Review

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Exploring Interplay of Polyunsaturated Fatty Acids: A Promising Approach for Treatment of Breast Cancer

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Cancer, characterized by uncontrolled cell division and potential tissue spread, remains a significant health problem, with breast cancer being the most common in women, accounting for 25% of all cancer cases. Natural compounds have recently gained attention as they can improve the efficacy of cancer treatment. The aim of this study is to shed light on the potential benefits of polyunsaturated fatty acids in the treatment of breast cancer. Overexpression of tyrosine kinase receptors and mutations in the breast cancer gene-1 (*BRCA1*) and *BRCA2* genes lead to breast cancer in women. Based on the findings of papers published in various scientific search engines, n-3 polyunsaturated fatty acid (PUFA) may reduce the likelihood of developing breast cancer due to their anti-inflammatory properties. According to several studies, women who consume more n-3 polyunsaturated fatty acids have a lower risk of breast cancer. n-3 polyunsaturated fatty acids regulate breast cancer by controlling the inflammatory mediators, gene expression transcription factor and signal transducer, peroxisome proliferator-activated receptor-gamma, B-cell lymphoma-2 (Bcl-2) associated X protein or B-cell lymphoma-2, Phosphatidylinositol 3-kinase or Protein kinase B, Nuclear factor-κB, and toll-like receptor-4. Polyunsaturated fatty acids are considered a successful treatment for breast cancer patients when combined with chemotherapy drugs. Doxorubicin is a first-line drug for the treatment of triple-negative breast cancer. Giving doxorubicin and polyunsaturated fatty acids together makes chemotherapy treatments for triple-negative breast cancer work better in the MDA-MB-468 and MDA-MB-231 cell lines. This review highlights the role of PUFAs in modulating cancer-related pathways, offering valuable insights for researchers, clinicians and the pharmaceutical industry in the fight against breast cancer.

Keywords: polyunsaturated fatty acids; breast cancer; anti-inflammatory; doxorubicin; triple-negative breast cancer

Introduction

The most prevalent form of cancer in females is breast cancer (BC). Studies have shown that BC is the second most common cancer (10.9% of all cancers) with an estimated 2 million cases detected in 2018, representing approximately 23% of all cancers. The prevalence rate is very high in most advanced and industrialized countries, such as the United States and Canada [1,2]. BC risk is generally due to genetics, history (how one has lived one's life so far) and environmental triggers in women [3]. All cancer drugs developed so far aim to kill cancer cells and shrink tumors. However, some of them seem to be ineffective at the stages of tumor development, making these costly chemotherapies ineffective over time [4]. To overcome this challenge, a more strategic framework for the development of cancer therapies for the treatment of BC is needed. A balanced diet and lifestyle have been shown in epidemiologic research to be essential for the prevention of BC several decades ago [5–8].

Various studies have shown that some polyunsaturated fatty acids, also known as n-3 polyunsaturated fatty acid (PUFA) possess the ability to fight cancer [9,10]. PUFAs, a class of important fatty acids, may help to regulate both malignant and healthy cells [11]. n-3 and n-6 are both important PUFAs as they can reduce inflammation. Fish, fruit,

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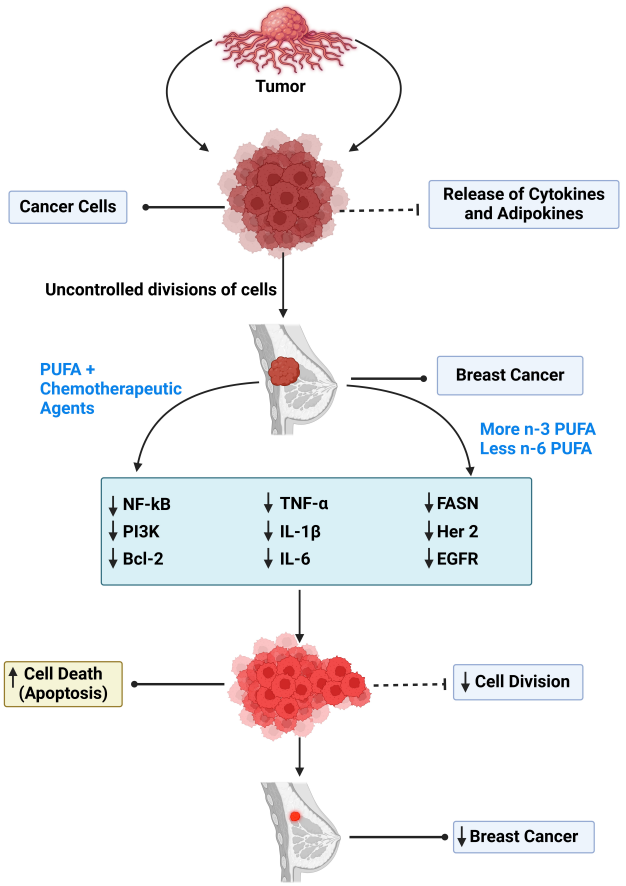

Graphical Abstract.

nuts, and oils are just a few examples of the foods that are necessary to supply n-3 through diet [12]. The human body cannot synthesize essential PUFA called linolenic acid (LA) (C18:2 n-6). It promotes healthy growth and development, reduces the risk of certain heart diseases and helps maintain the normal pumping action and rhythm of the heart which is why it must be supplied through the diet [13]. The most common types of n-6 PUFA in the American diet are (C18:2 n-6), linoleic acid (LA*) and (C18:3 n-3), α-linolenic acid (ALA). The different natural sources of PUFA are depicted in Table 1 (Ref. [14–27]). The human body can make Docosahexaenoic acid (DHA) (C22:6 n-3) from LA (C18:2 n-6) [28,29]. Eicosapentaenoic acid (EPA) and DHA are the longest chain n-3 PUFAs that are produced when ALA is desaturated [30]. Recent studies have shown that women who consume DHA and EPA have a lower risk of developing BC [31].

BC can be hereditary and is usually caused by mutations in the breast cancer gene-1 (*BRCA1*) and *BRCA2*; 80% of the risk is associated with *BRCA1* and 60% with *BRCA2* [32]. DHA has been found to produce its effects by increasing *BRCA1* transcription and protein levels to control the growth of cancer cell [33].

BC is associated with the overexpression of tyrosine kinase receptors, in particular the epidermal growth factor receptor (EGFR). It can be downregulated by DHA [34]. Chronic diseases including cancer and other inflammatory disorders have been linked to an imbalanced n-3 and n-6 PUFA intake [35,36]. Research has shown that genetic variations in the form of single nucleotide polymorphism (SNP) can influence the metabolism of PUFAs [37]. Most calories consumed in today's affluent cultures come from industrially processed meals that are high in n-6 fatty acids and low in n-3 fatty acids. 10:1 has taken the place of the assumed normal or balanced ratio of 2:1 in our ancestors' diets [38]. The increased levels of n-6 fatty acids in today's diets contribute to many chronic inflammatory diseases, including cancer [38,39]. The function of exercise is not limited to preventing the progression of disease, but also helps prevent numerous health consequences such as depression and anxiety [40]. Although n-3 PUFAs are anti-inflammatory and n-6 PUFAs are pro-inflammatory, chronic inflammation could be induced by consuming more n-6 PUFAs than n-3 PUFAs [41]. Preclinical studies have shown that n-3 PUFAs have a potential prophylactic role in reducing the risk of developing BC. n-3 PUFA has many effects that can be seen. One way is by breaking down lipid rafts in the plasma membrane, which changes how proteins that cause cancer signal [42]. Chronic inflammation can play a vital role in the emergence and progression of BC by fostering the growth of tumors and metastatic cancer. In addition, n-3 PUFAs show a protective role against colorectal cancer by inhibiting cyclooxygenase-2 (COX-2) which leads to a minimization of eicosanoid formation. They reduce the growth of tumors by controlling DNA methylation. In a model of lung cancer, 13-S-hydroxyloctadecadienoic acid helps fight the cancer by turning on the peroxisome proliferator-activated receptor gamma (PPAR-γ) [43].

Zheng *et al.* [44] performed an in-depth review of 21 independent retrospective cohort investigations which revealed that marine n-3 PUFA namely EPA (20:5 n-3) and DHA (22:6 n-3) ingestion was associated with a 14% decrease in the risk of BC.

Since the COX-2 enzyme prefers DHA over ARA as a precursor, it is thought that the anti-inflammatory actions of n-3 PUFA are triggered by the substitution of DHA for ARA in cellular barriers, which lowers lipoxygenase (LOX) and COX synthesis of pro-inflammatory cytokines namely Tumor Necrosis Factor-α (TNF-α) and Interleukin (IL)-1 *via* ARA [45,46].

SNP, a type of DNA variation, can occur when one nucleotide in the genome sequence changes. Studies reveal a strong association between SNPs and physiological PUFA levels, highlighting the significance of genetic diversity as a factor potential for BC [27]. The genes for fatty acid desaturase (*FADS*)*1* and *FADS2* are very important for PUFA metabolism. They can explain up to 12 and 28% of the differences in ALA and LA* levels in the blood, respectively. Therefore, genetic variations may have a significant impact on the difference between PUFA plasma levels and BC.

Table 1. Different sources of polyunsaturated fatty acid (PUFA).

Foods	PUFA (mg/100 g)				References
	LA (18:2 n6)	α-LA (18:3 n3)	AC (20:4 n6)	EPA (20:5 n3) + DHA (22:6 n3)	
Tuna	260	270	280	400	[14,15]
Linseed Oil	13,400	55,300	—	—	[15]
Cod	4	2	3	300	[16,17]
Salmon	440	550	300	1200	[18,19]
Rapeseed Oil	19,100	8600	—	—	[19]
Herring	150	61.66	36.66	1700	[19]
Soyabean	8650	1000	—	—	[20]
Sunflower Oil	60,200	500	—	—	[21]
Bacon	6080	250	250	—	[22]
Almond	9860	260	—	—	[23]
Soybean Oil	53,400	7600	—	—	[23]
Peanut	13,900	530	—	—	[24]
Chicken egg	3800	220	—	—	[24]
Corn Oil	50,000	900	—	—	[25]
Brazil Nut	24,900	—	—	—	[25]
Lard	8600	1000	1070	—	[26]
Cotton seed Oil	47,800	1000	—	—	[26,27]
Trout	74	—	30	500	[27]

LA, linolenic acid; EPA, Eicosapentaenoic acid; DHA, Docosahexaenoic acid.

Studies demonstrating a significant correlation between the PUFA metabolism genes *FADS1* and *FADS2* and the symptoms of aggressive disease suggest that genetic variations are crucial in controlling PUFA metabolism and need for further research. PUFA metabolism-gene-nutrient interactions may predict risk for BC [47]. In this review, it was aim to highlight the effect of n-3 PUFA on the complex signaling intricacies of BC. It also provides an overview of the role of n-3 PUFA in inhibiting BC progression, lipid peroxidation in oxidative stress and BC, the effects of PUFA on physical activity, the role of PUFA as an immunity enhancer, and their safety concerns.

Biochemistry and Metabolic Relationship of n-3 and n-6 PUFA

ALA is the most basic of the n-3 fatty acids. When ALA is metabolized, it is elongated so that more unsaturated fatty acids are produced. ALA is produced from LA by the desaturation of LA with the help of $^{\Delta}$15-desaturase, which serves as a precursor [48]. The synthesis of ALA is possible in plants due to the presence of enzyme $^{\Delta}$15-desaturase, which humans lack and therefore cannot produce. The process of elongation of ALA through a chain of processes takes place in the liver [49]. The conversion of ALA to stearidonic acid (SDA) and the subsequent elongation of SDA to eicosatetraenoic acid (ETA) is also feasible using the enzyme $^{\Delta}$6-desaturase. EPA is being yielded by $^{\Delta}$5-desaturase. As LA and ALA are converted using the same enzyme, converting LA to ALA competes with the process of desaturation. The enzyme $^{\Delta}$6-desaturase and $^{\Delta}$5-desaturase is controlled by hormones, diet, and feedback inhibition of the final product, and form an extensive network for the endogenous synthesis of long-chain fatty acids. EPA is converted into DHA by docosapentaenoic acid (DPA). This conversion involves $^{\Delta}$6-desaturase, which must include limited peroxisomal β-oxidation [50]. Various methods have been used to study the conversion of ALA to DPA, DHA and EPA in humans. All methodologies demonstrate poor conversion. It seems that just a small percentage of DHA can be converted into the finished product EPA. EPA is better converted from SA than from LA, probably because SDA conversion does not need the rate-limiting enzyme $^{\Delta}$6-desaturase. Retro-conversion refers to converting DHA to EPA and DPA by limited peroxisomal β-oxidation. They are typically called very long-chain PUFAs (n-3) [51].

The metabolism of PUFAs in the human body is highly dependent on enzymes [49,52]. PUFAs are essential fatty acids that must be obtained from the diet because the human body cannot synthesize them itself. ALA and LA are converted to long-chain PUFAs like ARA, DHA, and EPA by enzymes such as $^{\Delta}$6-desaturase and $^{\Delta}$5-desaturase [53].

PUFA Metabolism and Enzymes

Enzymes play a crucial role in the breakdown of PUFAs by helping to convert PUFAs into physiologically active forms The enzyme $^{\Delta}$6-desaturase, which is essential to this process, converts ALA and LA, which are both significant n-3 and n-6 fatty acids, into longer-chain PUFAs. Mackerel and salmon are two examples of cold-water seafood that are regularly consumed to meet physical requirements as they are rich in DHA and EPA. Variable

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amounts of ALA in plant foods such as walnuts, chia seeds and flaxseeds can be converted to DHA and EPA [54].

Humans also depend on plants as their main supply of γ-linolenic acid (GLA), another vital PUFA that is converted from ALA. The synthesis of GLA triggers the production of important signaling molecules related to the control of inflammatory and immunological responses. Plants such as evening primrose, borage, and blackcurrant contain high amounts of GLA. Particularly for people who are limited in their ability to synthesize GLA due to genetic or metabolic problems, these vegetable oils are frequently used as dietary supplements to ensure an adequate supply of GLA. Additionally, animal sources like meat and eggs can also be used to obtain some PUFAs, like ARA. However, by providing precursors such as LA, which can be converted to ALA, plants can also contribute indirectly to the ALA pool. A sequence of enzymatic processes involving the enzymes $^{\Delta}$6-desaturase and elongate leads to this conversion [55].

Potential of n-3 PUFA on Inhibiting BC Progression

The growth and development of BC can be slow down by consuming n-3 PUFAs. Over the past decade, several studies have been conducted in different geographical regions with varying results. According to several studies, the risk of developing BC is significantly reduced in Asian populations that consume a low fat, high fish, n-3 PUFA rich diet [56–58]. The risk of BC correlates with the number of fatty acids in the erythrocyte membrane. It is possible that the proportions of fatty acids in the fat cells or the membranes of erythrocytes have a greater effect than the individual fatty acids. In a recent investigation, Bougnoux *et al.* [59] discovered a link between a decreased risk of BC and a composite measure made up of a high concentration of monounsaturated fatty acids (MUFAs) and a low proportion of n-6 to n-3 PUFAs [60]. Retrospective studies examining the relationship between postmenopausal BC and erythrocyte membrane fatty acids revealed a preventive benefit of a higher saturation index (SI), i.e., membrane stearic to oleic acid ratio. In a study conducted by Pala *et al.* [61], a total of 4052 postmenopausal women were observed and 71 cases of advanced BC were detected. For each case-patient, two identical control subjects were randomly selected from the cohort data. The proportions of different fatty acids in erythrocyte membranes were calculated. The association between the possibility of BC and membrane fatty acid content was examined using conditional logistic regression modelling. The possibility of BC was strongly correlated with MUFAs (odd ratio-5.21 and 95% confidence interval-1.95 to 13.91) and oleic acid (odd ratio-2.79 and 95% confidence interval-0.13 to 0.64). BC probability was inversely related to SI (odd ratio-0.29 and 95% confidence interval-1.24 to 6.28). The studies by Pala *et al.* [61] showed that the development of BC and total PUFA were inversely correlated. The ratios 16:0 to 16:1 and 18:0 to 18:1 respectively express SI (n-3) and SI (n-6). The reciprocal of these ratios might partially represent the activity of the enzyme $^{\Delta}$9-desaturase. It has been established that $^{\Delta}$9-desaturase, a member of the sterol coenzyme-A desaturase gene family, is overexpressed in BC. Pala *et al.* [61] found that SI (n-6) in the erythrocyte membrane was a significant marker of postmenopausal BC. In several prospective studies conducted by Chajès *et al.* [62] in northern Sweden a correlation was also found between a lower incidence of BC and higher SI (n-9) in serum phospholipids.

Further research is needed to determine whether or not the consumption of EPA influences the risk of cancer [63]. Researchers working under Shannon and her colleagues investigated how n-3 and n-6 polyunsaturated fatty acids affected the progression of benign proliferative fibrotic conditions (PFC) and non-proliferative fibrotic conditions (NPFC) in BC patients [64].

Their research showed that women with higher levels of EPA in their erythrocytes had a 67% lower chance of developing NPFC on its own or in combination with BC. EPA also cut the chance of developing PFC in BC by about 43%. It was found that people with higher levels of palmitoleic and palmitic acid had a much higher rate of NPFC and BC with non-proliferative changes than normal participants. There was a big drop in the number of NPFCs, no matter how much n-3 PUFAs and EPA were present. Also, women with non-proliferative changes who ate docosapentaenoic acid (DPA), EPA, and n-3 PUFA had a much lower chance of getting BC than control participants.

Long-chain n-3 fatty acid EPA had a significantly negative relationship with all BCs compared to proliferative fibrotic conditions (PFCs). There was a similar but not significant relationship between BCs and proliferative changes. These findings suggest that all n-3 PUFAs, especially EPA, may help prevent cancer. They also show that BC and NPFCs are less likely to occur with or without other cancers when compared to PFCs alone [65].

In addition, a higher intake of n-6 PUFA was found to be associated with a higher incidence of BC in the United States, while a much greater amount of EPA and DHA was associated with a lower incidence of the disease. This was found when comparing women at different risks for BC [66]. It was difficult to determine whether higher intake of n-6 PUFA or lower intake of n-3 PUFA was the main factor in the progression of BC by focusing on the proportions of n-6 to n-3 PUFA. Research shows that the intake of n-3 PUFAs can be increased while improving the intake of n-6 PUFAs, which may reduce a person's risk of developing BC. Few clinical trials have explored the usefulness of n-3 PUFAs in the prevention and treatment of BC. Additionally, one randomized controlled trial (RCT) found that the combined advantages of n-3 PUFA and raloxifene (selective estrogen receptor modulator) were helpful in lowering the risk of postmenopausal cancer of the breast [67]. The results

Table 2. Summary of the scientific studies of n-3 PUFA using different groups of women with BC in different countries.

Sl. No.	Groups	Source of n-3/n-6 PUFA	Risk of BC	Country/Year	References
(1)	Control-1030; BC-2241; PFC-1185; NPFC-155	Nutritional consumption	Increasing EPA decreases the incidence of NPFC and decreases the advancement of PFC to BC; increases in γ-linolenic acid elevate the incidence of BC, PFC, and NPFC	China/2009	[65]
(2)	BC cases-342; 45–74 years; 35,298 women	PUFA, monosaturated, and saturated from fish and shellfish	An increase in n-3 PUFA from shellfish decreases BC prevalence and increases n-6 PUFA increase the prevalence of BC	Singapore/2003	[69]
(3)	BC cases-712; 40–70 years; Women-72,571	Marine-derived fish, red meat, and n-3 PUFA	The possibility of BC is reduced by improving the n-6/n-3 PUFA proportion.	China/2011	[70]

BC, breast cancer; NPFC, non-proliferative fibrotic conditions; PFC, proliferative fibrotic conditions.

showed that consumption of 25 g of flaxseed per day reduced cell growth and increased apoptosis in the tumors of postmenopausal BC patients. These results may encourage further exploration of the use of n-3 PUFA as an alternative treatment for BC [68]. Table 2 (Ref. [65,69,70]) provides an overview of the scientific studies on n-3 PUFA conducted in different countries on different groups of women with BC.

Effect of PUFA on Cell Membrane Constituents

Glycerophospholipids (GPLs) are a type of lipid found in almost every cell membrane. They are essential for the development of cell membranes [71]. GPLs usually contain stereospecifically (Sn)-1 fatty acids on their glycerol backbone, whereas Sn-2 fatty acids are n-6 PUFAs like ALA. n-3 PUFA can alter n-6 fatty acids in the Sn-2 GPL position by increasing daily intakes of n-3 PUFA [72]. n-3 PUFA aggregates similarly to the lipid-water interface in the membrane because it is denser than n-6 PUFA. This property may have a significant impact on the fluidity and permeability of the cell membrane (Fig. 1) [73]. These lipid rafts in the plasma membrane, which are organized in glycolipoprotein lipid microdomains, are important for cell signaling because they hold protein receptors, cholesterol, and glycosphingolipids [74–76]. The n-3 PUFAs have a very low affinity for cholesterol, and the accumulation of higher amounts of n-3 PUFAs in the cell leads to impaired cholesterol permeability. Also, cholesterol in the membrane helps the alkyl group of sphingolipids connect with each other and keeps the microdomains of lipid rafts organized. The decrease in cholesterol is therefore the cause of the disruption of the lipid rafts. Because they have a lot of protein regulators and growth factor receptors, lipid rafts are important parts of the cell membrane for signaling. Moreover, n-3 PUFA intake, particularly DHA and EPA, has the potential to disrupt lipid raft formation and inhibit cell-mediated signaling through rafts [75,76]. Consequently, n-3 PUFA may regulate BC progression.

PUFA Mediated Regulation of Membrane Biochemistry and Tumor Cell Membrane Integrity

Several studies have shown that n-3 PUFAs can prevent cancer cells from spreading and becoming invasive by blocking a few ion channel activities at the cell membrane [77]. The cell membrane includes over 300 distinct ion channels, such as ligand-gated, lipid-gated, and voltage-gated ion channels. Consequently, study has shown that among all these ion channels, the voltage-gated sodium (Nav) channel plays a key role in cancer progression [78]. Ions can pass through the semipermeable cell barrier due to its permeability. A transmembrane protein called the Nav channel facilitates sodium ion transit through the membrane, triggered by the electric current induced in the cell barrier. This channel can open and close with the aid of a voltage mechanism in the membrane [79]. A single polypeptide strand and four repetitive α and β subunits of a protein create this channel. Currently, several investigations have demonstrated the expression of Navα and Navβ subunits in non-excitable cancerous tissue, including colon, prostate, lung, and breast cancers. The Nav1.5 channel protein and n-3 PUFAs work synergistically effectively to mitigate cancer in a dormant stage, according to experimental evaluation [80]. Subsequently, it was shown that the use of DHA at a level of 0.5–10 µm decreased the dormant stage of Nav1.5 in BC cells from humans by interacting with the DHA lipid-based nuclear receptor and decreasing the activity of the *SCN5A* gene. In the MDA-MB-231 BC cell line, Na^+/H^+ exchanger type-1 (NHE1) proved to be an important modulator of hydrogen ion efflux, and Nav1.5 enhanced NHE1 function. NHE1 activity was significantly increased in hypoxic MDA-MB-231 cells and was also associated with lamellipodia development. Inhibition of NHE-1 contributes to the mitigation of cancer by reducing the stimulation of hydrogen ion efflux through suppression of extracellular matrix protease activity and cellular invasion mechanism. Intracellular pH was markedly decreased by inhibition of NHE1, preventing increased migration poten-

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tial under hypoxia.

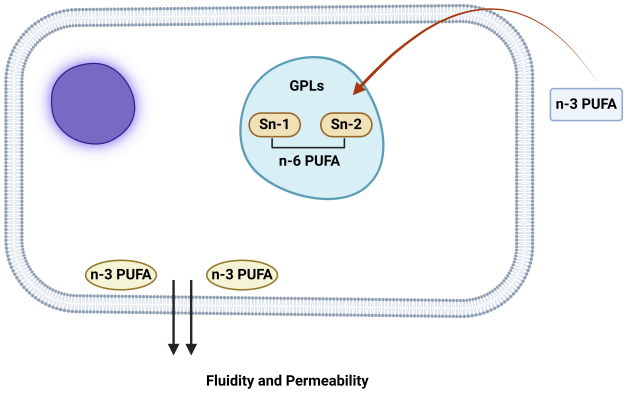

Fig. 1. Mechanism of the effect of polyunsaturated fatty acid (PUFA) on the cell membrane: Glycerophospholipids (GPLs), essential components of cell membranes, usually contain n-6 at the stereospecifically (Sn)-2 position. Increased intake of n-3 PUFA can replace n-6 PUFA in this position, potentially affecting membrane properties and interfering with the formation of specialized lipid raft microdomains, which play a crucial role in cellular signaling. Figure created with (BioRender.com).

Implications of n-3 PUFA-Derived Lipid Mediators on Cancer Progression

COX-Derived Lipid Byproducts in BC

The COX-2 mechanism plays an important role in inflammation, neovascularization, inflammation, tumor metastasis, and tumor growth [81,82]. Prostaglandin E2 (PGE2), a COX-2 by-product of ARA, induces blood vessel development, initial cell invasion and proliferation, and inflammation. COX-2 activity has been indicated to be upregulated in several tumor cells. COX-2 antagonists, such as COX-2 selective antagonists, and non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to reduce the risk of developing cancer [83]. The n-3 PUFAs reduce the incidence of cancer via COX-2-based mechanisms. Studies in humans demonstrate that *COX-2* gene mutations alter the anti-cancer properties of n-3 PUFAs [84]. The suppression of COX-2-mediated PGE2 brought about by DHA and EPA enhances the advantages of n-3 PUFAs [85].

It was once said that COX-2 changes DHA into hydroxyl-DHA, which is then mostly broken down to make lipid mediators that reduce inflammation. However, it is now generally thought that DHA is not a building block for COX enzymes [86]. EPA is a new substrate for COX-2, which changes it into different lipid mediators and the PGE3 subfamily of the n-3 series [87]. PGE3 has been shown to have less pro-angiogenic and pro-inflammatory properties than PGE2. PGE2 increased cell multiplication in NIH3T3 fibroblasts but PGE3 showed no impact at the same dose. In RAW 264.7 cells and NIH3T3 cells, PGE3 and PGE2 both increased the production of IL-6 and COX-2, but PGE3 had a much weaker effect on inflammation [88]. PGE3 has also been demonstrated to prevent the growth and migration of tumor cells. PGE2 exhibited no effect at a concentration of 1 μM, however, PGE3 prevented the lung cancer A549 cell line from proliferating [89]. In B16F10 melanoma cells, PGE3 also slowed growth and caused apoptosis by increasing the level of the phosphatase and tensin homolog (PTEN) protein [35].

LOX-Derived Lipid Byproducts in BC

Leukotrienes (LT) and hydroxyl fatty acids are produced because of PUFA degradation by LOX enzymes [90]. Due to the numerous variations of LOX enzymes, the LOX mechanism in cancer is more complicated. Overall, 15-LOX-1 and 15-LOX-2 are thought to have antitumor activity, while 5-LOX, 12-LOX and their by-products have been described as carcinogenic. The 5-LOX metabolite of ARA, 5-hydroxyeicosatetraenoic acid (HETE), has been observed to promote tumor growth, blood vessel development and inflammation. Therapeutic inhibitors of the 5-LOX enzyme have been demonstrated to decrease tumor growth in experimental animals [91]. In a fascinating turn of events, 5-LOX has been recently discovered to play a key role in the anti-angiogenic properties of DHA by creating 4-HDHA, an anti-angiogenic intermediate. In a model of oxygen-mediated retinopathy, dietary DHA intake has been demonstrated to reduce retinal neovascularization [92]. The 5-LOX enzyme facilitates DHA anti-angiogenic action by synthesizing 4-HDHA, which inhibits angiogenesis *via* a PPAR-γ-based pathway [93].

Impact of Oxidative Stress on BC and PUFA

In recent years, it has become increasingly clear that different types of cancer cells contain higher levels of reactive oxygen species (ROS) compared to their healthy counterparts [94–96]. Investigations have revealed increased levels of oxidative stress metabolites in BC, including oxidized bases of DNA (8OHdG), which is the most studied molecule due to its carcinogenic nature and the high sensitivity of its immunological detection [97,98]. Cell growth and development can be promoted by a minimal rise in ROS while an excess of ROS can lead to oxidative impairment [99,100]. An imbalance in the redox balance, which can cause either more ROS to be produced or less ROS to be scavenged, is linked to abnormal cancer cell growth. In fact, it has been shown that ROS-scavenging enzymes like peroxiredoxin, glutathione peroxidase, and superoxide dismutase are much lower in breast cancer cells [101]. It is extensively recognized that the generation of ROS by inflammatory cells like macrophages and neutrophils serves as a method of eliminating cancer cells. Tumor-associated

macrophages have been reported to cause high levels of oxidative damage in mouse BC cells. This may be due to the release of the pro-inflammatory cytokine TNF-α [102]. A rise in the production of superoxide in macrophages and neutrophils, mainly due to Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, causes the production of hydrogen peroxide. This can then cause oxidative damage-mediated apoptosis [103]. The release of 8-OHdG was much lower in metastatic BC than in benign tumors in malignant breast disease. On the other hand, 4-hydroxy-2-nonenal (HNE) immunostaining was strongest in metastatic breast tumors. Other research, on the other hand, showed that the lipid peroxidation intermediates HNE and malondialdehyde (MDA) were increased in BC tissues [104,105].

The C7, C10, and C13 positions of arachidonate, the C-H bond at the site of bisallyl, and the C-11 position of linoleate are all successfully removed from the hydrogen atom by the reactive peroxyl. After that, the lipid hydroperoxides (LOOH) can break down into hydroxy or epoxy molecules, as well as keto, SCFA, and aldehyde mixtures. The two most well-known are 4-hydroxy-2-nonenal (HNE) (from n-6) and 4-hydroxy-2-hexenal (HHE) (from n-3). HHE triggers several apoptotic mechanisms in the cell. In YPEN-1 epithelial cells, giving HHE lowered the transcription of the B-cell lymphoma-2 (Bcl-2) protein and increased the expression of the Bcl-2 associated X protein (Bax) protein, which helps cells die. It can also control the ROS pathway and peroxy-nitrite synthesis [106]. Additionally, HHE modifies the inflammatory cascade under NF-κB control by upregulating the production of nuclear p65 protein and downregulating the cytosolic Nuclear factor-light polypeptide gene ($I\kappa$-$B\alpha$) [107]. HNE modifies DNA, phospholipids, and proteins covalently to have an impact on the physiological process. Among the signaling pathways that HNE sets off are the apoptotic pathway, the inflammatory response, the detoxification process, and the mitogen-activated protein kinase (MAPK) system. These may be linked to ways for cells to survive cytotoxic effects [108].

The non-enzymatic oxidation of PUFAs by the free radical mechanism can also produce a wide range of cyclic endoperoxides and peroxides. The oxidation of arachidonic acid (AA) is replaced by six stereochemical hydroperoxide substitution molecules at C5, C8, C9, C11, C12, and C15, all of which are categorized as hydroperoxy eicosatetraenoic acid. These hydroperoxides undergo cyclization to produce endoperoxides with ring members unique to F-type prostaglandins (PGs), which are then referred to as F2-isoprostanes. Isoprostanes are now the most significant molecules for quantifying oxidative stress-mediated pathophysiology [95]. The concentration of F2-isoprostanes rise in oxidative degradation to lipids and can be utilized as an oxidative stress marker, according to two investigations on the liver toxicity of doxorubicin in humans and carbon tetrachloride (CCl_4) in rats [109].

The enzymatic breakdown of PUFAs is extensively documented and frequently discussed in the research. AA and EPA are produced by the metabolism of LA and ALA. LOX and COX break down EPA to produce eicosanoids, 5 types of Leukotrienes (LTs), and 3 types of PGs whereas AA degradation produces 4 types of LTs and two series of PGs. The enzymatic breakdown of EPA results in the synthesis of physiologically reactive molecules such as the E1 family hypoxins, lipoxins, and resolvins. Eicosanoids produced from n-6 fatty acids cause cellular reactions that are pro-inflammatory [110,111].

Effects of n-3 PUFA on the Cellular Signaling Pathway of BC

Effect of PUFA on Inflammatory Mediators

To promote the occurrence of BC and accelerate the process of carcinogenesis, researchers often administer chemical carcinogens [such as 3,4-benzopyrene, 3-methylcholanthrène (MCA), 7,12-dimethylene anthracene (DMBA), and urethane] to animals either intravenously or orally [112]. When breast tumors are developed in female (BALB/cDBA/2) F1 mice with DMBA, the great majority of these tumors are type B adenocarcinomas and adenomas have a period of incubation of seven months [113,114]. The incubation time can be decreased to three months by taking DMBA with medroxyprogesterone acetate (MPA), which can also enhance the possibility of BC [115–117].

In chemically generated, transgenic, and xenograft animal models of BC, n-3 PUFA sourced from marine sources have been demonstrated to prevent tumor development [118]. These physiologically relevant utilization thresholds were reproduced in dietary intervention studies of BC rodents, suggesting that n-3 PUFA have a beneficial effect on the BC phenotype [119]. Researchers have discovered that n-3 PUFA can lower obesity-related inflammation, thus the risk of tumor formation [45]. As a result of decreased cell proliferation and increased apoptosis, they exhibit reduced BC tumor occurrence, development, proliferation, and metastasis in BC mouse models [120]. In a model of postmenopausal breast cancer with obesity, n-3 PUFA therapy also lowered signs of inflammation caused by macrophage infiltration [121]. According to research, the inflammatory microenvironment directly targets n-3 PUFAs, which reduces tumor burden. In obese humans, n-3 PUFA intake enhanced the action of many genes related to cell regulation, leading to similar antitumor effects. n-3 PUFAs can differentially influence he response of cells to proliferative or apoptotic signals.

Adipocytes in white adipose tissue are the main producers of adipokines, which are small peptide hormone growth factors [122]. The two most significant adipokines associated with BC development are leptin and adiponectin. The obese (ob) genes on chromosome 7 in humans are responsible for expressing leptin [123]. It contains 167 amino

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acids and has a molecular weight of 16 kDa. Depending on the menopausal state, leptin can either increase or decrease the likelihood of BC. Leptin concentrations in serum increase the incidence of BC in postmenopausal women, whereas they decrease the incidence in premenopausal women [124]. Breast tumors have high levels of leptin and its receptors, which are associated with metastatic dissemination [125,126]. Leptin is associated with the modulation of endothelial cell growth and the stimulation of blood vessel development [127]. Leptin helps endothelial cells make more COX-2 through Phosphatidylinositol 3-kinase (PI3K)/Protein kinase B (Akt) and p38-MAPK-dependent pathways [128]. Leptin may enhance angiogenesis in mouse breast cancer cells *via* vascular endothelial growth factor (VEGF) signaling mechanism [129]. The likelihood of breast cancer may be influenced by leptin, which either promotes or suppresses the release of follicle estradiol [130,131]. The upregulation of the leptin receptor and its signaling are associated with the presence of estrogen receptor-α (ERα) in human BC cell lines [132].

Another adipokine associated with BC triggered by obesity is adiponectin having a molecular weight between 28–30 kDa and is mostly secreted by adipocytes but may also be produced by different kinds of cells [133,134].

Due to their significant and well-established selectivity for adiponectin receptors, globular adiponectin (gAcrp30) and full-length adiponectin (Acrp30) are essential [135]. AdipoR1 and AdipoR2 are the two most prevalent adiponectin receptors. AdipoR1 has a high sensitivity for gAcrp30, but AdipoR2 has an average sensitivity for both Acrp30 and gAcrp30 [133,136]. The activity of the adiponectin receptor was altered in most BC cell lines.

Fig. 2 depicts the influence that n-3 PUFA has on the thresholds of major adipokines and inflammatory mediators in the microenvironment of obese malignant cells. At these levels both the proliferative and apoptotic natures of the tumor cell are affected. The following are some of the ways in which n-3 PUFAs act as anti-inflammatory agents:

➢ Nuclear factor-κB (NF-κB), protein kinase C, and mitogen-activated protein kinase (MAPK) are part of the pathway for cell signaling through n-3 PUFAs [137].

➢ n-3 PUFA helps to curtail oncogenes by controlling intracellular homeostasis through the regulation of Ca^{2+} channels found on plasma membranes [137].

➢ n-3 PUFA serves as a binder for PPAR [138].

➢ Additionally, n-3 PUFA affects apoptosis through their modification of plasma membrane lipids [139].

One of the most important functions of PUFAs in the body is the enzymatic conversion of PUFA into eicosanoids. The inflammatory response, platelet aggregation, cellular proliferation, and cell differentiation can all be modulated by eicosanoids. Eicosanoids are formed from EPA, ARA, and dihomo-γ-linolenic acid. The release of PUFAs from membrane phospholipids is the first step in the generation of eicosanoids, which is caused by the action of a number of different phospholipases. Following this, the COX, 5-LOX, 12-LOX, and 15-LOX, as well as the cytochrome P450 monooxygenases, use these PUFAs as substrates. LOX is involved in the production of lipoxins, LT, and hydroxy fatty acids, whereas COX is involved in the production of PGs and Thromboxane (TXA) 2. The production of epoxy fatty acids, dihydroxy fatty acids, and hydroxy fatty acids results from the oxidation of PUFAs that is mediated by cytochrome P450 monooxygenase. 12-hydroxyeicosatetraenoic acid, TXA2, LT, and PGs are all examples of eicosanoids that can be produced from ARA. These eicosanoids have been shown to suppress apoptosis and stimulate cell proliferation, both of which are necessary for tumor survival. n-3 PUFA may limit tumor growth because it inhibits the production of inflammatory eicosanoids [140–142].

Effect of PUFA on the Activity of Gene Expression Transcription Factor and Signal Transducer

A single breast cell is involved in a series of genetic changes that are crucial to the cause of BC (Fig. 3). Recent studies have shown that the control of intracellular signaling is an important reason for the regulation of cellular function in various types of cancer. The (n-3) and (n-6) series of PUFA holistically exhibit the influence on gene regulation, which is the focus of this part, which aims to examine the diverse effects of PUFA on gene expression in various tissues. Most cancer cells grow and develop irregularly because they proliferate and metastasize so rapidly.

Researchers have revealed that n-3 PUFAs found in fish oil (EPA and DHA), can influence gene expression by modulating transcription factors. These PUFAs can affect the activity of transcription factors like NF-κB, which plays an essential role in the regulation of inflammation and immune responses [143]. The investigation reported that n-3 PUFAs can inhibit NF-κB activity, leading to reduced inflammatory gene expression. This anti-inflammatory effect of n-3 PUFAs has potential implications for various health conditions, including cardiovascular disease and inflammatory disorders [144].

Adding n-3 PUFAs to the diet reduced the number of breast tumors and raised COX-2 levels in a mutant mouse strain that encodes human epidermal growth factor receptor-2 (HER-2). Mediators in the ARA-5-LOX cascade can start cancer growth and make it take longer for breast cancer to develop in mammary tissue. A study on the BC cell line MCF-7 demonstrated that DHA raises the levels of syndecan-1 (a transmembrane proteoglycan) and speeds up cell death by blocking the activity of Bad/MAPK/extracellular signal-regulated kinases (Erk). According to various studies, supplementation with n-3 PUFAs decreased the activity of E2 on EGFR, Akt, and Erk1/2, while increasing the activity of protein kinase-A (PKA)/Cyclic adenosine 3′-5′-monophosphate (cAMP)/G protein-coupled estrogen receptor-1 (GPER1) [145].

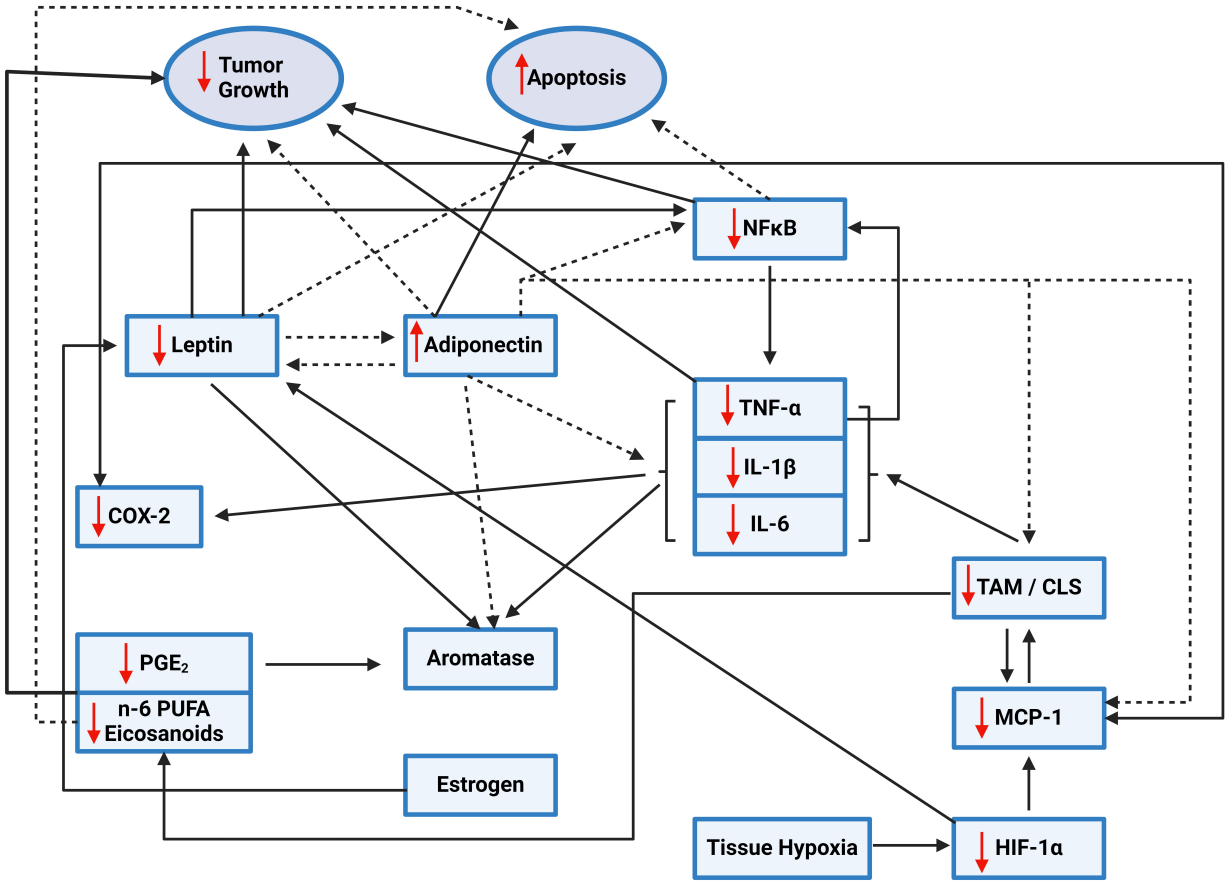

Fig. 2. Mode of action of the inhibitory effect of AA. TNF-α, Tumor Necrosis Factor-α; IL, Interleukin; MCP, Monocyte chemoattractant protein; COX-2, cyclooxygenase-2; AA, arachidonic acid; TAM, arachidonic acid; CLS, crown-like structures; HIF-1α, hypoxic inducible factor-1α.

Effect of PUFA on Peroxisome Proliferator-Activated Receptors-Gamma (PPAR-γ)

Peroxisome proliferator-activated receptors-gamma (PPAR-γ) are members of the nuclear receptor protein family that play the role of transcriptional regulators [146,147]. The retinoid X receptor (RXR) and PPAR-γ work together to form a heterodimer. This lets PPAR-γ move into the nuclei and connect to the peroxisome proliferator-activated receptor response element (PPRE) in the PPAR-γ target region [148,149].

PPAR-γ may also influence gene expression *via* nongenomic methods [150]. PPAR-γ has been shown to bind directly with several transcription factors, such as activator protein 1 (AP-1) and NF-κB, to prevent genes that cause inflammation in a way that does not depend on DNA [151].

PPAR-γ is mainly activated by dietary n-3 and n-6 PUFAs [152,153]. A reduced prevalence of coronary artery disease (CAD) and a lower chance of acquiring various forms of cancer, particularly BC, prostate cancer, and colorectal cancer, are both associated with dietary intake of high n-3-PUFA-rich foods walnuts and fish [154–156]. Some of the pharmacological effects of n-3 PUFAs have been shown to depend on PPAR-γ stimulation, one of the many molecular mechanisms through which they act.

PPREs have long been associated with the regulation of genes involved in lipid metabolism and homeostasis, but a new study reveals that they also participate in cell differentiation, proliferation, and inflammation. n-3 PUFA is one that is like PPAR and has antitumor properties through the activation of PPAR [157]. A diet that had a narrow n-6/n-3 PUFA proportion (1:14.6) led to an increase in PPAR protein content within rats with BC [158]. Thus, activation of PPAR-γ may reduce the risk of BC (Fig. 4).

Effect of PUFA on Bcl-2 Associated X Protein (Bax)/B-Cell Lymphoma-2 (Bcl-2)-Mediated Apoptosis in BC

Cell death occurs in a variety of circumstances caused by genes that may play an important function in aiding or preventing apoptosis [159]. BC cells exhibit resistance to apoptosis when Bcl-2 is upregulated [160]. Contrarily, Bax causes apoptosis through the formation of Bcl-2 [161,162]. Higher consumption of n-3 PUFAs, typically found in canola oil and fish, reduces Bcl-2 and enhances apoptosis, which reduces the risk of BC (Fig. 5).

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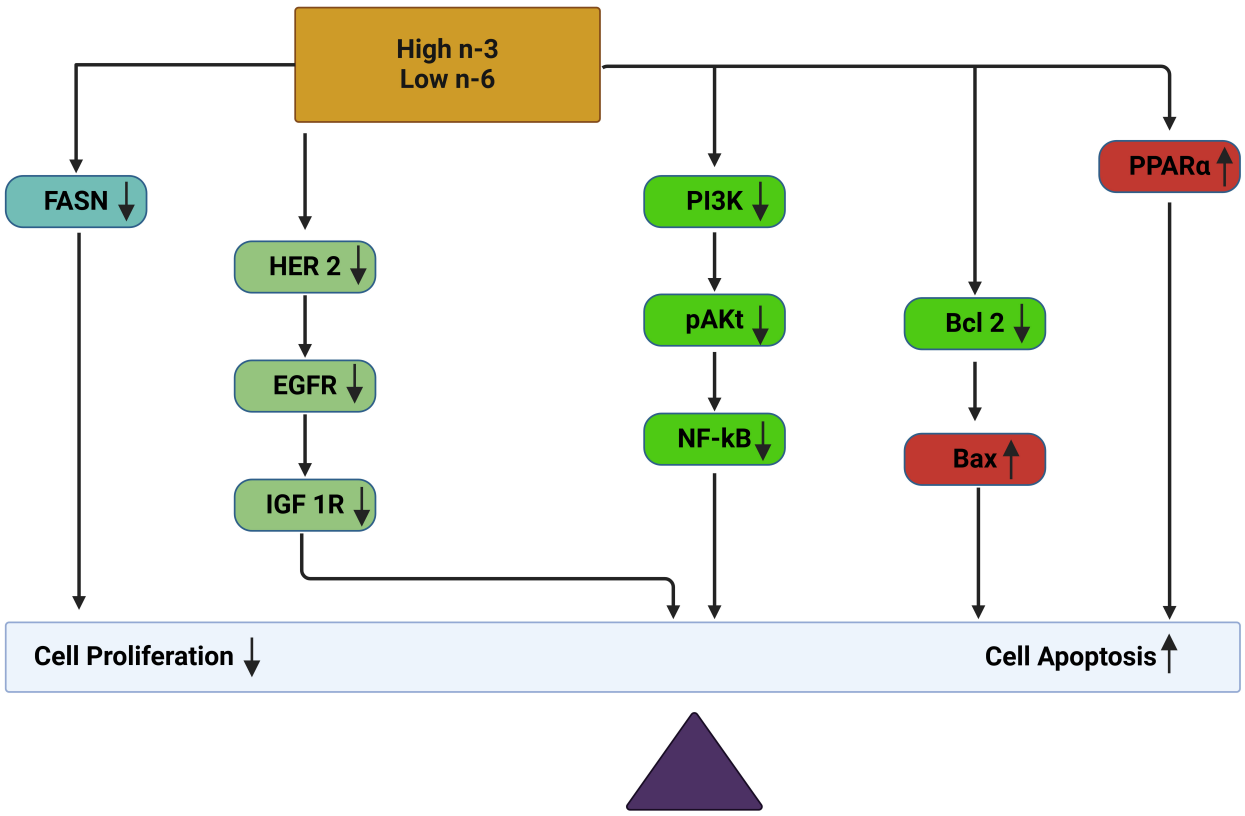

Fig. 3. Diagram illustrating how n-PUFAs regulate cell function through intracellular signaling molecules and a slow rate of cell death (*i.e.*, apoptosis). A diet rich in PUFAs can suppress gene expression and regulate the development and cell death of cancerous cells by inhibiting the action of signal transduction molecules. By inhibiting gene growth factors such as insulin-like growth factor 1 (IGF-1R), human epidermal growth factor receptor-2 (HER-2) and epidermal growth factor receptor (EGFR); activating PPAR or reducing fatty acid synthase (FAS) protein levels to inhibit cellular multiplication; and regulating cellular apoptosis by inhibiting the Phosphatidylinositol 3-kinase (PI3K)/Protein kinase B (Akt) cascades, suppressing phosphorylated Akt, and blocking Nuclear factor-κB (NF-κB). Figure created with (BioRender.com). Bcl-2, B-cell lymphoma-2; Bax, Bcl-2 associated X protein; PPAR, peroxisome proliferator-activated receptor; FASN, fatty acid synthase.

According to research, n-3 PUFAs, particularly DHA and EPA, can change the Bax/Bcl-2 ratio. Some studies have indicated that these n-3 PUFAs can downregulate Bcl-2 expression, an anti-apoptotic protein, while potentially upregulating Bax (pro-apoptotic proteins), leading to a shift in the ratio in favor of cell survival. These effects may contribute to the potential benefits of n-3 PUFAs in reducing inflammation, promoting cardiovascular health, and potentially influencing cancer cell survival [163].

LA* is an example of an n-6 PUFA whose effects on the Bax/Bcl-2 ratio may be complex and context-dependent. Some studies have reported that a high proportion of n-6 to n-3 PUFAs in the diet may have effects on inflammation and cell survival. However, the specific effects on Bax/Bcl-2 modulation might depend on other factors, such as the overall dietary pattern and cellular environment [164].

The relationship between PUFAs and the proportion of Bax to Bcl-2 in cancer cells is the subject of research, as apoptosis regulation is often disturbed in cancer. Modulation of this ratio by PUFAs could have an impact on cancer cell survival and susceptibility to treatment, but the exact mechanisms and outcomes are likely to depend on the specific cancer type and cellular context [165].

Phosphatidylinositol 3-Kinase (PI3K)/Protein Kinase B (Akt), Nuclear Factor-κB (NF-κB), and Toll-Like Receptor-4 (TLR4)

Cell death is dependent on both PI3K/Akt and Bcl-2. There are different genes encoding the catalytic and regulatory subunits of PI3K [157]. When PI3K is activated, phosphatidylinositol (3,4,5)-triphosphate is formed in the membrane. This triggers Akt, a serine/threonine kinase that is downstream of PI3K [158]. Phosphorylation at Thr308 and Ser473 activates Akt, which then moves to the plasma membrane [159]. This mechanism enables Akt to act as an inhibitor of apoptotic processes. Therefore, tumor cell proliferation and apoptosis resistance are associated with increased phosphorylated Akt [160]. Overexpression of HER-2 activates Akt in processes related to cell survival

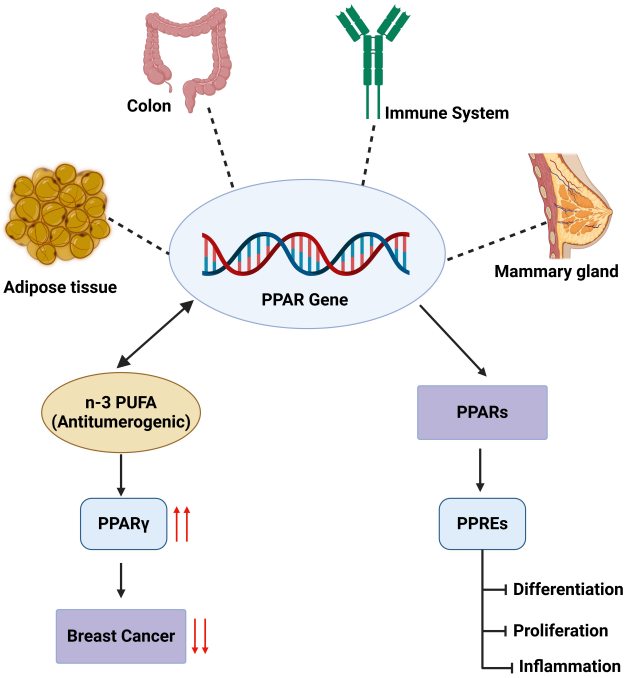

Fig. 4. Effect of PUFA on peroxisome proliferator-activated receptor gamma (PPAR-γ): PPARs are nuclear receptor proteins that triggered gene transcription, with a subtype found in various tissues, including the immune system, adipose tissue, colon, and mammary gland. PPARs control lipid metabolism and have now been found to also impact cell differentiation, proliferation, and inflammation. A recent study showed that n-3 PUFA, similar to PPAR-γ, has anti-tumorigenic potential by activating PPAR-γ, and a diet with a low n-6/n-3 PUFA proportion was linked with increase higher PPAR levels in rats with BC. Figure created with (BioRender.com). PPRE, peroxisome proliferator-activated receptor response element.

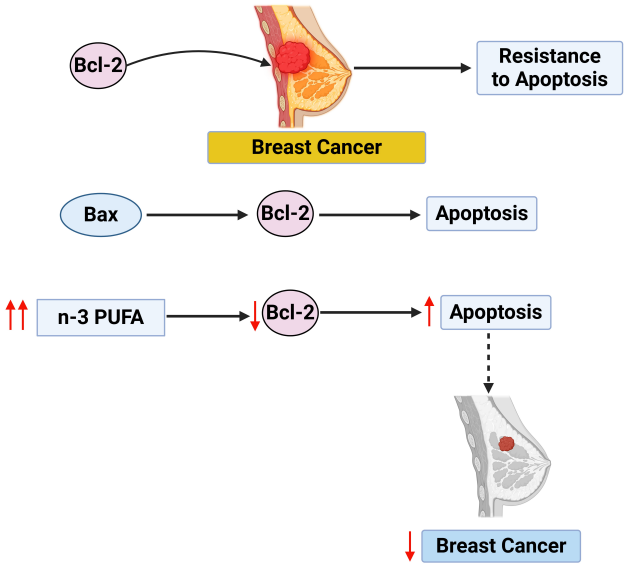

Fig. 5. Effect of n-3 PUFA on Bcl-2 associated X protein (Bax)/B-cell lymphoma-2 (Bcl-2): Cell death, known as apoptosis, is influenced by genes that can either promote or inhibit this process. In breast cancer, resistance to apoptosis is linked to upregulated Bcl-2, while Bax promotes apoptosis by interacting with Bcl-2. Higher intake of n-3 PUFAs from sources like canola oil and fish reduces Bcl-2 levels, enhancing apoptosis and potentially lowering the risk of breast cancer. Figure created with (BioRender.com).

and growth, but n-3 PUFAs control Akt expression or inhibits its phosphorylation [161]. n-3 PUFAs present in the membrane of cancer cells could influence Akt phosphorylation until it reaches the plasma membrane, which is crucial for its activation [162]. Additionally, researchers have found that PI3K/Akt triggers the transcription factor NF-κB to increase cell survival (Fig. 6).

Cell proliferation, migration, and angiogenesis are regulated by Nuclear factor-κB (NF-κB) [166]. PUFA can turn on NF-κB, which then changes important genes connected to inflammation, including chemokines, matrix metalloproteinase (MMP), COX-2, cytokines, inducible nitric oxide synthase (iNOS), and adhesion molecules [167]. It was observed that DHA could inhibit the expression of NF-κB in bovine mammary epithelial cells (BMEC) provoked by Lipopolysaccharides (LPS), which further led to inhibition of mRNA of pro-inflammatory mediators (Fig. 7). These findings also suggested that the PPAR-γ signaling pathway may be based on the inhibition of NF-κB [168].

There are several pathologic conditions involving the PI3K/Akt and NF-κB mechanisms, such as cancer cell adhesion, angiogenesis, inflammation, and metastasis [169]. Reducing NF-κB stimulation suppresses multiple migration and invasion mediators, including urokinase-type plasminogen activators (uPA), VEGF, MMPs, and tumor metastasis [170]. Cancer cells must be able to overcome the vessels walls to invade the surrounding tissue. To aid this process, they release uPA, MMPs and VEGF, all of which are vital components in cancer cell metastasis and invasion [171–173]. Inhibition of NF-κB function can prevent tumorigenesis and metastasis as well as the binding of associated factors to these promoters. Suppression appears to be a viable option to limit the expression of uPA, MMP, and VEGF. The PI3K/Akt family of transcription factors plays a significant role in stimulating cancer cell proliferation, and stimulation of Akt has been linked to tumor invasion and metastasis. PI3K/Akt is activated by the transcription factor NF-κB and has been linked to cancer invasion and metastasis [174]. It is possible that inhibition of PI3K/Akt/NF-κB enhances the anti-metastatic potential of several anti-breast cancer drugs.

Stimulation of TLR4 in tumor cells could promote tumor growth and resistance to apoptosis [36]. Activation of TLR4 signaling favors the development of epithelial ovarian cancer cells and chemoresistance [31]. Inhibition of

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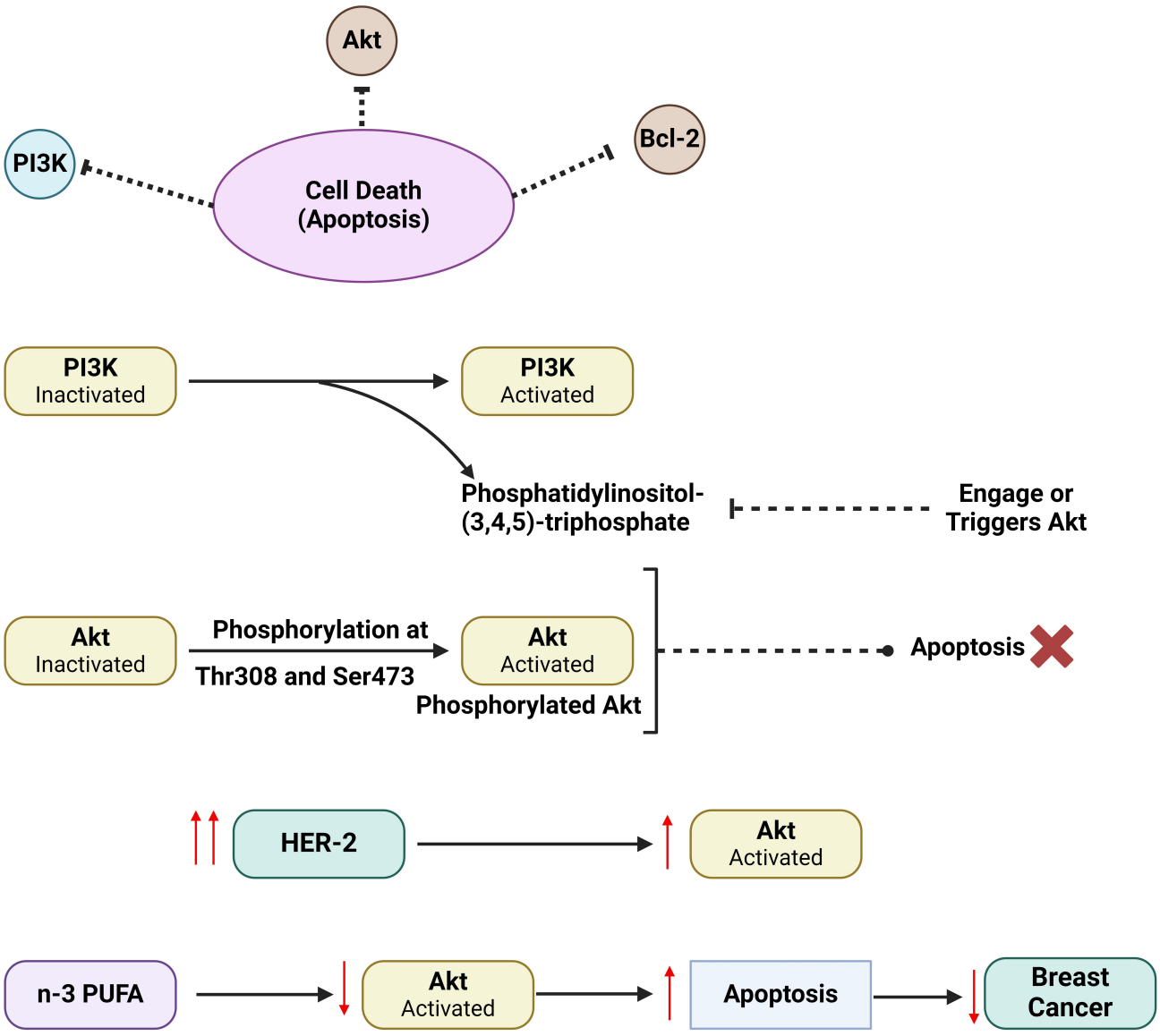

Fig. 6. Effect of n-PUFA on PI3K/Akt: Cell death regulation involves the PI3K/Akt mechanism and the anti-apoptotic protein Bcl-2. Phosphatidylinositol (3,4,5)-triphosphate is produced as a result of PI3K stimulation, triggering Akt, which, when phosphorylated, inhibits apoptosis. n-3 PUFAs can modulate Akt, affecting tumor cell proliferation and apoptosis resistance, potentially by influencing Akt phosphorylation, and the PI3K/Akt pathway also activates NF-κB to enhance cell survival. Figure created with (BioRender.com).

TLR4 signaling has been shown to inhibit tumor development and enhance animal survival [37,38]. In an animal model of stage-2 chemical carcinogenesis, in which inflammation promoted lung cancer development, TLR4 was demonstrated to suppress lung cell development, potentially providing a preventative measure (Fig. 8) [39].

MDA-MB-231 cells express TLR4 at high levels, and RNA interference (RNAi) has been chosen as a method to reduce TLR4 expression. Several studies have shown that inhibition of TLR4 expression significantly reduces the progression and spread of BC cells. TLR4 has been demonstrated to have a beneficial effect on the development of breast carcer [5]. In a study, found that n-3 PUFA-enriched meals given to children had therapeutic effects in addition to providing energy by blocking the expression of TLRs 2 and 4, which are involved in the production of inflammatory components [5]. n-3 PUFAs have been studied for their anti-inflammatory properties, including their effect on TLR4-mediated signaling, especially DHA and EPA.

Some studies suggest that n-3 PUFAs can downregulate the TLR4 signaling pathway. They may reduce the activation of TLR4 and downstream signaling molecules, resulting in lower release of pro-inflammatory cytokines (such as IL-6 and Tumor Necrosis Factor-α (TNF-α)) [175].

n-3 PUFAs may attenuate the inflammatory process triggered by TLR4 activation. This modulation of TLR4-mediated inflammation could be beneficial in diseases as-

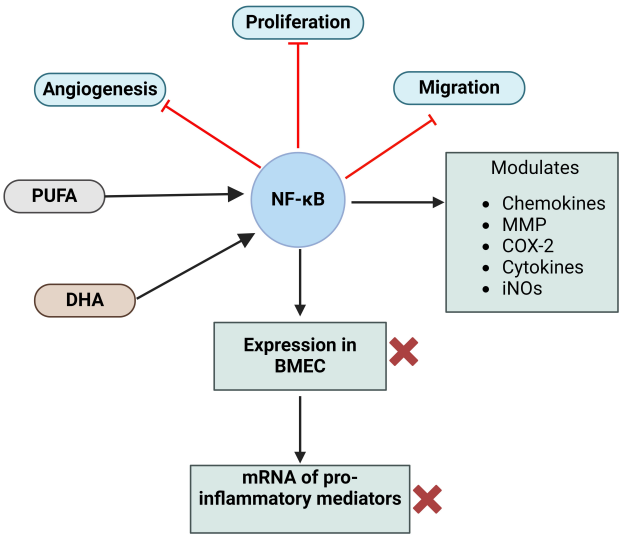

Fig. 7. Effect of n-3 PUFA on Nuclear factor-κB (NF-κB) regulates key processes such as cell proliferation, migration, and angiogenesis. PUFAs, specifically DHA, can inhibit NF-κB expression, which in turn modulates genes involved in inflammation, as demonstrated in bovine mammary epithelial cells under LPS-induced conditions, leading to a reduction in pro-inflammatory mediator mRNA expression. Figure created with (BioRender.com). BMEC, Bovine mammary epithelial cells; MMP, matrix metalloproteinase; iNOS, inducible nitric oxide synthase.

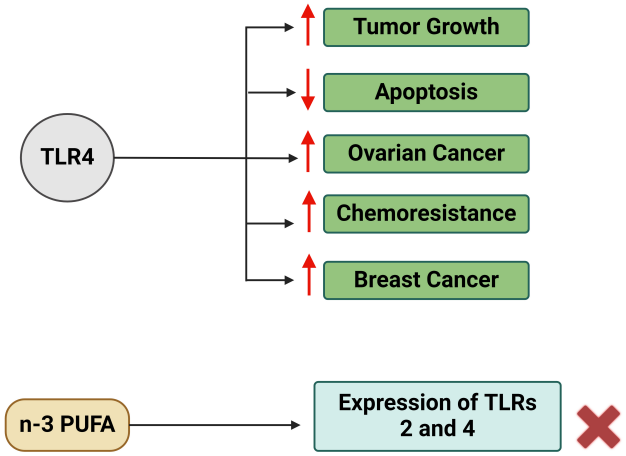

Fig. 8. Effect of n-3 PUFA on Toll-like receptor-4 (TLR4): Stimulation of TLR4 in tumor cells may promote tumor growth and resistance to apoptosis, as seen in ovarian cancer. Inhibition of TLR4 signaling has demonstrated effectiveness in inhibiting tumor development and improving animal survival, even in cases of inflammation-associated carcinogenesis. A study aimed to investigate whether TLR4 affects the advancement of the MDA-MB-231 human BC cell line model. Figure created with (BioRender.com).

sociated with chronic inflammation, such as cardiovascular diseases, autoimmune disorders, and certain inflammatory conditions [176].

n-6 PUFAs *i.e.*, LA*, are essential fatty acids, but their effects on TLR4 signaling have not been studied as extensively as those of n-3 PUFAs. However, the proportion between n-3 and n-6 PUFAs in the diet is of interest.

Maintaining a balanced ratio of n-6 to n-3 PUFAs in the food is essential for immune and inflammatory responses. A high ratio of n-6 to n-3 is thought to promote a pro-inflammatory environment, potentially impacting TLR4-mediated signaling and exacerbating inflammatory conditions [177].

Effect of PUFA on Physical Activity in BC Patients

In both humans and animal models, n-3 PUFA consumption could enhance anaerobic resistance and modify oxygen uptake during strenuous exercise, increase metabolic capacity, delay the onset of fatigue, postpone tiredness appearance, and promote muscle development and neuromuscular activity [178].

Zhou *et al.* [168] used 14 case-control studies and 7 cohort studies to investigate whether exercise may influence susceptibility to BC. The results of a study of 1504 women revealed that women in the third exercise group had a 30% chance of developing BC [168]. Previous research has demonstrated that exercise reduces the incidence of BC by 25% [179–181]. Stress-induced apoptosis and lipid peroxidation are both mechanisms that reduce exercise-induced BC risk [182]. Additionally, exercise can alleviate the symptoms of menopause and improve quality of life. Regular exercise helps maintain bone and muscle health and increases maximal oxygen uptake. Physical health and mortality rates are linked to lower oxygen consumption. In several studies, a higher risk of mortality in BC has been associated with peak oxygen consumption. Participation in aerobic exercise after BC therapy increases peak oxygen consumption and reduces mortality risk [183]. BC is associated with obesity, which is characterized by physical inactivity and a sedentary lifestyle [31]. Obesity is known to increase adipocyte hypertrophy and hypertension, which are associated with hypoxia. Several mechanisms contribute to obesity-related BC risk, including inflammation of breast adipose tissue, release of adipokines adipokine, and activation of Akt [184].

Serum adiponectin, leptin, estrogen, and insulin concentrations are among the prognostic markers for BC that can be influenced by physical activity and n-3 PUFA meal. BC patients may develop resistance to adiponectin, insulin, and leptin, resulting in decreased forkhead box (FOX), inflammation, and insulin sensitivity. However, these changes can be modified by an n-3 PUFA meal and physical activity, which could improve leptin-activated FOX and

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insulin-activated glucose transport. Risk factors for possible BC are increased with higher circulating levels of leptin, insulin, and estrogen. It has been established that n-3 PUFA and physical activity play an important role in the regulation of these parameters. Overall, the combined effect of physical activity and n-3 PUFA intake in BC patients leads to a down-regulation of estrogen receptor, leptin receptor, and insulin receptor gene expression activity [185].

Role of PUFA as an Immunity Booster

Fish fats and PUFAs are macronutrients that not only provide energy but also control essential cellular processes. It is known that the n-3 PUFAs found in seafood support the function of immune cells. According to the findings, n-3 PUFAs influence both innate and adaptive immunity [186]. Lactating women who took fish oil supplements produced more IL-10 and had babies with higher levels of the probiotic bacteria *Lactobacillus* and *Bifidobacterium*. Patients with chronic inflammatory conditions like Crohn's disease, ulcerative colitis, asthma, inflammatory bowel disease, and rheumatoid arthritis benefit greatly from the substantial anti-inflammatory and protective activities of n-3 PUFAs [187]. Aqua foods rich in n-3 PUFAs have recently gained popularity as dietary supplements and pharmaceuticals [188]. Against this background, it has been proposed that n-3 PUFAs are crucial for immunological regulation and act as a preventive measure against the onset of new diseases.

Like seleno proteins, PUFAs have a significant impact on the innate and adaptive immune system. n-3 PUFAs and their analogs function not only as a necessary component of the cell membrane, but also as signaling components [189]. Specialized pro-resolving mediators (SPM), or derivatives of n-3 and n-6 PUFAs, include prostaglandins, protectins, TXA2, resolvins, LTs, and maresins. Several enzymes, including cyclooxygenase, lipoxygenase, and cytochrome P450, are responsible for controlling the synthesis of these metabolites [190]. ALA, DHA, and EPA are the main n-3 PUFAs that suppress immune cell activation while promoting certain immunological processes such as phagocytosis and neutrophil differentiation. For this reason, n-3 PUFAs are thought to have no effect on non-specific responses [189].

Efficacy of PUFA on Suppression of BC Progression

Efficacy of n-6 Fatty Acids in Suppression of BC Progression

n-6, particularly ARA are much more prevalent in the everyday diet and are associated with a multiple of negative effects on the human body, such as promoting cancer. There is evidence that n-6 PUFA can change the structure of cell membranes and have antiproliferative effects by inducing the expression of proteins in the progression of cell cycles or activating apoptosis [191–193]. The efficacy of some antineoplastic drugs was also increased when n-6 PUFA or their metabolites were combined. For example, the combination of GLA/docetaxel or paclitaxel inhibited cell growth in the human BC cell lines MCF-7, SK-Br3, T47D, MDA-MB-231, and DGLA/vincristine accelerated death in vincristine-resistant cells (KBC-hR-8-5) compared to normal treatments [194,195].

Efficacy of n-9 Fatty Acids in Suppression of BC Progression

Hypogenic acid (16:1 (n-9), (Z)-hexadec-7-enoic acid), oleic acid (18:1 (n-9), (Z)-octadec-9-enoic acid), elaidic acid (18:1 (n-9), gondoic acid (20:1 (n-9), mead acid (20:3 (n-9), erucic acid (22:1 (n-9) and (Z)-tetracos-15-enoic acid) are the most abundant n-9 fatty acids. The anti-neoplastic effects of n-9 fatty acids is more controversial than their anti-inflammatory function, with the effect varying depending on the type of malignant tissue and the route of action. The most well-documented anti-neoplastic activity of n-9 is seen in diets high in olive oil. These diets rich in oleic acid are thought to have chemo preventive properties against BC [196].

Efficacy of Mixtures of n-3 and n-6 Fatty Acids in Suppression of BC Progression

In animal models, immune-compromised mice are injected with human BC cells [81]. In mice, n-6 PUFA-rich foods increased the growth and metastasis of human BC cells, while an EPA or DHA-rich diet been shown to inhibit growth and migration [118]. According to the literature, consumption of n-3 PUFA lowered COX-2 and antigen Kiel-67 (Ki-67) levels. This inhibited cell proliferation and atypical hyperplasia, leading to the prevention of HER-2/neu BC in its earlier stages [119]. Daily consumption of n-3 PUFAs was shown to halt tumor growth in mice with a more aggressive form of HER-2-positive BC called MMTV-neu (ndl)-YD5. Investigations focusing on both nutrition and genetics have led researchers to conclude that n-3 PUFAs have a protective effect [45]. It was observed that n-3 PUFAs inhibited the progression of BC in MMTV-neu-YD5 mice in a dose-dependent manner. The mice were fed diets containing varying proportions (% w/w) of menhaden fish oil. The diets used in the study consisted of three different compositions: 0% n-3 PUFA [10% w/w safflower oil (rich in n-6 PUFA)]; 3% n-3 PUFA (7% safflower oil and 3% menhaden oil); or 9% n-3 PUFA (1% safflower oil and 9% menhaden oil). In MMTV-neu-YD5 mice, a significant decrease in tumor mass and proliferation was observed when fed a diet containing 3% and 9% menhaden oil compared toa diet containing 10% (w/w) safflower oil [120]. When mixed with the same amount of corn oil, feeding of menhaden oil at a concentration of 24% (w/w) slowed the formation of BC in mice by 15 weeks [121]. Numerous

chemo preventive experiments for the prevention of mammary cancer in rats have demonstrated the anti-cancer effects of n-3 PUFA in the context of mammary cancer using carcinogenic compounds namely, N-methyl-N-nitrosourea (MNU) and DMBA [197,198]. When menhaden fish oil is included in the diet, the presence of DHA and n-3 PUFA reduces tumor incidence. Further, dietary EPA also slows chemically induced tumor growth and metastasis. Liu *et al*. [137] distinguished between the effects of n-3 and n-6 PUFA content on the development of BC in rats. The findings demonstrated that the supernatant of LPS-stimulated BV2 cells dramatically reduced the survival of SH-SY5Y cells and the expression of PI3K, p-Akt, tropomyosin-related kinase-B (TrkB), brain-derived neurotrophic factor (BDNF), which was substantially restored by DPA pretreatment. Furthermore, BDNF-siRNA inhibited the neuroprotection of DPA. n-3 DPA could thus protect neurons from neuroinflammation-mediated destruction by regulating the M1 and M2 polarizations of microglia, blocking microglia-NF-κB and mitogen-activated protein kinase (MAPK) p38 while stimulating the BDNF/TrkB-PI3K/Akt mechanism of neurons [137].

Wei *et al.* [138] administered MNU to rats in various ratios of n-6 to n-3 PUFA. They discovered that a diet consisting of n-6 to n-3 PUFA in a 1:1 ratio was more beneficial for inhibiting tumor growth. Increased n-3 PUFA content and decreased expression of genes involved in lipid metabolism were both used to achieve this. When EPA and DHA are consumed instead of n-6 polyunsaturated fatty acids, the expression of genes that break down fats decreases. This prevents the growth of breast tumor cells [144]. A lot of different types of fatty acids were studied in the human BC cell line MDA-MB-231, such as n-3, n-6, and n-9 polyunsaturated fatty acids [139]. While EPA and DHA restrict cell growth in a dose-dependent manner, LA and OA increase cell proliferation even at incredibly low doses [139]. The n-3 fatty acids EPA and DHA, in combination with LA, induce DNA breakage and cell death in MDA-MB-231. A similar discovery was made when studying the BC cell line MCF-7 [140]. While ALA significantly slows the growth of MDA-MB-231 and HBL-100 human BC cells, but not MCF-7 cells, EFA and DHA decrease the growth of all tumor cells [141]. All cancer cells are slowed in their development by EFA and DHA. The addition of n-3 PUFAs to the cell membrane alters the structure, function, and signaling mechanism of BC cells. n-3 PUFAs inhibit the growth of cells, switch on PPAR, which helps the cells to differentiate, and stop the cyclin-dependent kinase 1 (CDK1)-cyclin B1 complex. Also, eating n-3 PUFAs raised the level of pro-caspase-8, an enzyme that starts apoptosis, while lowering the level of Bcl-2 [199].

Efficacy of EPA and DHA in Suppression of BC Progression

Men in Australia, Europe, and North America consume between 0.6 and 1.7 g of ALA daily, while women consume between 0.5 and 1.4 g. The amounts of EPA and DHA in the phospholipids of plasma cells and tissue are greater than the amounts of ALA [200]. This is even though the intake of EPA and DHA in North America is expected to be ten times lower than the intake of ALA. The question arises as to whether human conversion of ALA to EPA and DHA is a practical substitute for dietary intake of EPA and DHA, since dietary intake of EPA and DHA is inversely related to risk of developing BC [146]. Dietary intake of ALA reduces the growth of BCs in rats exposed to chemical carcinogens. In ovariectomized athymic mice with elevated estrogen levels, the growth of MCF-7 BC was reduced when the mice were fed flaxseed oil, which is a potent source of ALA. Flaxseed oil and other diets with a higher ALA composition inhibited the growth of MCF-7 BC. An increase in apoptosis and a decrease in cell formation were both necessary to achieve this. In a laboratory study, pure ALA was shown to reduce the growth of MCF-7 cells by 33%. This corresponds to what was observed in real life, where tumors grew less rapidly. ALA can be utilized as a stand-alone antitumor agent, as shown in this study [157]. An *in vivo* study was also carried out to find out whether ALA, a component of flaxseed, or secoisolariciresinol diglucoside lignan (SDGL) is responsible for tamoxifen being better at preventing the growth of the known MCF-7 BC cells at low estrogen levels. SDGL is less effective than ALA-rich flaxseed oil in reducing the size of detectable tumors in tamoxifen-treated tumors. Research suggests that ALA inhibits the expression of HER-2 and then controls growth factor-related signaling pathways by lowering the receptor for insulin like insulin-like growth factor 1 (IGF-IR) and Bcl-2 [158]. In a recent study, canola oil containing 10% ALA was used instead of corn oil containing 1% ALA in the diet of MDA-MB-231 mice. The result was a significant slowdown in tumor development [159]. Studies suggest that the combination of ALA and trastuzumab (HER-2 inhibitor) has a synergistic effect and increases efficacy in HER-2 increased BC cells [162]. In another study, ALA was found to have limited tumor-reducing capabilities in the presence of trastuzumab [201]. In conclusion, a diet high in ALA has been shown to inhibit the development of pancreatic cancer in both animal models and *in vitro* research, with most of the effect being due to the conversion of ALA to DHA and EPA. When EPA and tamoxifen are combined, MCF-7 cells exhibit growth inhibition, proving that EPA as a dietary supplement can reduce the risk of BC [202]. In MCF-7 xenografts, EPA inhibits a G-protein coupled receptor-mediated pathway that regulates cell proliferation. It was found that the cells can only prevent the growth of lipid rafts (Akt and FAS) when exposed to DHA. This prevents HER-2 activity and signaling

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Table 3. Inhibitory concentration 50 (IC_{50}) value of EPA and DHA in different BC cell lines [206].

Sl. No.	EPA (IC_{50})	DHA (IC_{50})	Cell lines
(1)	57.4	20.2	MCF-7
(2)	>200	70–100	MDA-MB-231
(3)	>200	70–100	MDA-MB435s cells

molecules from killing cells [203]. According to Menendez *et al.* [201] external DHA supplementation reduced HER-2/neu oncogene expression in human BC cell lines SK-Br-3 and BT-474. It was also discovered that pretreatment with DHA increases the efficacy of antimitotic drugs such as Taxol against BC cells with high metabolism. This opens the door for the development of new EGFR-targeted combination therapies. DHA incorporation into cellular lipids influences membrane fluidity and function, resulting in better drug absorption. A recent human clinical study found that utilizing DHA in chemotherapy improves the survival rate of people with metabolic BC. According to study by Mandal, DHA increases apoptosis in MCF-7 cells *via* a number of mechanisms [204]. The main reason was increased lipid peroxidation, which leads to the formation of ROS that increase stress and eventually lead to cell death. Higher levels of DHA inside cells have been shown to help cells die by making apoptosis effector enzymes like caspase-8 and caspase-3 work better. DHA has been shown *in vitro* to inhibit the growth of KPL-1 cells, leading to suppression of Bcl-2 [166]. DHA inhibits the growth of tumors both in chemically produced carcinomas and in rodent xenograft models. This suggests that the apoptotic effect of DHA is caused by its control of Bax and Bcl-2. DHA has been shown to reduce the risk of BC by 60%, consistent with a 60% increase in the *BRCA1* protein [140]. Consequently, ALA, EPA, and DHA have an antagonistic effect on BC formation *in vivo*.

In vitro investigations have shown that DHA and EPA alone have a suppressive effect on the growth of almost all forms of cancer cells while the effect of ALA is limited to BC cells that are HER-2 positive and ER-negative. Only 30 µM DHA or 50 µM EPA can significantly reduce the survival of cancer cell while 72 µM ALA has only a minor effect on the growth of ER-negative cells [205]. DHA was also found to be more effective than EPA in suppressing the development and occupancy of MDA-MB-231 (ATCC HTB-26) and MCF-7 cells when tested with multiple BC cell lines [206]. Table 3 (Ref. [206]) summarizes the information on the inhibitory concentration 50 (IC_{50}) value of EPA and DHA in different BC cell lines. However, since the number of tumor cells and the duration of therapy vary, it is a challenge to correlate the optimal dose of a single n-3 PUFA from the different types of tests. Further studies are needed to evaluate the efficacy of each individual n-3 PUFA in the same situations.

Safety Concerns

Although n-3 fatty acids have significant health benefits, such as preventing cardiovascular disease, there are concerns about their safety. n-3 supplementation can increase the risk of bleeding, and this is a major concern. At very high doses (15 gm/day), n-3 fatty acids have shown an antithrombotic effect in certain studies, which can lead to bleeding or even early cardiac death. An open-label randomized experimental investigation in Italy with 2836 subjects prior to statin use showed that supplementation with 1g of n-3 PUFA per day significantly reduced the number of non-fatal strokes and heart attacks as well as overall mortality during a follow-up period of 42 months [207].

A randomized double-blind placebo-controlled study in Italy involving 3494 people with heart failure found that regular use of 1 g of n-3 PUFA supplements over an average of 3.9 years slightly reduced the likelihood of hospitalization for cardiovascular indications and deaths [207].

In a study conducted by Liao *et al.* [208], TXA2 synthesis is inhibited for 1 month after administration of EPA (10 g/day). Administration of EPA (10 g/day) also suppressed platelet-mediated thrombus formation. TXA2 is described as an essential mediator in the mechanism of platelet aggregation through interaction with platelet PGH2 receptors which was inhibited by EPA. Another study conducted by Bhardwaj *et al.* [209] revealed that taking n-3 PUFA (1.3 g/day DHA and 3 g/day EPA) for 28 days reduced blood TXA2 levels in 36% of subjects and prolonged bleeding time by 40% in subjects with angiographically confirmed coronary artery disease. The safety of n-3 PUFA is also compromised by the high stability and resistance to oxidation of fish oil, which could make patients more susceptible and thus increase the risk of toxicity [210]. Fish consumption has also been associated with hypervitaminosis due to the high levels of fat-soluble vitamins A and D found in fish oils. These risks can be greatly reduced by purification processes in fish oil supplements and by the production of medicinal products containing n-3 fatty acids from plants [58]. Fish oils are composed of persistent organic contaminants, minerals, free fatty acids, primary oxidizing agents, phospholipids, moisture and insoluble impurities, and must be purified after isolation to meet the high standards that make them suitable for ingestion by animals and humans [211].

Future Perspectives

The consumption of n-3 PUFA has been shown in epidemiologic studies and in clinical practise to reduce the prevalence of BC Oral ingestion of n-3 PUFA may be a viable option that could be of concern to the pharmaceutical industry as well as a source of inspiration for future studies. For the treatment of BC, numerous studies have been conducted on the efficacy of n-3 PUFA supplements, especially

those found in fish oil and seafood. Vegetable oils, which typically contain ALA, are just as effective and beneficial as fish oil supplements, which usually contain EPA and DHA fatty acids. Although ALA is less susceptible to oxidation than EPA because it has fewer double bonds whereas EPA has five bonds.

The anti-inflammatory potential of n-3 PUFA has been demonstrated, which is relevant considering that prolonged inflammation is associated with to the onset and progression of BC. It is possible that future studies will focus on determining the mechanisms by which n-3 PUFAs influence inflammation and the affect this has on cancer patient outcomes.

N-3 PUFAs facilitate the inhibition of angiogenesis, which causes tumor shrinkage. To gain a comprehensive understanding of the role that n-3 PUFAs play in regulating angiogenesis, researchers need to develop models that can be tested both *in vitro* and *in vivo*. In upcoming, clinical trials n-3 PUFAs could be investigated in combination with conventional anti-cancer drugs to improve the efficacy of BC treatment.

During the first step of oxidation, fish oils produce more hydroperoxides, which break down into other types of radicals. There are several ways to reduce the oxidation of lipids in fish oils, including the use of clean, high-quality raw components and a low-temperature separation process. The use of antioxidants is one of the most effective ways to reduce the oxidation of lipids. Synthetic antioxidants frequently added to fish oil include ascorbyl palmitate, butylated hydroxytoluene, propyl gallate, butylated hydroxyanisole, and vitamin-E [212]. This suggests that further research is needed to control the oxidation of lipids in fish oil, which is attracting researchers.

Conclusion

BC is the leading cause of death in women worldwide. Recent research has shown that n-3 PUFAs play an important role in limiting the growth, proliferation, and metastasis of cancer cells without harming normal cells. n-3 PUFAs have anti-cancer properties by reducing pro- inflammatory eicosanoids, modulating transcription factors (NF-κB, PI3K/Akt and TLR4) and enhancing PPAR-γ. They also reduce free radical formation and lipid peroxidation, which contributes to the prevention and therapy of BC.

There is evidence that n-3 PUFAs may contribute to cancer prevention and improve the efficacy of conventional treatments. However, further *in vitro* and *in vivo* research and clinical studies are needed to fully understand their molecular processes and impact on BC outcomes.

Availability of Data and Materials

All experimental data included in this study can be obtained by contacting the first author if needed.

Author Contributions

Conceptualization, RS and AI; data collection, AM, AI, BB, RW and ND; formal analysis, JK, BB, MB and ND; validation, RS, MA and AI; writing-original draft preparation, AI, BB, JK, AM, and ND; writing-review and editing, MA, JK, RS, RW, AM, MB and ND; supervision, RS. All authors have read and agreed to publish the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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