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REVIEW PAPER

Omega-3 polyunsaturated fatty acids of fish and their role in cancerous cell lines: A review of *in-vitro* studies

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Abstract. Fish are a major dietary source of n-3 and n-6 polyunsaturated fatty acids (PUFAs) in humans since the human body lacks the necessary enzymes required to synthesize them. Diets rich in fish oil containing n-3 fatty acids have been shown to lower the incidence rates of cancer. They have also been shown to have cytotoxic or anti-proliferative effects on a variety of human cancer cell lines, and they are known to nurture overall human health without any observable side effects. The present review focused on *in-vitro* research findings regarding the apoptotic and anti-proliferative role of n-3 fatty acids FAs that highlight the important mechanisms and pathways of their action in inhibiting the progression of cancer. A survey of the literature indicated the paucity of information on the use of n-3 FAs in combination with other anticancer substances. Therefore, further research needs to be undertaken on the use of n-3 FAs in combination with other anticancer phytochemicals and drugs, the use of antibodies as specific carriers of n-3 FAs, and different increasing ratios of n-3/n-6 FAs that not only control the side effects of chemotherapy but also enhance its efficacy and selectivity. These FAs might also prove to be a pioneer therapy against cancer.

Keywords: anti-proliferation, apoptosis, arachidonic acid, combination chemotherapy, n-3 fatty acids

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Introduction

Fish are highly recommended to be included in the human diet because of the content in the muscles of polyunsaturated fatty acids (PUFAs), essential amino acids, fat-soluble vitamins, and micro and macro elements (Mahmoud et al. 2007, Łuczyńska et al. 2008, Ljubojevic et al. 2013). Fish are the major dietary source for biologically active omega (n)-3 and omega (n)-6 PUFAs, which are beneficial to human health (Suzuki et al. 1995, Domingo 2007, Guil-Guerrero 2007, Huynh 2007, Ugoala et al. 2009, Sharma et al. 2010). These PUFAs are deposited in the phospholipids of cell membranes (Schmitz and Ecker 2008) and are known to perform several specific cell functions, *inter alia*, maintaining cell membrane structure, membrane fluidity, cell signaling, and cell to cell communication (Colomer et al. 2007). It has been reported that n-3 fatty acids (FAs) can reduce the risk of neurological disorders (Crawford 1993), coronary artery disease, rheumatoid arthritis, and cancer (Simopoulos 2002). Epidemiological studies carried out in Japan and in the Mediterranean regions showed a low incidence rate of cancer in populations that consumed diets rich in fish oils containing n-3 FAs (Baracos and Mazurak 2004, Gerber 2012). A number of *in-vitro* studies suggest the cytotoxic or anti-proliferative effects of n-3 FAs

on a variety of human cancer cell lines, including A549 (Yang et al. 2013), BxPC3 (Funahashi et al. 2008), MDA-MB-231 (Barascu et al. 2006), etc., without exerting any adverse effect on normal cells (Cantrill and Ells 1997, Griffiths et al. 1997, Solomon et al. 1998, Das 1999). Roynette et al. (2004) reported that n-3 FAs increased cancer cell apoptosis, decreased tumor cell growth, promoted cell differentiation, and limited angiogenesis. The present work aimed to review research findings based on the cytotoxic or anti-proliferative effects of n-3 fatty acids (FAs) that highlight the important mechanisms and pathways of their action that inhibit the progression of cancer. Efforts were also made to discuss the use of n-3 FAs in combination with other anticancer substances such as phytochemicals and drugs in order to control the side effects of drugs, and also to increase their efficacy.

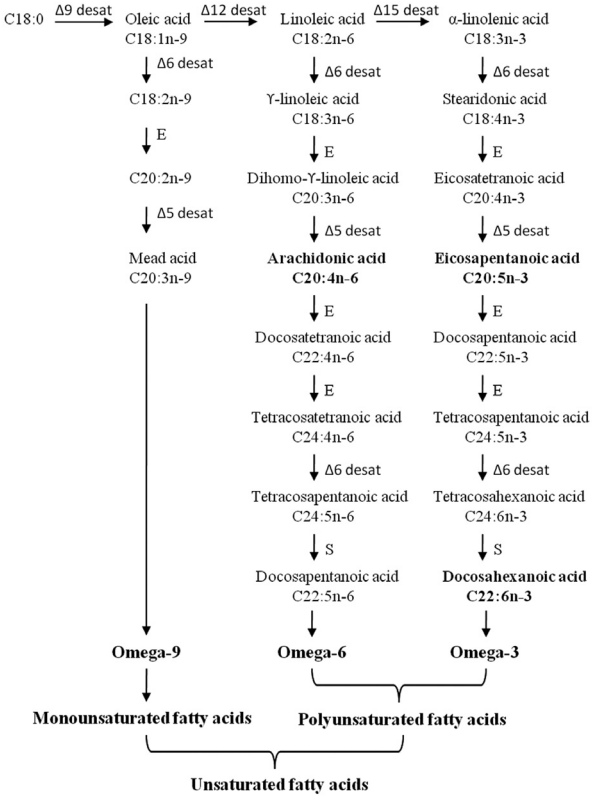

Figure 1. Biosynthetic pathways of n-3 and n-6 FAs from n-3, n-6, and n-9 C18 precursors.

Abbreviations : C = number of carbon atoms; n= position of first double bond; Δ5 desat, Δ6 desat, Δ9 desat, Δ12 desat, Δ15 desat = Fatty acyl desaturases; E = Fatty acyl elongases; S = Chain shortening.

Materials and methods

The authors conducted a survey of research articles on n-3 and n-6 FAs of fish and effect of n-3 FAs on cancer cell lines. The search included publications spanning 36 years from 1981 to 2017, and the data were collected using the electronic databases PubMed, Google Scholar, Science Direct, Scopus, and Springer. The study did not incorporate abstracts of conferences, symposia, or patents because they contained inadequate information. The literature was scanned to examine how n-3 and n-6 FAs are synthesized in fish (Fig. 1), why these are essential for humans to ingest them with their diets, and how they affect human cancer cells *in vitro*. The mechanisms of action of n-3 FAs on cancer cells were evaluated and compiled into figures using Microsoft PowerPoint (Figs. 3, 4, 5). *In vitro* studies elucidating the anti-proliferative or apoptotic activity of n-3 FAs on different human cancer cell lines are summarized in Table 3.

n-3 and n-6 FAs in fish

Omega-3 and n-6 FAs are considered to be essential nutrients in the human diet because the human body is incapable of synthesizing them (Omar et al. 2010). However, these FAs are synthesized by aquatic micro-organisms that are consumed by fish, and, thus, they are distributed throughout the aquatic food web (Napier 2002). Therefore, fish are an important dietary source of these FAs for humans (Sushchik et al. 2007, Jabeen and Chaudhary 2011). No vertebrates, including human beings, can synthesize n-3 and n-6 FAs *de novo* because they lack Δ12 and Δ15 desaturase enzymes, without which alpha-linolenic acid (ALA, 18:3 n-3) and linoleic acid (LA, 18:2 n-6) cannot be formed from oleic acid (18:1 n-9); thus, ALA and LA are essential fatty acids in all vertebrate diets (Tocher 2003). The FA desaturases that introduce ethylenic bonds at carbon positions 12 and 15 from the carboxyl end of the molecule are termed Δ12 and Δ15 desaturases, respectively (Higashi and Murata 1993). Fish ingest short chain precursors (18:3 n-3,

ALA and 18:2 n-6, LA) by consuming phytoplankton and zooplankton, which synthesize these FAs, and, thus, they are concentrated in the food chain (Almatsier 2003). These can be further desaturated and elongated to form C20 (20:5 n-3, 20:4 n-6) and C22 (22:6 n-3) FAs, which are considered to be physiologically essential (Tocher 2003). However, humans have a restricted capacity to synthesize these C20 and C22 FAs from short chain precursors. The biosynthetic pathway of n-3 and n-6 FAs from n-3 and n-6 C18 precursors is shown in Fig. 1. Fish are heterogeneous groups living in different habitats characterized by different environmental conditions. A number of researchers such as Ratkowsky et al. (1996), Kinsella (1988), Saito et al. (1999), Haliloglu et al. (2004), and Çelik et al. (2005) report that the composition of n-3 and n-6 FAs differ in different fish groups and species because of differences in their environmental conditions, diet, age, and maturity. Freshwater fish contain low levels of n-3 FAs compared to marine and estuarine fish because of differences in their feeding habits (Rahman et al. 1995). Therefore, the tissues of marine fish are preferable for use in diets to treat cancer. Freshwater fish feed primarily on phytoplankton and plant vegetation, whereas marine fish feed on small planktonic animals rich in PUFAs (Brett and Müller-Navarra 1997). The amounts of n-3 and n-6 FAs are elevated in fish inhabiting cold waters since these FAs enhance tolerance to low water temperatures (Stancheva et al. 2014). The two families of FAs (n-3 and n-6) are not inter-convertible and are functionally and metabolically distinct from each other (Simopoulos 2002). Therefore, n-3/n-6 ratio can be a good index when comparing the relative nutritional values of different fish, and higher n-3/n-6 ratios are frequently cited as indicators of high nutritional value (Dhaneesh et al. 2012). The content of n-3 and n-6 FAs and their ratios in freshwater and marine fish are listed in Tables 1 and 2.

Chemistry of n-3 and n-6 FAs

Triacylglycerols in fish are invariably oils and FAs of lipids that are rich in long hydrocarbon chains with greater numbers of double bonds, and they play important roles in animal nutrition, including human beings. FAs with one or many double bonds are termed monounsaturated FAs (MUFAs) and polyunsaturated FAs (PUFAs), respectively (Johnson et al. 2009). The two families of PUFAs namely the n-3 and n-6 series, are derived from α-linolenic acid (ALA, 18:3 n-3) and linoleic acid (LA,18:2 n-6), respectively. The FAs in the n-3 series are docosahexaenoic acid (DHA, 22:6 n-3) and eicosapentaenoic acid (EPA, 20:5 n-3), while the fatty acids in the n-6 series are arachidonic acid (AA, 20:4 n-6) and docosapentaenoic acid (DPA, 22:5 n-6) (Sahena et al. 2009). Fish oils are rich in FAs with three or more double bonds that are considered to be important in the human diet. The details of the chemical structure of FAs are shown in Fig. 2.

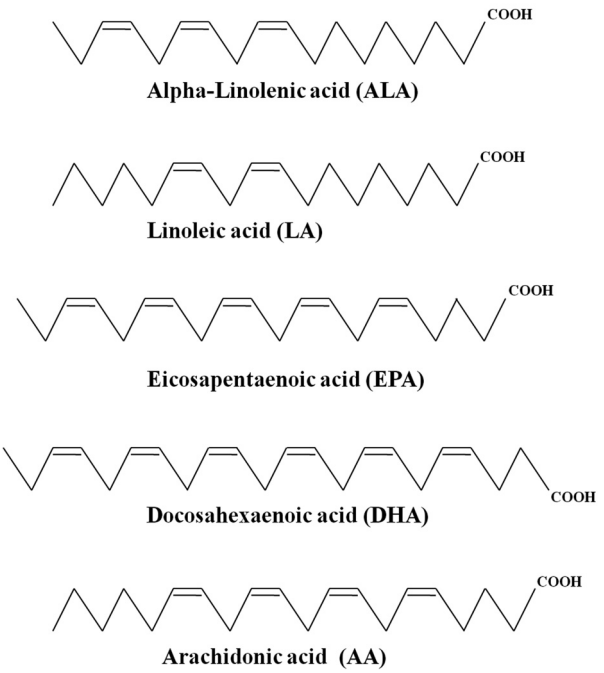

Figure 2. Structure of some biologically essential n-3 and n-6 FAs.

n-3 FAs in cancer

Cancer develops from genomic disturbances in cells triggered by genetic, organismic, or environmental factors that affect all the physiological conditions of cells including differentiation, division, migration,

Table 1
PUFA profile of some important freshwater fish

Species	Source	Total lipid (g/ 100 g)	Total PUFA (% of Total Lipid)	n-3 PUFA (%)		n-6 PUFA (%)	
				EPA	DHA	AA	n-3/n-6
Silurus glanis	Stancheva et al. 2014	-	21.64±1.51	1.85±0.32	6.17±0.35	6.42±0.55	0.93±0.07
Pangasius pangasius	Asmah et al. 2014	7.96±1.06	12.09	2.45±1.74	0.23±0.12	-	-
Aspius aspius	Ljubojevic et al. 2013	2.78±0.11	24.60±0.3	3.09±0.11	5.22±0.1	2.71±0.12	1.29±0.03
Abramis brama	Ljubojevic et al. 2013	3.24±0.15	17.07±0.27	3.94±0.11	2.58±0.16	2.18±0.00	1.53±0.06
Barbus barbus	Ljubojevic et al. 2013	7.78±0.15	26.31±0.27	5.41±0.1	5.55±0.09	1.48±0.06	2.04±0.03
Cyprinus carpio	Ljubojevic et al. 2013	7.13±0.1	19.7±0.27	1.36±0.08	0.87±0.08	2.42±0.09	0.44±0.02
Acipenser ruthenus	Ljubojevic et al. 2013	5.39±0.14	22.17±0.37	4.93±0.09	3.79±0.09	1.54±0.08	2.9±0.19
Esox lucius	Ljubojevic et al. 2013	1.61±0.06	28.15±0.24	1.94±0.08	7.58±0.26	3.85±0.14	1.0±0.04
Catla catla	Jakhar et al. 2012	1.2±0.08	12.50	1.9	5.4	-	6.544
Labeo rohita	Jakhar et al. 2012	2.9±0.21	15.84	1.29	3.74	2.87	1.046
Clarius batrachus	Jakhar et al. 2012	7.90±0.63	25.56	2.10	3.76	-	0.706
Pangasiano hypophthalmus	Jakhar et al. 2012	4.98±0.38	23.37	1.93	4.48	0.98	0.74
Channa micropellets	Omar et al. 2010	5.8±2.2	36.40	5.1±1.1	13.9±3.5	11.4±2.3	1.19
Schizothorax zarudnyi	Rahimabadi et al. 2009	6.36±0.16	21.996	6.514±0.108	9.425±0.389	2.567±0.052	3.90625
Schizocypris altidorsalis	Rahimabadi et al. 2009	4.52±0.14	15.775	7.098±0.116	4.391±0.740	1.527±0.029	4.90196
Alburnus mossulensis	Cengiz et al. 2009	-	31.76	1.54±0.36	3.97±0.35	4.79±0.65	0.39
Chondrostoma regium	Cengiz et al. 2009	-	55.59	17.30±0.98	16.82±1.01	26.89±1.31	3.53
Barbus rajonorum	Cengiz et al. 2009	-	69.48	13.39±1.12	26.89±1.31	10.12±0.75	2.61
Carasobarbus luteus	Cengiz et al. 2009	-	56.39	6.87±0.78	11.97±0.81	12.27±0.95	1.11
Leuciscus lepidus	Cengiz et al. 2009	-	59.78	6.25±0.69	27.08±1.26	9.14±.085	2.31
Acanthobrama marmid	Cengiz et al. 2009	-	48.87	7.97±1.01	10.75±0.78	10.67±0.68	1.04
Cyprinion macrostomus	Cengiz et al. 2009	-	72.65	20.15±1.52	22.19±1.00	11.33±0.96	2.99
Liza abu	Cengiz et al. 2009	-	9.75	0.65±0.07	0.72±0.01	0.75±0.01	0.67
Silurus triostegus	Cengiz et al. 2009	-	57.19	10.87±0.86	20.61±1.11	9.86±0.36	2.5
Piaractus brachyponus	Rahman et al. 1995	34.00±0.02	34.00±0.20	0.05	0.04	0.65	-
Monopterus albus	Rahman et al. 1995	6.25±0.38	6.25±0.38	2.66	0.21	0.67	-
Channa striatus	Rahman et al. 1995	3.25±0.63	3.25±0.63	0.32	1.54	2.22	-
Leptobarbus hoevenii	Rahman et al. 1995	7.92±0.16	7.92±0.16	0.15	0.71	1.30	-
Aristichthys nobilis	Rahman et al. 1995	1.75±0.87	1.75±0.87	0.26	-	14.0	-
Hypophthalmichthys molitrix	Rahman et al. 1996	7.08±0.48	7.08±.48	0.04	0.79	0.84	-
Catla catla	Rahman et al. 1995	1.92±0.56	1.92±0.56	0.19	0.07	0.43	-
Clarias gariepinus	Rahman et al. 1995	20.00±0.20	20.00±0.20	0.08	0.14	1.30	-
Puntius gonionotus	Rahman et al. 1995	5.17±0.64	5.17±0.64	0.22	-	0.45	-
Anguilla mauritiana	Rahman et al. 1995	10.67±0.94	10.67±0.94	3.48	0.89	2.48	-
Pagasius pangasius	Rahman et al. 1995	5.67±0.39	5.67±0.39	0.08	-	-	-
Trichogaster trichopterus	Rahman et al. 1995	4.50±0.03	4.50±0.03	0.41	1.57	0.66	-
Trichogaster pectoralis	Rahman et al. 1995	1.17±0.05	1.17±0.05	0.44	1.88	0.24	-
Oreochromis mossambicus	Rahman et al. 1995	2.75±0.09	2.75±0.09	0.84	-	0.53	-

and angiogenesis (Hanahan et al. 2000). Cancer cells develop resistance to cell death by down regulating the function of pro-apoptotic proteins and increasing the amount of anti-apoptotic molecules (Fulda et al. 2009). Research is being carried out globally to identify dietary components based on natural products that can be used as anticancer substances, in addition to chemically synthesized compounds. *In vitro*

Table 2
PUFA profile of some important marine fish

Species	Source	Total lipid (g/ 100 g)	Total PUFA (% of Total Lipid)	n-3 PUFA		n-6 PUFA	
				EPA	DHA	AA	n-3/n-6
Rainbow sardine	Homayooni et al. 2014	-	43.74±1.61	15.39±0.73	17.45±2.09	2.10±0.29	3.74±0.05
Hilsa clupea macrura	Asmah et al. 2014	10.97±1.61	27.82	11.83±0.02	5.96±0.31	-	-
Epinephelus tauvina	Dhaneesh et al. 2012	3.55	32.71	13.05	8.94	1.68	1.46
Carangoides orthogrammus	Dhaneesh et al. 2012	4.21	32.52	13.86	9.29	1.98	1.49
Tylosurus crocodilus crocodilus	Dhaneesh et al. 2012	4.56	35.11	15.06	9.34	1.11	1.61
Lutjanus gibbus	Dhaneesh et al. 2012	4.78	30.34	15.81	8.27	1.32	1.91
Seriola lalandi	Dhaneesh et al. 2012	3.11	31.22	15.70	9.82	1.57	1.6
Thunnus albacares	Dhaneesh et al. 2012	2.96	31.96	20.27	7.13	0.16	2.84
Parupeneus bifasciatus	Dhaneesh et al. 2012	5.56	31.51	20.67	6.88	0.17	3.00
Chelinus undulates	Dhaneesh et al. 2012	5.28	30.32	17.55	8.05	0.18	2.18
L. bohar	Dhaneesh et al. 2012	4.54	33.73	21.14	8.37	0.01	2.53
Hyporhamphus dussumieri	Dhaneesh et al. 2012	6.97	33.01	20.15	8.69	0.66	2.32
Lutianus agentimaculatus	Osman et al. 2007	-	27.43	7.51	8.18	0.34	2.17
Arius cumutranus	-	-	48.58	10.81	20.06	1.05	4.13
Epinephelus sexfasciatus	Osman et al. 2007	-	41.55	8.81	17.19	5.24	2.11
Scomberomorus commersoni	Osman et al. 2007	-	37.69	9.44	17.34	4.38	2.83
Pristipomodes typus	Osman et al. 2007	-	39.72	10.02	16.44	3.72	2.68
Congresax talabon	Osman et al. 2007	-	54.36	19.61	16.48	4.52	2.27
Rastrelliger kanagurta	Osman et al. 2007	-	40.37	10.12	16.33	4.45	2.25
Psettodes crumei	Osman et al. 2007	-	51.29	16.08	19.25	4.15	2.63
Scolidon sorrakowah	Osman et al. 2007	-	50.84	7.13	14.75	13.41	1.68
Acanthurs nigrosis	Osman et al. 2007	-	50.75	10.72	21.4	5.21	2.00
Anadontostoma chacunda	Osman et al. 2007	-	53.11	14.89	19.46	1.87	1.95
Sciaena dussumieri	Osman et al. 2007	-	52.88	11.53	23.95	7.16	2.18
Gymnura spp.	Osman et al. 2001	1.95±0.14	91.5	5.15	17.5	0.26	-
Eleutheronema tradactylum	Osman et al. 2001	2.24±0.20	89.5	5.93	9.89	0.22	-
Plotosus spp.	Osman et al. 2001	2.79±0.37	84.0	6.76	10.4	0.68	-
Parastromateus niger	Osman et al. 2001	2.79±0.25	74.4	5.18	9.36	0.52	-
Pampus argenteus	Osman et al. 2001	2.91±0.11	81.5	0.82	18.9	0.6	-
Clupea fimbriata	Osman et al. 2001	3.06±0.06	76.9	4.35	17.3	0.19	-
Magalapsis cordyla	Osman et al. 2001	3.08±0.11	86.9	5.76	28.6	0.45	-
Selarides leptolejus	Osman et al. 2001	5.77±0.52	85.5	3.97	27.3	0.26	-

studies suggest that EPA and DHA from fish n-3 enhance apoptosis in tumor cells (Ramesh et al. 1992, Madhavi and Das 1994, Ramesh and Das 1998, Das et al. 2002, Trombetta et al. 2007, Chapkin et al. 2008). The n-3 FAs are involved in tumor suppression by altering the phospholipid composition of cell membranes, and this affects multiple mechanisms of cancerous cells (Larsson et al. 2004, Chapkin et al. 2007). Several signaling pathways are now known by which n-3 FAs exert anti-tumor action by enhanced apoptosis and reduced proliferation. The n-3 FAs also interfere with cell cycle components, cell replication, and apoptosis-induced cell death (Field and Schley 2004, Serini et al. 2008). The findings of *in-vitro* research work carried out by various scientists on n-3 FAs to control the growth of cancerous cells are shown in Table 3. The *in vivo* studies also provided evidence to support the effect of omega-3

Table 3
In Vitro studies of the effect of ω-3 FAs on various cancer cell lines

Author	Type of PUFA	Cell Line	Method/ Design	Result	Outcome
Pogash et al. 2014	DHA, 4-OH-DHA and 4-OXO-DHA	MDA MB-231, BT-549, MCF-10F, bsMCF, trMCF (triple-negative breast cancer cell lines) and T-47D, MCF-7 and SK-BR-3 (luminal breast cancer cell lines)	MTT assay for Cell viability	↓ Growth of all basal and two luminal (T-47D, SK-BR-3) breast cancer cell lines but MCF-7 showed proliferation after DHA and 4-OXO-DHA treatment.	Anti-proliferative effect was more evident on triple negative breast cancer cell lines for which currently no targeted operation is available.
Zajdel et al. 2013	EPA, DHA and AA	A375, A2058, G361 (melatonic melanoma cell lines) and C32 (amelatonic melanoma cell line)	TOX-2 test for cytotoxicity Aldehyde Site Detection Kit for oxidative protein and DNA modifications	All FAs ↓ proliferation in A375, A2058, G361 at 50 mM, followed by oxidative protein and DNA damage at 100 mM. Only EPA and DHA ↓ proliferation in C32 at 100 mM in which the effect of DHA was more pronounced.	Anti-proliferative action of FAs depends on the type and concentration of FAs and type of melanoma cell lines on which effect is being observed.
Yang et al. 2013	EPA and DHA	CSCs (colorectal cancer stem cells)	DNA fragmentation. Annexin V-PI double staining. Flow cytometry for apoptosis detection. MTS assay for comparison of sensitivity of spheroid cells.	↑ Annexin V expression. ↑ Apoptosis. ↑ Sensitivity of 5-Fu and mitomycin C to chemotherapy.	n-3 FAs act as direct pro-apoptotic or anti-proliferative agent for cancer stem-like cells and also as a potential adjuvant for colorectal cancer therapy.
Fukui et al. 2013	EPA and DHA	MIA-PaCa-2 and Capan-2 (human pancreatic cancer cell lines)	MTT assay for Cell viability. H2-DCF-DA for ROS accumulation. Western blot for gene expression. Monitoring LC3B- positively staining cells for autophagy assessment. Transfection with Beclin 1 siRNAs for autophagy inhibition.	↓ Cell viability. ↑Intracellular ROS accumulation. ↑ Caspase-8 dependent cell death. Autophagosome formation in EPA supplemented cells. Autophagy inhibition in Beclin 1 siRNAs transfected cells.	EPA along with an autophagy inhibitor can increase the effectiveness of EPA in inducing apoptotic cell death in human pancreatic cancer cells.
Dai et al. 2013	LA, ALA, AA, EPA and DHA	MGC, SGC (gastric carcinoma cell lines) and GES1 (normal gastric cell line)	MTT assay for Cell viability. Flow cytometry for measuring the rate of apoptosis. GC for studying fatty acid profile of cells. DCFH-DA for ROS generation. ELISA test to determine levels of lipoxin A4 generated.	↓ growth of MGC, SGC and GES1 cell lines by all FAs, indicating a very little differential effect on normal and tumor cells. Lipid droplets accumulated in cells treated with PUFAs. ↑ ROS generation in GES1 cells by LA, ALA and EPA, MGC cells by DHA, SGC cells by all PUFAs. AA produced highest level of lipoxin A4 in MGC cells as compared to GES1.	Close sensitivity of normal and cancer cells of stomach to anticancer agents may explain the reason of significant side effects of gastric cancer treatment, since normal stomach cells are affected.

Table 3

Author	Type of PUFA	Cell Line	Method/ Design	Result	Outcome
Notarnicola et al. 2011	EPA and AA	HepG2 (human hepatoma cell line)	MTT assay for cell viability. ELISA test for apoptosis detection. Real-time PCR to determine levels of FAS and HMG-CoAR mRNA in the treated cells.	EPA showed pro-apoptotic effect and ↓ cell growth at lower doses (1 μM and 25 μM respectively) while AA require higher doses (100 μM) for the same. ↓ Gene expression of HMG-CoAR and FAS (10 μM).	HepG2 cells were more sensitive to EPA than AA, determining more efficacy of n-3 FAs as strong anticancer agents.
Corsetto et al. 2011	EPA, DHA, and AA	MDA-MB-231 (ER-negative) and MCF-7 (ER-positive) breast cancer cell lines.	MTT assay for cell viability. Western blot for Bcl2, caspase-8, EGFR and pEGFR HPLC/GC for evaluation of FAs incorporation into membrane phospholipids.	↓ Cell viability. ↓ Cell proliferation. ↓ Bcl2 and procaspase-8 expression. Activation of EGFR. FAs incorporated with different degrees of specificity, n-6 FAs are influenced by n-3 FAs and vice-versa.	n-3 FAs might induce modifications in cell membrane structure of breast cancer cells by increasing the degree of unsaturation in FAs.
du Toit-Kohn et al. 2009	DHA	$CaCo_2$ (human adenocarcinoma cell line), NCM460 (normal colon cell line).	MTT assay for cell viability. Western blot for analyzing activity of p38 MAPK, ERK, Akt and p53. Specific protein inhibitors and siRNA for analyzing cross talk among signalling pathways.	↓ Cell viability in $CaCo_2$ cells. ↑ caspase-3 activation. ↓ Akt phosphorylation. No effect on NCM460 cells. siRNA experiments assessed p38 MAPK's role in p53 phosphorylation, associated with DNA damage.	DHA exerts cytotoxic/ apoptotic effect specifically on colon cancer cells without affecting the normal cells, suggesting the use of n-3 FAs as tumor preventive agent.
Heimli et al. 2002	EPA	Ramos (lymphoma cell line).	[3H]thymidine and [3H]valine incorporation for DNA and protein synthesis. DNA staining with PI and HO342 for cell viability microscopic analysis. Flow cytometry for cell cycle analysis. Annexin V–FITC binding and PI staining for PS translocation. Colorimetric activation assays for caspase-3, -8 and -9 activity.	↓ DNA and protein synthesis. PI stained cells indicate leaky cell membrane. HO342 stained cells indicate intact or distorted cell membrane. No cell cycle arrest. ↑ Annexin V–FITC binding and PS flipping followed by PARP cleavage. ↑ caspase -3, -8 and -9 activity.	EPA in Ramos cells promote cell death via intrinsic apoptotic pathway and not via cell cycle arrest.

Abbreviations: ↑ = Increase; ↓ = Decrease; AA = Arachidonic acid; ALA = α-Linolenic acid; ANOVA = Analysis of variance; DCFH-DA = Dichloro-dihydro-fluorescein diacetate; DHA = Docosahexaenoic acid; EGFR = Epidermal growth factor receptor; ELISA = Enzyme-linked immunosorbent assay; EPA = Eicosapentaenoic acid; ER = Estrogen; ERK = Extracellular signal-regulated kinase; FAs = Fatty acid synthase; GC = Gas chromatography; HMG-CoA-R = 3-Hydroxy-3-methyl-glutaryl-coenzyme A reductase; HPLC = High performance liquid chromatography; LA = Linoleic acid; M-APK = Mitogen activated protein kinase; MTT = 3-(4,5-Dimethylthiazol-2-Yl)-2,5-diphenyltetrazolium bromide; OXO-DHA = α,β-unsaturated keto-derivative of docosahexaenoic acid; PARP = Poly-ADP-ribose polymerase PI = *Propidium iodide;* PS = Phosphatidylserine; PUFA = Poly unsaturated fatty acid; ROS = Reactive oxygen species; SiRNA = Small interfering RNA

FAs on various types of tumor cells (Liu et al. 2000, Latham et al. 2001, Tsujita-Kyutoku et al. 2004, Wynter et al. 2004, Edwards et al. 2008).

Changes induced by EPA-derived eicosanoids in cell membranes

Dietary or supplemented n-3 FAs are incorporated into the phospholipids of tumor cell membranes and affect lipid packing, membrane permeability (Stillwell et al. 1997), lipid microdomains (Shaikh et al. 2001, Ma et al. 2004, Schley et al. 2005), and fusion (Ehringer et al. 1990), and they alter the signaling pathways of apoptosis (Chapkin et al. 2002, Ng et al. 2005, Schley et al. 2005). Diets rich in n-3 FAs partially replace n-6 FAs in cell membranes and lower the production of AA-derived prostaglandins (PGs), thromboxanes (TXs), and leukotrienes (LTs) (Crawford et al. 2000). Incorporated n-3 FAs (EPA and DHA) compete with n-6 FA (AA) to reduce the availability of n-6 FA for esterification at the sn-2 position of phospholipids (PLs) of cell membranes (Arterburn et al. 2006), which is followed by the hydrolytic release of EPA/DHA and AA from the membrane stores by the action of phospholipase A_2 (Larsson et al. 2004). The released EPA/DHA and AA act as substrates for two different groups of enzymes, cyclooxygenases (COXs) and lipooxygenases (LOXs), and convert them into their metabolites known collectively as eicosanoids (20 carbon, short-lived) (Smith and Murphy 2002). The biosynthesis of eicosanoids from AA or EPA is catalyzed by COX enzymes (Hinz and Brune 2002). From three isoforms, COX-2 expression is induced by inflammatory and mitogenic stimuli (Warner and Mitchell 2004) that promote tumor, metastatic processes, the inhibition of apoptosis, and the formation of carcinogens and angiogenesis (Dannenberg et al. 2001). Ermert et al. (2003) reported that the increased expression of COX-2 is directly related to elevated levels of the downstream enzymes needed for the synthesis of prostanoids, which may increase products of AA metabolism. In *in-vitro* studies, n-3 FAs were found to play an active role in reducing the migration and invasiveness of COX-2 to decrease the products of AA in brain-metastatic melanoma and prostate cancer cells (Denkins 2005, Brown et al. 2006). Earlier studies posited that the anti-cancer effect of n-3 FAs is mainly due to reductions in PGE2, but, later, Yang et al. (2013) and Funahashi et al. (2008) reported that PGE3 is also responsible for anti-proliferation in A549 and BxPC3 cancer cells, respectively, by inducing apoptosis. PGE3 also antagonized the pro-tumorigenic effect of PGE2 in HT-29 CRC cell transfection with EP4 in which the expression of COX-2 and other EP receptors were lacking, but the same result was not observed in HCA-7 CRC cells with high levels of endogenous PGE2 (Hawcroft et al. 2010). In RAW264.7 macrophage cells, cells supplemented with EPA showed increased amounts of PGE3 and PGD3 (EPA-derived COX metabolite) and decreased AA derived metabolites as compared to the control (Norris and Dennis 2012). Diets rich in EPA increased the formation of LTB5 and reduced the formation of LTB4 (an inducer of tumor cell adhesion) (Damtew and Spagnuolo 1997). EPA-derived LOX products are anti-inflammatory, and AA-derived LOX products are pro-inflammatory where inflammation was positively linked to cancer (Grivennikov et al. 2010), but lipoxins derived from AA are anti-inflammatory, which indicated the role of AA-derived eicosanoids in the anti-inflammatory response (Janakiram et al. 2011). Some AA-derived prostanoids, like PGI2 and 15d-PGJ2, were also found to be anti-mitotic and anti-metastatic (Honn et al. 1981, Bishop-Bailey et al.2002). COX and LOX activities on n-3 and n-6 FAs and the role of 2, 3, 4, and 5 series prostanoids are shown in Fig. 3.

Alternation of key proteins and enzymes involved in apoptosis

Multiple reports indicate that n-3 FAs can alter the expression or activity of a number of genes, signaling molecules and certain transcription factors associated with cell proliferation and apoptosis. The constitutive over-expression of Bcl-2, NFκB (Nuclear tran-

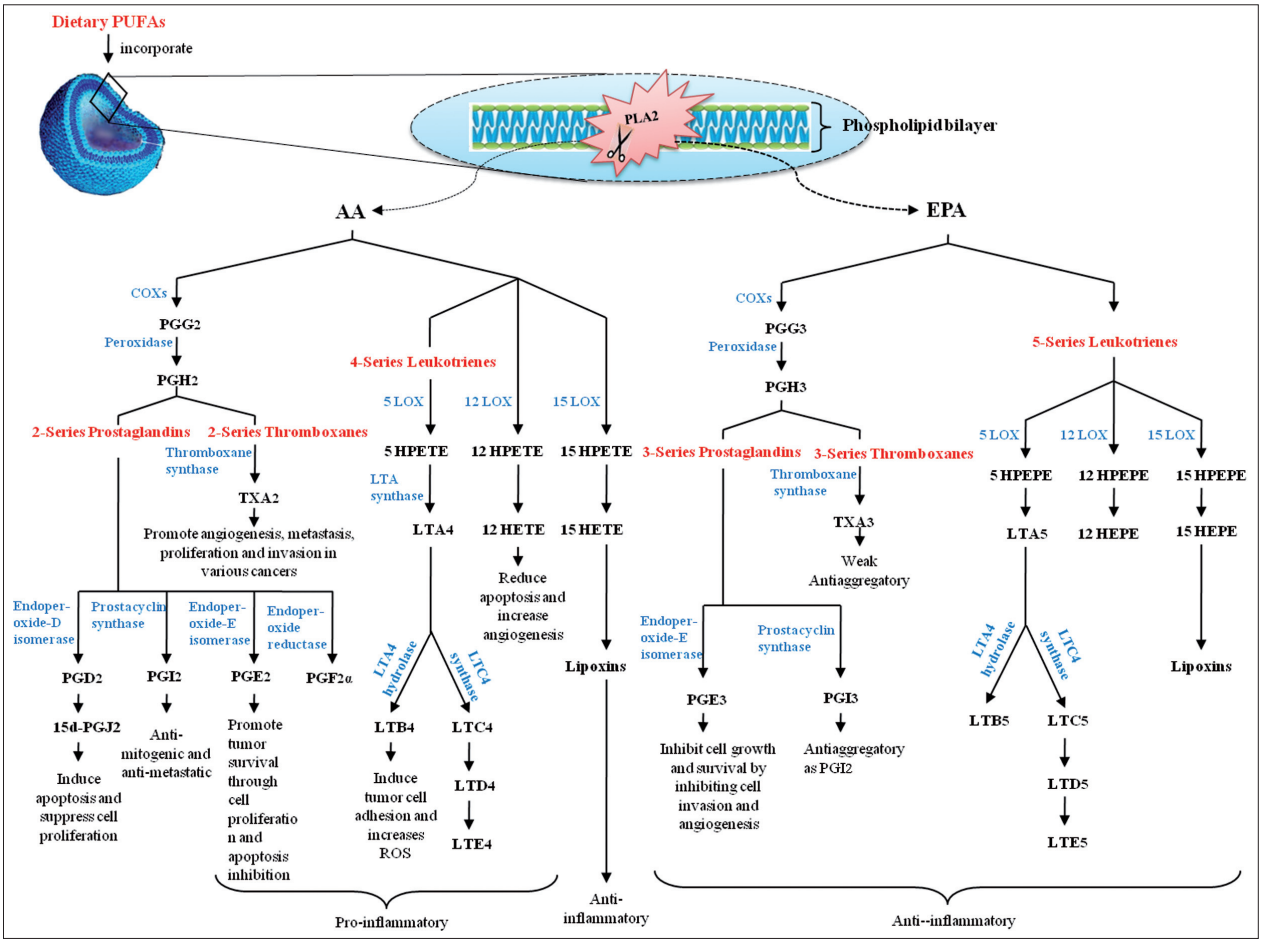

Figure 3. Competition between EPA and AA for COX and LOX for the formation of eicosanoids.
Abbreviations: PLA2 = phospholipase A2; AA = arachidonic acid; EPA = eicosapentaenoic acid; COX = cyclooxygenase; LOX = lipooxygenase; HPETE = hydroperoxyeicosatetraenoic acid; HPEPE = hydroperoxyeicosapentaenoic acid; HETE = hydroxyeicosatetraenoic acid; HEPE = hydroxyeicosapentaenoic acid; PG = prostaglandin; LT = leukotriene; TX = thromboxane.

scription factor κB), Ras, and wnt/β-catenin signaling molecules causes cell proliferation, and DHA has been shown to down-regulate their expression to induce apoptosis (Chiu and Wan 1999, Chen and Istfan 2000, Collet et al. 2001, Fuchs et al. 2005, Calviello et al. 2007, Song et al. 2011). Wild type p53, Bax, caspases-3, -8, and/or -9, and PPAR (peroxisome proliferator-activated receptor, a transcription factor) are known for their pro-apoptotic functions that induce apoptotic cell death. Different studies indicate that EPA/DHA up-regulate the expression of these apoptotic markers to activate the cell death pathway (Arita et al. 2001, Narayanan et al. 2001, Heimli et al. 2002, Jumb 2002, Fan et al. 2003, Chi et al. 2004, Okada and Mak 2004, Hostetler 2005, Edwards et al. 2008, Fulda 2009). Details are in Fig. 4.

Association between n-3 FAs and lipid peroxidation

The supplementation of n-3 FAs in cancer cells appears to enhance lipid peroxidation and the generation of free radicals (Das 1991, Sangeetha and Das 1992), which reduce anti-oxidants and increase cytotoxicity in cancer cells (Padma and Das 1986). Free radicals generated can damage DNA and proteins and inactivate enzymes that induce cell death (Das 1999). Lipid peroxidation has been found to

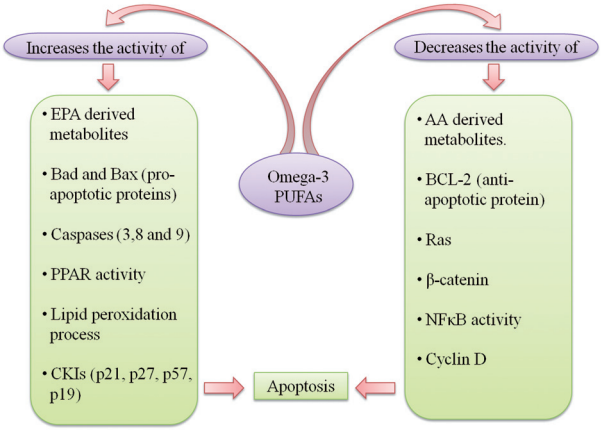

Figure 4. Model of signaling pathways of anti-cancerous actions of n-3 FAs.

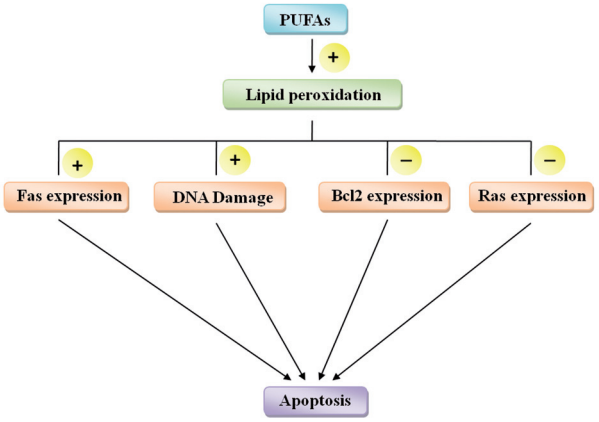

Figure 5. Schematic diagram of apoptosis induction by FAs through lipid peroxidation. + Indicate activation, – Indicate inhibition.

inhibit the expression of Ras (Cheokin et al. 1997) and Bcl-2 oncogenes and enhances Fas expression that promotes apoptosis (Halder et al. 1995). Investigations have focused on the question of whether peroxidation products of EPA, DHA, and AA possess the ability to bind with Bcl-2 oncogenes, which leads to their inactivation by phosphorylation. Phosphorylated Bcl-2 increases lipid peroxide formation that ultimately leads to apoptosis (Halder et al. 1995). Fig. 5 shows the interactions among lipid peroxidation, n-3 FAs, Bcl-2 and Fas expression, and the induction of apoptosis. Szatrowski and Nathan (1991) reported that tumor tissues produce large amounts of ROS because of the insufficient blood flow as compared to surrounding normal tissues. Moreover, tumor cells treated with n-3 FAs show low levels of anti-oxidants that enhance the damaging actions of lipid peroxides that cause cytotoxicity (Padma and Das 1986, Kumar and Das 1995).

Effect on cell cycle regulation

Cell cycle is mediated by two types of control mechanisms, i.e., the coordinated interaction of cyclins with their respective cyclin dependent kinases (CDKs), and a set of checkpoints (Collins and Jacks 1997). The cyclin-CDK complexes are inactivated by cyclin-dependent kinase inhibitors (CKIs). These CKIs are categorized into two families: the Cip/Kip family (p21, p27 and p57), and the INK4 family (p15, p16, p18 and p19) (Morgan 1995, Sherr and Roberts 1999, Canepa et al. 2007). DHA-treated leukemic cells (Siddiqui et al. 2003) and colon and breast cancer cells (Danbara et al. 2004, Tsujita-Kyutoku et al. 2004) showed increases in p21 expression that arrested the cell cycle prior to the induction of apoptosis. These results were supported by a microarray study on CaCo-2 colon cancer cells that showed increased p21, p27, p19, and p57 mRNA levels after treatment with DHA, which indicated the involvement of both CKI families in inhibiting cell cycle progression in the course of cancer inhibition (Narayanan et al. 2001).

The main checkpoints involved in cell cycle control are the G1/S and G2/M checkpoints (Foijer and Riele 2006). At the G1/S transition, cyclin D binds to CDK4 or CDK6 and phosphorylate Rb protein to release the transcription factor, E2F to transcribe the genes required for cell cycle progression and DNA synthesis (Kato et al. 1993, Delston and Harbour 2006). Omega-3 FAs have been shown to suppress the expression of cyclin D in various cancer cells such as those of the colon (Danbara et al. 2004, Narayanan et al. 2004, Jakobsen et al. 2008) breast (Tsujita-Kyutokuet al. 2004, Lu et al. 2010), and prostate (Lu et al. 2008). Moreover, n-3 FAs also repress the proliferation of cancer cells by mediating the G2/M transition. Barascu et al. (2006) reported

that in MDA-MB-231 breast cancer cells, EPA and DHA markedly increased the duration of the G2/M phase with decreased activity of the cyclin B1-CDK1 complex, an essential regulator involved in the progression from G2 to M.

n-3/n-6 ratio

Omega-3 and n-6 FAs have been shown to manifest opposing roles in cancer progression. Excessive n-6 FAs, which are noted in today's western diets, have serious health implications, whereas, excess n-3 FAs exert suppressive effects. James and Cleland (1997) reported that drug therapy with the dietary intake of a higher n-3/n-6 ratio (i.e., increased n-3 and decreased n-6 FAs) provides a suitable biochemical environment in which drugs show their potential effect. Mansara et al. (2015) showed the effect of low and high ratios of n-3/n-6 FAs in an *in vitro* study on cellular mechanisms in cancerous and non-cancerous cell lines. A high n-3/n-6 ratio was reported to decrease the cell viability of MCF7 and MDA-MB-231, while no reduction was observed in the cell viability of MCF10A. On the other hand, decreasing ratios of n-3/n-6 FAs were linked with a ratio-dependent decrease in cell viability in both breast cancer (MCF7 and MDA-MB-231) and a non-cancerous cell line (MCF10A).

Future prospects

Several mechanisms have been discussed by which n-3 FAs inhibit the development and progression of cancer. In this context, different ratios of n-3/n-6 FAs require special attention as is evident from the preceding discussion since limited studies have been carried out to scrutinize their effect on cancer cell lines. Therefore, more *in vitro* research needs to be undertaken that mimics the diet ratios of today's world, to evaluate the potential benefits and harmful effects of the FAs and to unravel the possible mechanisms and pathways responsible for such effects.

Studies have revealed that n-3 FAs can be used as effective adjuvants for chemotherapy (Vaughan et al. 2013), and that they also minimize secondary complications associated with cancer. When administered with n-3 FAs, the anticancer drug doxorubicin showed enhanced efficacy in its cytotoxic effect on various cancer cell lines such as the human breast cancer cell line, MDA-MB-231 (German et al. 1998), murine leukemia cells (Guffy et al. 1984), and small-cell lung carcinoma cell lines (Zijlstra et al. 1987). A synergistic interaction was observed by Siddiqui et al. (2011) between anticancer drugs and DHA along with increased drug transport particularly in cells that are normally resistant to these drugs. Similarly, cisplatin, paclitaxel, and docetaxel are some other curative anti-cancer drugs that are used to treat a wide range of cancers including head and neck, cervical, ovarian, and non-small-cell lung cancer (NSCLC), gastroesophageal, endometrium neoplasma, and bladder cancer (Wang and Lippard 2005, Nobili et al. 2009). These drugs also have certain serious side effects like neurotoxicity, nephrotoxicity, and emetogenesis (Wang and Lippard 2005, Hershman et al. 2011). Therefore, in future studies, these drugs should be tested in combination with n-3 FAs to help mitigate side effects and increase their efficacy.

Phytochemicals such as piperine (Siddiqui et al. 2017), naringenin (Ahamad et al. 2014), and curcumin (Iqbal et al. 2016) are also known to have anti-cancerous effects against human oral squamous carcinoma (KB cell line), human epidermoid carcinoma (A431 cell line), and human myeloid carcinoma (KCl-22cell line). Therefore, investigations on the use of EPA and DHA in combination with phytochemicals should be conducted with the aim of enhancing their cytotoxic effect on various cancer cell lines. Furthermore, antibodies like trastuzumab, a humanized anti-HER2 antibody, as specific carriers of n-3 FAs can also be used (Pegram et al. 2004) to target tumor cells in particular. This can improve the selectivity of n-3 FAs specifically against tumor cells.

Conclusion

In light of the data reviewed, n-3 FAs can be considered as anti-proliferative and/or apoptosis-inducing agents for cancerous cells. They exert their anti-cancer effects by influencing multiple mechanisms involved in cancer development. These include changing the composition of cell membranes, blocking cell cycle, and altering the activity of key proteins, enzymes, and transcription factors involved in apoptosis. Some of the effects of n-3 FAs may not be directly related to fatty acid molecules themselves but rather to their metabolites such as eicosanoids and lipid peroxides. Research on the use of antibodies as specific carriers of n-3 FAs is needed to target tumor cells specifically. Research on the combination of n-3 FAs with anti-cancerous plant products, anti-tumor drugs, and increasing ratios of n-3/n-6 FAs are considered to be important and can be employed for the prevention of cancer and/or as adjuvants to chemotherapy.

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