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Eicosapentaenoic Acid and Docosahexaenoic Acid from Fish Oil and Their Role in Cancer Research

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ABSTRACT

Omega-3 fatty acids are long chain polyunsaturated fatty acids (LCPUFAs) have been the source of interest because of their beneficial pharmacological activities. These omega 3 LCPUFAs, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have shown anti-inflammatory activity, which increased the research interest on EPA and DHA for their possible effectiveness against cancer. EPA and DHA offer safe and non-toxic approach (as compared to anti-cancer drugs) to prevent or inhibit carcinoma cell growth. The present review article outlines research on omega-3 fatty acids on various carcinomas to understand the mechanism and effectiveness of EPA and DHA against different cancerous diseases. In this article, the increased interest in fish oil and the positive outcome of omega-3 fatty acids in the cancer research is highlighted. It suggests that the research on the natural compounds like omega-3 fatty acids should be encouraged to understand the mechanisms against tumor and to improve the quality of life.

KEYWORDS

Eicosapentaenoic acid; Docosahexaenoic acid; omega-3 fatty acids; fish oil; carcinoma

Introduction

Cancer is a collection of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body. The abnormal growth influenced by cancer can result into tumors, damage to the immune system, and other impairment that can be fatal. It is estimated that only in 2018, 18.1 million new cases of cancer have been reported and 9.6 million deaths occur globally.[1] There are several types of cancer, including breast cancer, skin cancer, lung cancer, colon cancer, prostate cancer, etc and researchers are actively working on drug development to combat cancerous diseases. One of most current interest of research is pharmacological activities of natural products from plants and animals. Natural products derived from medicinal plants of marine and microbial origin have an important contribution to the discovery and development of new substances with therapeutic potential against cancer and as a possible alternative to resistance demonstrated by cancer cells at multidrug.[2]

Fatty acids are the main source of energy in the body, contain a hydrocarbon chain and a terminal carboxylic group, and are classified according to the chain length and the degree of unsaturation. Dietary fatty acids, especially long-chain polyunsaturated fatty acids (LCPUFAs), are organic compounds essential for growth and development of mammals, including

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humans.[3–5] Both linoleic acid (C18:2 n-6, LA) and alpha-linolenic acid (C18:3 n-3, ALA) received the designation of essential fatty acids because mammals do not have all the necessary desaturation enzymes to synthesize those fatty acids.[5,6] Decades later, several investigations established the physiological importance of LA and ALA and their fatty acid derivatives in human beings, especially arachidonic acid (C20:4 n-6, ARA) for the n-6 series and eicosapentaenoic acid (C20:5 n-3, EPA) and docosahexaenoic acid (C22:6 n-3, DHA) for the n-3 series.[4–6]

Fish oil, a natural product, is extracted from tissues of marine or freshwater fish,[7,8] and is a primary source of long chain omega-3 fatty acids, especially EPA and DHA.[9] Apart from fish oil, omega-3 fatty acids can also be obtained from various plant sources (flaxseed, kiwifruit, chia etc) but they contain low level of EPA and DHA and are also very rich in alpha-linoleic acid (ALA).[10] The percentage composition of omega-3 fatty acids depends on the body part of fish, method employed to extract the fish oil and source of fish.[8,10–13] The common sources of fish for the production of fish oil are mackerel (*Scomberomorus regalis*), herring (*Clupea pallasii*), Salmon (*Salmo salar*), trout (*Salmo marmoratus*), tuna (*Thunnus thynnus*) and cod fish (*Gadus morhua*).[8,13,14]

The omega-3 fatty acids are considered to have a pharmacological role for the treatment against various ailments, reducing inflammation and therefore there is a significant increase in consumption of fish oil in human food and supplements and such products have been labeled as nutraceuticals.[15–17] The importance of omega-3 fatty acids (especially EPA and DHA) have been documented for many health benefits such as in cardiovascular diseases,[18] diabetes mellitus,[19,20] rheumatoid arthritis,[21] and anti-inflammatory effectiveness.[22] Researchers have also shown interest in EPA and DHA for cancer studies.[23–26] The aim of this review is to highlight the research on omega-3 LCPUFAs against various types of tumors and defining their possible mechanism of action. Furthermore, we also attempt to provide an insight about the current trends and the scope of fatty acids as an anti-cancer against various cancers.

Methodology

The review article aimed to highlight research done on omega-3 fatty acids in relation to cancer treatment in last 15 years. Literature search was undertaken between years 2005–2019 to identify published peer-reviewed articles. The databases for search included: Google Scholar, Cochrane Library, Springer links, Science Direct, PubMed, and Medline. The timeline of year 2005–2019 effectively covers all the research performed on influence of omega-3 fatty acids against different types of cancers. Newspaper clippings, general online articles or articles, which are not published in English were excluded from the study. The exclusion and inclusion criteria of the study are given in Table 1. A total of around 36,922 articles were identified using database searches for the relevant literature. Articles which were duplicated and titles/abstracts unrelated to health economic evaluations of hospital and pharmacy services (and methodologies utilized) were removed based on our inclusion and exclusion criteria provided in Table 1, The number of articles found against each key word are given in Table 2. All the articles from which this review has been extracted are given as references.

General mode of antitumor action

The omega-3 LCPUFAs are important biomolecules in the regulation of hepatic lipid metabolism, which is accomplished through down-regulation of the expression and processing of

Table 1. Exclusion and inclusion criteria of the study.

Inclusion/Exclusion	Category	Criteria
Inclusion	Year of publications	2005-2019
	Publication type	Full text articles published in peer reviewed scientific journals
	Language of publication	English
	Region of research	Global
	Medicine type	Omega-3 fatty acids
	Methodology	Review of published research and review articles in indexed journals
	Topic of research	Eicosapentaenoic acid and Docosahexaenoic acid from Fish Oil and their role in Cancer Research
Exclusion	Publication type	Online articles which are not present in indexed journals and the news reports
	Publication language	Articles published in languages other than English

Table 2. Keywords used and the number of publications found.

Keywords	No of Publications found
EPA and DHA	13,631
Fish oil and cancer	8,875
Omega 3 fatty acids and cancer	7,295
Eicosapentaenoic acid and cancer	3,380
Docosahexaenoic acid and cancer	3,741

transcription factor sterol regulatory element-binding protein 1c (SREBP1c) leading to depressed lipogenic and glycogenic capacity, and up-regulation of peroxisome proliferator-activated receptors (PPARs) favoring fatty acids oxidation.[4,27] PPARs constitute a group of transcription factors that are known to regulate several metabolic and cellular processes, including lipid and glucose metabolism linked to energy homeostasis, adipogenesis, inflammatory responses or oxidative stress, besides exerting a fundamental role in embryonic and fetal development. Signaling by PPAR transcription factors as a crucial cellular event regulating energy availability through balance in glucose and lipid metabolism, which can be triggered by ligands, mainly omega-3 LCPUFAs. PPAR activation by omega-3 LCPUFAs, and the consequent promotion of gene transcription may have a fundamental role in first stages of life and in the prevention and treatment of several diseases such as cardiovascular, metabolic, neurodegenerative pathologies, inflammatory diseases and cancer.[4,27,28] The Omega-3 fatty acids (especially EPA and DHA) are known to show anti-inflammatory activity.[29–32] Due to its role in inhibition of proinflammatory prostaglandins, it may also influence the inhibition of growth of tumor cells.[33–35] The roles of EPA and DHA in tumor inhibition have been thoroughly investigated against various carcinoma cell lines and animal models to understand their mode of action.[36–38] Generally, there have been four pathways that have been utilized by EPA and DHA to exert their anti-tumor activity. These pathways are carcinoma cell growth inhibition of apoptosis, oxidative stress, and angiogenesis and COX2/PGE2 inhibition.

Apoptosis

Apoptosis is generally defined as programmed cell death and omega-3 fatty acids, EPA and DHA, have shown to induce dose-dependent apoptosis effect of carcinoma cells.[39,40] Omega-3 fatty acids cause the increase in pro-apoptotic proteins levels and reduce level of the anti-apoptotic proteins.[41,42] Physiological levels of reactive oxygen species (ROS) are very critical

and excessive levels may cause irreversible cellular damage, thus provoking apoptosis.[43] There are many studies that have reported the influence of DHA and EPA in regulating the concentration of ROS and inducing apoptosis.[42,44,45] Figure 1 illustrates the brief pathway of omega-3 fatty acids in influencing apoptosis. The pathway begins with increased ROS induced by omega-3 fatty acids, which leads to the activation of PI3K/Akt and translocation of Nrf2 from the cytosol to the nucleus. This then leads to up-regulation of the tumor-suppressing protein OKL38, which results in both the increase of the Bax/Bcl-2 ratio and translocation of p53 to the mitochondria. p53 then induces the release of cytochrome c from the mitochondria, which results in the death of the cancer cells.[46]

Oxidative stress

The imbalance between the presence of ROS and a biological system's ability to detoxify the reactive intermediates is called as oxidative stress. The oxidative stress is utilized by EPA and DHA causing oxidative metabolism and removal of hydrogen. Oxidative stress occurs at an increased rate when the redox balance inside the cell is seriously disturbed and the production of initiators (ROS), cannot be sufficiently suppressed as in tumor cells. The most common ROS are hydroxyl radicals, superoxide radicals, alkoxyl radicals, peroxyl radicals, singlet oxygen, ozone, anions, and hydrogen peroxide.[47] Oxidative stress will lead to programmed cell death through apoptosis because of Intracellular accumulation of ROS will disrupt the mitochondrial membrane potential, that leads to release of cytochrome c with consecutive activation of the caspase cascade, and, ultimately, to apoptosis (Fig. 2).[48,49] Oxidative stress have been investigated in several animal models,[50–52] in which it was indicated that there is a significant influence of omega-3 fatty acids on oxidative stress. It has also been reported that oxidized EPA inhibits the inflammatory nuclear factor kappa B cells (NF-kB) pathway that be mediated by omega-3 derived isoprostanes, as these peroxides have been shown to be

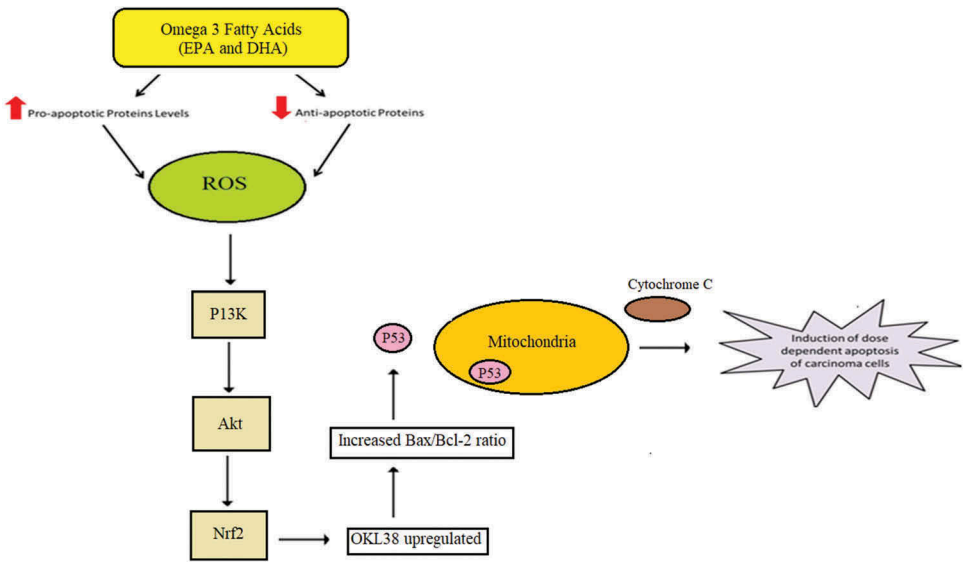

Figure 1. Pathway of omega-3 fatty acids inducing apoptosis.

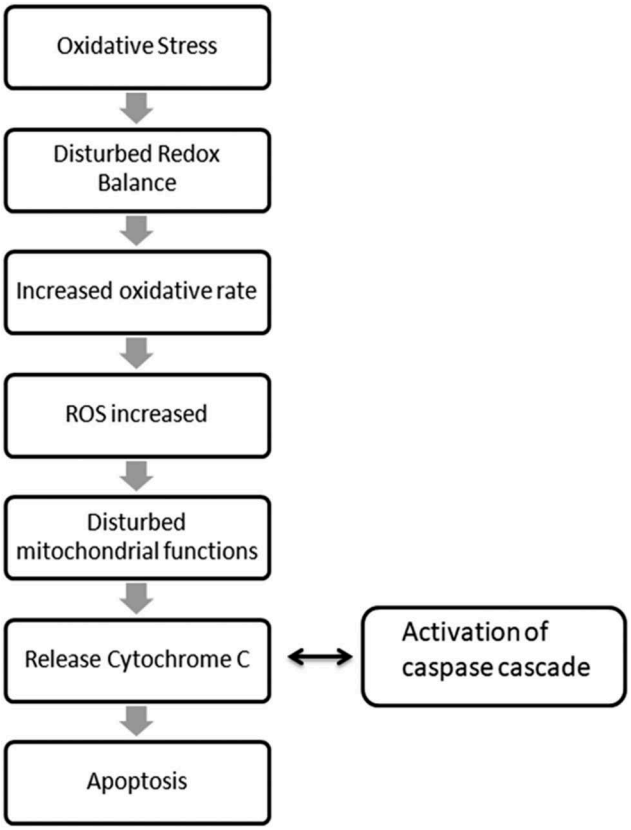

Figure 2. Flow chart representation of oxidative stress.

biologically active, inhibiting macrophage NF-kB activation in tissue culture.[53]Oxidative stress has a significant role in cancer, it mediates the inflammatory response when activating NF-kB. As mentioned earlier omega-3 fatty acids are considered as PPAR- agonists, in addition to that these LCPUFAs (EPA and DHA) are also effective inhibitors of nuclear factor-B (NF-B) DNA binding activity, which limits inflammatory gene responses.[54] Oxidative stress as an early event in inflammatory diseases and to prevent abnormal oxidative stress, several physiological anti-oxidant systems such as microsomal glutathione S- transferase 1 (MGST1) and heme oxygenase (HO-1). These enzymes act as protective mechanism, which detoxifies reactive intermediates. Nitric oxide is a free radical that is catalyzed by nitric oxide synthase (NOS) as a defense mechanism. During pathological inflammation, nitric oxide is produced in an excessive manner leading to cell damages. n-3 FAs act on oxidative stress by reducing the expression of a pro-oxidative gene (*NOS2*) and enhancing the expression of *MGST1*, an anti-oxidative gene.[55]

COX2/PGE2 inhibition

The anti-inflammatory activity of omega-3 fatty acids,[56] has also proven beneficial for inhibition of cancer growth. Both EPA and DHA have shown the ability to inhibit the

arachidonic acid pathway to produce anti-inflammatory effect which later may result into inhibition of tumor.[29,34] Cyclooxygenase (COX)-2 and microsomal prostaglanding synthase 1 (mPGES-1), the enzyme responsible for converting arachidonic acid (AA) to prostaglandins (PG)-2 (Fig. 3),[57] are highly expressed in tumors and EPA and DHA inhibition of these enzymes has profound effects on the inhibition of these tumors growth.[58,59]

Arachidonic acid, a polyunsaturated fatty acid, is released from membrane phospholipids through the action of phospholipase A2 (PLA2) enzymes and then leading to the formation of group of inflammatory mediators. It acts as a substrate for cyclooxygenase (COX), lipoxygenase, or cytochrome P450 enzymes. COX enzymes lead to PG and thromboxanes, lipoxygenase enzymes lead to leukotrienes (LT), and cytochrome P450 enzymes lead to hydroxyeicosatetraenoic and epoxyeicosatrienoic acids. Omega-3 fatty acids (EPA and DHA) incorporation in cell membrane decreases their AA content and reduces the amount of substrate available to produce inflammatory and immunoregulatory eicosanoids.[60] LTB5, a product of EPA, is a competitive antagonist to LTB4, a highly proinflammatory eicosanoid derived from AA.[61] Omega-3 fatty acids supplementation may also significantly decrease phospholipase 2 (PLA 2) activity. It has been reported that administration of omega-3 LCPUFA can decrease lipoprotein-associated PLA2 in patients with stable angina undergoing percutaneous coronary intervention.[62]

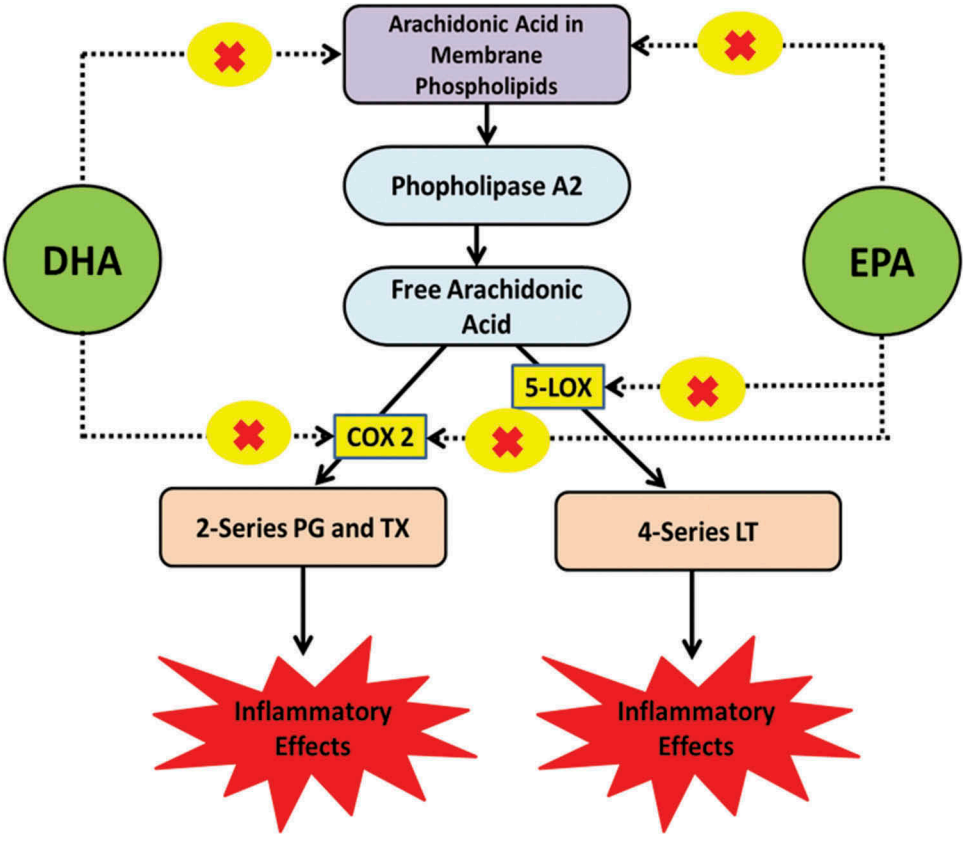

Figure 3. Mechanism of COX 2 inhibition for EPA and DHA.

Angiogenesis and adhesion

Angiogenesis is the growth of new blood vessels, which in case of tumor growth is an abnormal phenomenon. Angiogenic growth factor proteins are released by cancerous tumors that stimulate blood vessels to grow into the tumor. The reduction in angiogenesis is perhaps because of decreasing levels of vascular endothelial growth factor,[63,64] platelet-derived growth factor, and platelet-derived endothelial cell growth factor caused by omega-3 fatty acids (**as shown in** Fig. 4).[37] Cancer cell-adhesion is one of fundamental mechanism in initiating the angiogenesis and growth of tumor.[65] Omega 3 fatty acids can inhibit adhesion,[37,66]and has also been shown to decrease TNFα- induced monocyte rolling, adhesion, and transmigration.[67] These effects might also be applicable to tumor cells in the process of adhering to tissue sites.

Various cancer types have been studied in relation to EPA and DHA, and it was observed that EPA and DHA induced carcinoma growth inhibition that is accomplished by one or more above-mentioned mechanism. Following are the few types in anti-tumor role of omega-3 fatty acids from fish oil have been investigated, and we included in this review.

Pancreatic cancer

Pancreatic cancer is one of the leading causes of cancer mortality worldwide.[68] Pancreatic cancer can be initiated due to the mutation in KRAS- proto-oncogene or due to inactivation of

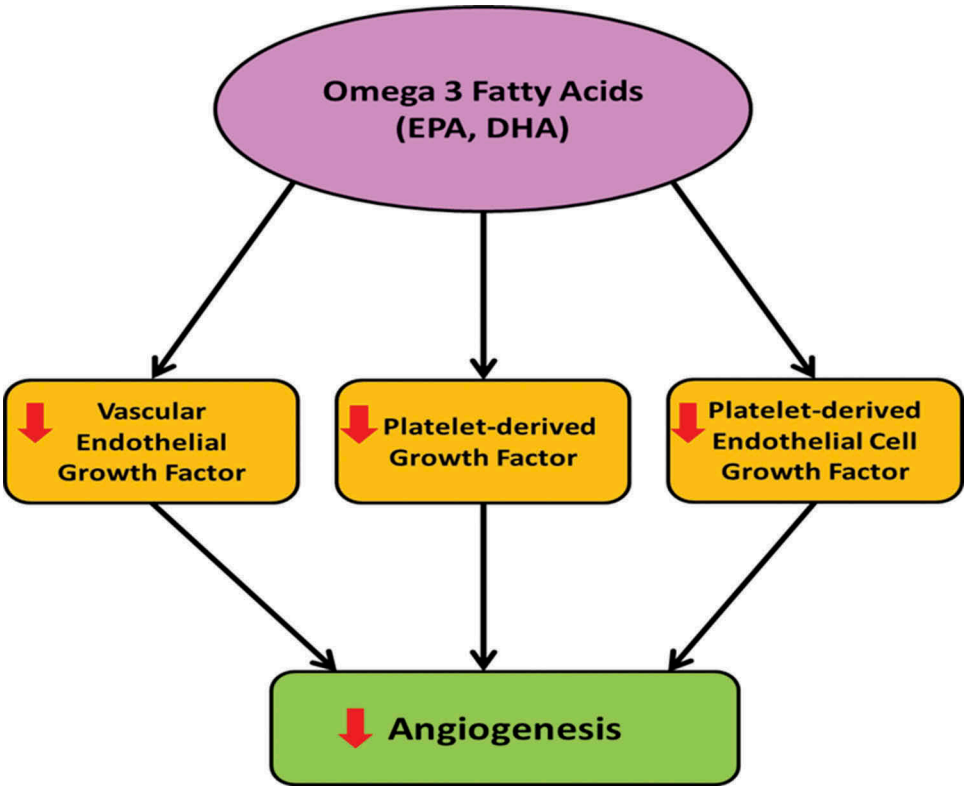

Figure 4. Mechanism of decrease in angiogenesis by omega 3-fatty acids.

TP53 genes.[69] Hamster models have been utilized to understand the effectiveness of omega-3 fatty acids, and it was observed that fish oil rich with omega-3 fatty acids significantly decreased the pancreatic tumors thus effective in respect to inhibition of tumor growth.[70] EPA and DHA as single or as combined therapy with some additional chemotherapeutic agent have been investigated on various pancreatic cell lines.[71,72] Synergetic effect of DHA and curcumin exhibited tumor inhibitory properties on pancreatic cell lines (BxPC-3), by down regulating COX-2 and 5-LOX and up regulating *p*-21 protein.[71] The DHA is also reported to influence glutathione (GSH) extrusion that resulted into increased levels of ROS and caspase activation leading to apoptosis.[73] Inhibitory effects of omega-3 faty acids were also investigated on many human pancreatic cancer cell lines (SW1990, AsPC-1 and PANC-1),[42,74] and it was also observed that DHA suppressed pancreatic cancer cell growth by inhibiting the activation of Wnt/β-catenin signaling. Both EPA and DHA were also reported to induce ROS-medicated apoptosis, caspase-3 activation and decreased levels of intracellular COX-2 proteins in pancreatic cell line.[44,73,75] Thus, highlighting the importance of omega 3 fatty acids enriched fool in prevention of pancreatic cancer.

Breast cancer

Breast cancer accounts for estimated 29% of cancer in women.[76] Genetic factors (breast cancer genes BRCA1 and BRCA2) are the indicators used to assess the cancer risk,[77] and early detection along with effective treatment regimen is considered best for improved survival rates.[76,77] Fish oil, omega-3 fatty acids have also been utilized for the inhibition and treatment of breast cancer,[47,78,79] and the diet containing EPA- and DHA-enriched fish oil was also considered to reduce the growth of breast carcinoma.[80–82] The metastasis of breast carcinoma to bone and to lungs have also been reported to be prevented by EPA and DHA.[3,23] The influence of DHA was investigated on MCF-7 human breast carcinoma cell line model and 4T1 of mouse breast carcinoma cell lines models, the inhibitory effect was reported due to reduction of beta-catenin expression and causing apoptosis.[23] DHA has also been combined with several chemotherapeutic agents to produce synergetic effect in the treatment of metastatic breast cancer.[83,84] During research on human breast cancer cell line (MDA-MB-231), it was suggested that DHA is responsible for increasing the ROS level by inhibition of glutathione peroxidase (GPx1) activity (an enzyme for protection against hydrogen and lipid peroxides) which increases the treatment level of chemotherapeutic agent.[84] Although EPA and DHA both have shown effectiveness breast carcinoma,[85–87] but DHA is believed to be more potent against breast cancer as compared to EPA.[88–91] Recently, effectiveness of DHA-enriched oil was investigated on surgically obtained tissue cultures of human malignant breast cancer, and it was reported that antitumorigenesis properties of DHA is due to its ability to significantly promoting the expression of Toll-like receptor 4 (TLR-4) and peroxisome proliferator activated receptor (PPAR)-α, thus leading to DHA induced breast tumor cells apoptosis.[27]

Colorectal cancer

Colorectal cancer is a worldwide problem and led to an increased mortality rate,[92] from year 2002–2012, a remarkable increase in the occurrence of colon cancer war reported primarily due to the diet.[92] Clinical studies conducted on the patients suffering

from colorectal cancer displayed the reduction in EPA and DHA content of about 37–87% in the colorectal tissues.[93] The fish oil fatty acids (EPA and DHA) have shown the potential to reduce the risk of colorectal cancer and slow its progression.[49,92,94–97] Omega 3 fatty acids not only enhance the chemotherapeutic sensitivity effect of anticancer agents but it can also exert a direct anticancer action that may contribute to their antiproliferative and proapoptotic effect on the stem-like cells.[98] DHA is considered as a primary tumor suppressing fatty acid in colon cancer.I It has been reported to influence extensive changes in gene expression patterns at mRNA level in the colon cancer cell line SW620 and induces endoplasmic reticulum stress, which disturbed the calcium channel pathway and resulted in growth inhibition of cancerous cells.[99] Furthermore, studies on various colon cancer cell lines (HT29, HCT116, Caco-2 and SW480) revealed that the DHA treatment induced apoptosis,[100,101] and GRP78 protein in endoplasmic reticulum and is a molecular target for DHA.[102] Efficacy of omega-3 fatty acids in colon cancer is well supported by animal studies as well. These include mouse models with transplantable tumors as well as rats with chemically induced colon cancer.[36,103,104]

Prostate cancer

Cancerous tissue growth in prostate gland is termed as prostate cancer and it alone accounts for 27% of total cases of cancer among men and 2nd most leading cause of cancerous death in men.[76] A study of omega-3 fatty acids on prostate cancer have been bit controversial. Many studies have indicated that the omega-3 fatty acids its self has very little or no effect on the reduction of prostate cancer,[105] and the combination of omega-3 and omega-6 fatty acids may result into risk of prostate cancer as the dietary fatty acids were found in the tissues of the prostate cancer.[106,107] But still there is a lack of significant data that indicated the involvement of EPA and DHA in the occurrence of prostate cancer or its treatment.[108,109] Inhibition of prostate cancer cell growth and slow down the histopathalogical progression have been observed by a fish oil diet.[36,110,111] A study conducted on omega-6 and omega-3 fatty acids concluded that the increase in omega-6 fatty acids increases prostate cancer risk whereas omega-3 fatty acids rich diet reduces the prostate cancer risk.[112] EPA and DHA target 15-lipoxygenase and cyclooxygenase-2 pathway to inhibit the proinflammatory effect and prevents prostate cancer.[112] Apoptosis induced by DHA is also thought to exert inhibition of prostate cancer.[111] Synergetic effect of omega-3 fatty acids along with vitamin D has also been investigated in reduction of prostate carcinoma and the combination is thought to be capable of inhibiting the prostate carcinogenesis at the initiation and progression stages in cell cultures and animal models.[113]

Liver cancer

Liver or hepatic cancer refers to the cancerous growth in the tissue lining of liver or bile duct and is the 5th major cause of death from cancer in men and 9th among women.[76] Hepatocellular carcinoma is a common human cancer with high mortality.[114] It usually develops in the presence of continuous inflammation and hepatocyte regeneration in the setting of chronic hepatitis and cirrhosis.[115] A clinical study consists of total of 90,296 subjects concluded that the use of omega-3 fatty acid appeared to reduce the risk of development of hepatocellular

carcinoma in the subjects.[116] Parenteral nutrition of omega-3 fatty acids also helped into the improvement of hepatitis virus (HBV)-associated liver carcinoma which was attributed to the suppressed production of proinflammatory cytokines in the patients.[117] Omega-3 fatty acids has also shown therapeutic potential in nonalcoholic fatty liver diseases.[118,119] DHA is believed to be more potent in treatment of liver cancer as compared to EPA.[45] It is thought DHA induces apoptosis in human hepatocellular carcinoma cells,[45] most probably by blocking the beta-catenin, which are involved in promotion of tumor cell growth,[114] and by up-regulating the NADPH-oxidase-2 and helps in reduction of hepatocellular carcinoma progression.[120]

Non-alcoholic fatty liver disease (NAFLD) is an another pathological entity that is becoming a major cause of chronic liver disease associated with obesity and type 2 diabetes, a condition also found after the administration of amiodarone, tamoxifen, or antiretroviral drugs.[121,122] NAFLD includes the development of simple triacylglycerol accumulation in hepatocytes (hepatic steatosis) to steatosis and inflammation, fibrosis, and cirrhosis (non-alcoholic steatohepatitis, NASH). Under conditions of overnutrition-induced liver oxidative stress, obese NAFLD patients exhibit due to diminution in EPA and DHA levels.[121]

Renal cancer

Renal cell carcinoma originates in the lining of proximal convoluted tubules of the kidney and is one of the major cancer occurrences.[76] Renal cell carcinoma is characterized by enhanced levels of the metastasis promoting gene matrix metalloproteinase-2 (MMP-2).[123,124] Omega-3 LCPUFAs (EPA and DHA) from fish oil have shown to reduce of MMP-2 mRNA protein levels and killing of tumor cell line.[125] DHA has shown to significantly reduce the growth of renal cell carcinoma, and that this reduction is regulated by levels of prostaglandins 2 (PGE2).[126] EPA and DHA both known to retard the PGE2 production and progression of renal disease, and shown to activate PPARs, which inhibit the production of proinflammatory cytokines in human renal tubular cells.[28] Omega-3 fatty acids also effectively decrease lipopolysaccharide (LPS)-induced nuclear factor-kappaB (NF-$_k$B) activation and monocyte protein-1 (MCP-1) expression. This overexpression of PPAR activation by EPA and DHA resulted into LPS-induced apoptosis,[127]and inhibition of NF-kB is one of the additional beneficial effects of fish oil.[28] Recent studies also revealed dominant role of DHA in reducing the growth of renal cell carcinoma.[128]

Ovarian cancer

Ovarian cancer is a lethal gynecologic malignancy and the fifth leading cancer cause of death among women.[76] Egg laying hens have been found as useful animal model for the study of ovarian cancer.[129,130] It has been suggested that increase consumption of omega 3 fatty acids may be a nontoxic way to prevent or suppress ovarian cancer.[131,132] It is generally believed that the anti-inflammatory effect of EPA and DHA, blocks the cyclooxygenase pathway (COX2) which resulted into the reduced level of prostaglandins that leads to the prevention of ovarian cancer.[133] Studies on ovarian cancer cell lines SKOV-3, TOV-21G and OVCAR-3 showed the inhibition on growth of ovarian carcinoma progression,[134] by omega-3 fatty acids. Omega-3 fatty acids are also thought to be responsible for the increased level of transforming growth factor (TGF) beta-1 and p21

proteins level in ovarian cancer cell lines, which resulted into inhibition of growth of cancer cells.[134,135] Recent studies on dietary fat or fish intake also revealed omega-3 fatty acids plays a protective role against ovarian cancer,[136–138]

Lung cancer

Lung cancer and bronchitis is the top major cancerous cause of death. From 2014 statistics data,[76] 28% men and 26% of females died suffering from lung cancer and bronchitis. The effectiveness of EPA and DHA against lung cancer has also been investigated thoroughly.[139,140] It has been reported that the EPA and DHA supplementation may cause suppression of both primary tumor growth and lung metastasis occurrence.[141] EPA and DHA from fish oil have been demonstrated to affect the cancer cell replication and have shown significant suppression of lung adenocarcinoma proliferation by induced apoptosis.[142] Polyunsaturated fatty acids especially DHA are thought to induce oxidative stress to inhibit tumor cell growth in lung cancer and the mechanism of tumor growth inhibition was studied in A549 lung adenocarcinoma cell line.[143]

Other types of cancer

The research on fish oil and its fatty acids (EPA and DHA) is a continuous process. It have been proved to be beneficial in many other cancerous cases like gastrointestinal carcinoma and leukemia. The anti-inflammatory effect of fish oil has been proved beneficial in patients suffering from gastrointestinal surgery.[144] It has been suggested beneficial in improving post-operative immune response of gastrointestinal cancer patients.[145] EPA and DHA have showed to enhance the action of chemotherapeutic agents and also exerted its own anti-inflammatory effect while treating lymphoma cell cultures.[146] It was found that the patients suffering from multiple myeloma suffer from low amount of omega-3 LCPUFAs, and it was suggested that the fatty acids content inside the erythrocyte membrane can be used as a biomarker or a diagnostic tool in multiple myeloma.[147] Another study showed that fish oil supplementation with various ratio of EPA and DHA could exert different effect on blood chemistry such as neutrophils, monocytes and lymphocyte function that could be related to specific changes in gene expression.[148]

Conclusion

Fish oil omega-3 fatty acids (EPA and DHA) are natural compounds that are easy to obtain, commercially economical, non-toxic as compared to anticancer agents and has proven beneficial pharmacological activities. It exerts anti-proliferative effects on cancer cells and works in synergy with chemotherapeutic agents. Many studies have been conducted to outline the beneficial properties of fish oil and as an adjuvant to chemotherapy. Clinical studies on various cancer types also highlighted the huge scope of fish oil and omega-3 fatty acids as a pharmacological agent alone or as a synergistic agent in combination therapy. The present article outlines the beneficial role omega-3 fatty acids, EPA and DHA, in various carcinoma treatments and can act as both aggressive and defensive. In conclusion, the extensive research on fish oil is leading to superior understanding of

pharmacology of the omega-3 fatty acids in the treatment of carcinoma-associated diseases is needed. This non-toxic approach toward carcinoma should be promoted and encouraged to address the carcinoma diseases. Further studies on omega-3 fatty acids and promotion of this therapy in clinical trials will possibly reduce the number of carcinoma cases per year.

Conflicts of interest

Authors have no conflict of interest to report.

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