MB-468, MCF-7	No	Apoptosis	(326)
	SK-BR-3	Yes		
Doxorubicin (Anthracycline)	MDA-MB-231	Yes	Growth	(327,328)
	MDA-MB-231, MCF-7 resistant doxorubicin	Yes	Cytotoxicity	(324)
	MCF-7	No	Cytotoxicity	
Paclitaxel (Taxane)	MDA-MB-231	Yes	Cytotoxicity	(329)
Tamoxifen (SERM)	MCF-7	Yes	Growth	(223)
Genistein (Isoflavone)	MDA-MB-231, SK-BR-3	Yes	COX-2/NF-κB	(330)

CONCLUSIONS

Diversity in inhibitor effects of omega fatty acids in cancer and in breast cancer particularly, may reflect methodologic differences in the realization of studies, and the lack of recognition of the importance of these fatty acids, at cell level, generates controversy.

Nevertheless, low efficiency of conventional neoplastic therapy in the long term and the need of new therapeutic alternatives, allow exploring other therapeutic designs that include new options of combined treatments in which omega fatty acids could strengthen drugs in a different way. Despite alternative combined treatments could increase the toxicity of the normal cell and cause adverse effects in patients, ω-3 fatty acids, for their nutraceutical characteristics and antitumor potential, are strong candidates of the adjuvant therapy in diverse neoplasias.

Breast cancer requires alternatives of therapies with multiple treatment targets as the high proportion between the disease and its estrogen dependence in most cases generates difficulties in breast cancer treatment, mainly in triple negative cancer, (it does not express the receptors estrogenic, progesterone or Her-2).

In this sense was designed letrozole, aromatase inhibitor, to block the estrogen production, for which this drug also causes secondary effects in the treated patient. Considering that omega fatty acids are known nutraceutical and their use is desirable in combination with other conventional drugs as alternative therapies, there is consensus over

the utility of anticancer treatments in the cellular response through different signaling pathways related to the cell cycle regulation and differential death inductor pathways of the tumor cell, such as apoptosis and necrosis, among others.

Moreover, given the controversy between epidemiologic studies and *in vivo* tests in animal and human models, and that there is discrepancy in the evaluation criteria, such as the fatty acids supplementation levels, supplementation duration, ethnic origin, migrations, etc., it is required an agreement in medical and scientific fields that formulates excluding or including parameters of the individuals to suppress the confusing factors and allows to collect reproducible data with solid grounds for the design of new alternative therapies for cancer.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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AUTHORS' CONTRIBUTIONS

Conceived, designed and written by ME. Revised by MC. All authors read and approved the final manuscript.

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