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Role of Polyunsaturated Fatty Acids in Cancer and Their Use in Cancer Treatment

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ABSTRACT

Cancer is defined as uncontrolled cell division, which could spread or invade various tissues. There are more than 200 types of cancer, including breast, skin, lung, colon, and prostate cancer, and lymphoma, the symptoms and indications of which vary depending on the type of tissues. Cancer has several treatments with different applications. For instance, chemotherapy, radiation therapy, surgery or their combination are common treatment modalities for cancer. However, a complete cure for cancer has not been achieved yet. On the other hand, novel drugs for cancer treatment are not efficient due to the ability of cancer cells to develop resistance against chemotherapeutic agents. Recently, natural compounds have been reported to improve the efficiency of cancer treatment. Polyunsaturated fatty acids (PUFAs) are natural compounds that could be used as dietary supplements in cancer patients. PUFAs are classified into two main categories, including n-3 and n-6 PUFAs. According to the literature, n-3 PUFAs exert protective effects against cancer through the induction of apoptotic pathways and suppressing cell proliferation, while n-6 PUFAs cause tumor formation by inducing cell growth and proliferation. Using PUFAs in combination with chemotherapeutic agents is considered to be an effective approach to the treatment of cancer patients through increasing cancer cell death. This review aimed to discuss the interactive effects of the structure and function of PUFAs on cancer and cell processes through various signaling pathways.

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Introduction

This review aimed to discuss the current literature regarding polyunsaturated fatty acids (PUFAs) and their role in cancer progression and treatment based on the articles published in databases such as PubMed-NCBI. Initially, the chemistry and structure of PUFAs and their effects on the function of PUFAs have been elucidated. Furthermore, the interactions between the structure and function of PUFAs have been discussed by summarizing the major research articles in this regard. Following that, the role of PUFAs in cancer progression has been discussed, as well as their effects on various signaling pathways. Finally, the potential usage of PUFAs in cancer treatment has been explained based on in-vitro, in-vivo, and clinical studies.

Literature Review

Structure and Function of PUFAs

PUFAs are composed of a long carbon chain with one or a double/triple carbon-carbon bond. These compounds could be classified into three groups based on their contained bonds, including monounsaturated, polyunsaturated, and acetylenic fat-

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ty acids (Figure 1) (1,2). PUFAs are found in cell membrane phospholipids and are also involved in the cell membrane structure, fluidity, signaling, and cell-to-cell interaction (3). With their involvement in these cellular events, PUFAs play a key role in cancer progression (4,5).

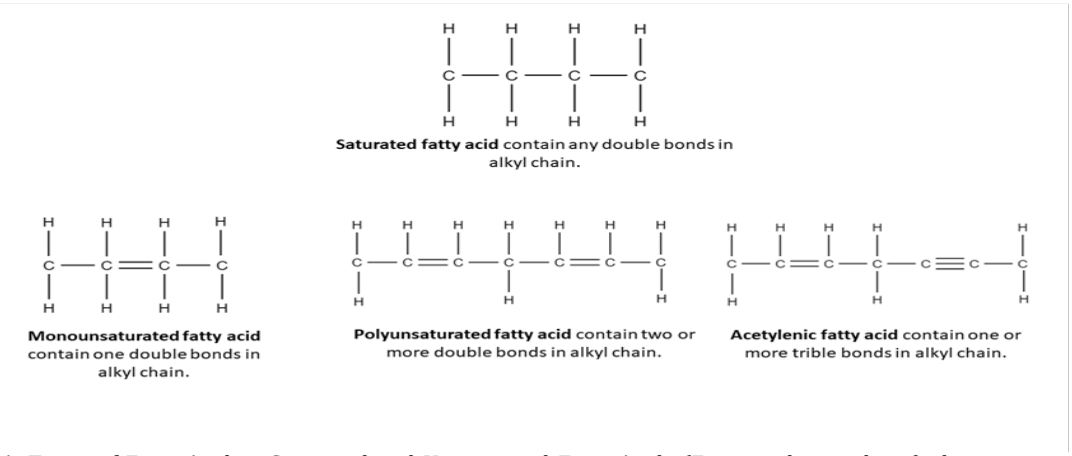

Figure 1. Types of Fatty Acid as Saturated and Unsaturated Fatty Acids (Fatty acids are classified as saturated and unsaturated fatty acids; Saturated fatty acids contain saturated hydrocarbon chain, while unsaturated fatty acids have double or triple carbon-carbon bond chain; Unsaturated fatty acids are saturated with hydrogen.)

Determining the structure of PUFAs clarifies the function of various PUFAs that needs to be predicted. In addition, PUFAs could be categorized into three groups based on the position of their double bonds, including conjugated, non-conjugated, and methylene-interrupted PUFAs (6-8). Conjugated PUFAs contain single bonds between the two double bonds, and unconjugated PUFAs consist of more single bonds between their two double bonds (8,9). In a study, De la Torre et al. elaborated on the differences between conjugated and non-conjugated linoleic acid, which are known as polyunsaturated n-6 fatty acids. Accordingly, conjugated linoleic acid derivatives were less efficient compared to unconjugated linoleic acid derivatives in various cancer cells, with the exception of MCF-7 (breast cancer cell line). Moreover, the findings of the mentioned study indicated that growth inhibitory activity was significantly regulated depending on the number of the double bonds in linoleic acid (10). PUFAs with methylene-interrupted arrangement are classified based on the methyl groups (-CH2) that provide flexibility through free rotation. This feature also affects the function of the membrane components in embedded proteins (11).

PUFAs could also be divided into various subclasses depending on the distance of their double bonds from the methyl side. N-3 and n-6 PUFAs are considered to be essential human nutrients (6). N-3 PUFAs include alpha-linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid (DHA), and n-6 PUFAs include linolenic acid (LA) and arachidonic acid (AA) (12). Each PUFA plays a different, key role as a precursor to mediate inflammation, angiogenesis, and cancer through multiple mechanisms (13,14). It is notable that n-3 and n-6 PUFAs have contrary effects on cancer, while n-3 PUFAs have antitumor activities, and n-6 PUFAs induce tumor growth (5,15).

The activity of fatty acids could be determined based on key factors such as the carbon chain length, number of the double bonds, and configuration of the bonds. In a research in this regard, Costabile M. et al. screened various structures of fatty acids to assess their function. Although the correlation of the carbon chain length and biological activity of monounsaturated fatty acids could not be clearly established, other properties were reported to affect the activity of these acids. This issue was investigated differently in case of PUFAs as their activity increased with the lengthening of the carbon chain. Moreover, the PUFAs in Z configuration were observed to have higher inhibitory effects compared to the PUFAs in E configuration, with the exception of 9(Z),12(Z)-octadecadienoic acid (18:2 n-6), as its activity had no significant changes (16).

Various formulations of n-3 PUFAs are found as free fatty acids, ethyl esters, monoacylglycerides, triacylglycerides, and phospholipids, which have variable beneficial effects at different doses. In this regard, the findings of Cruz-Hernandez C. et al. demonstrated that the n-3 PUFAs in monoacylglycerides are more bioavailable and easily delivered in tissues since monoacylglycerides are not absorbed by lipase in pre-clinical tests (17). Furthermore, Morin C. et al. examined the anti-effects of n-3 PUFAs in monoacylglycerides on colorectal carcinoma cancer, and the obtained results indicated that the n-3 PUFAs in monoacylglycerides could

reduce cell proliferation and induce apoptosis by decreasing the activtion of nuclear factor kappa-light-chain-enhancer of activated B cells, which occurred through the down-regulation of Bcl-2, cyclin D1, c-myc, and COX-2 proteins (18).

Role of PUFAs in Cancer Progression

N-3 PUFAs have long been considered to be beneficial for human health. In the early 1980s, studies showed that n-3 and n-6 PUFAs could regulate the level of blood lipids and blood pressure, while preventing the risk of cardiovascular diseases (19). In addition, several studies have been focused on the role of PUFAs in cancer. For instance, Bartoli G. M. et al. reported that n-3 PUFAs could decrease the risk of colon cancer through the reduction of arachidonic acid in cells (20). Following the mentioned study, Lockwood K. et al. evaluated the effects of treatment with n-3 PUFAs and nutritional antioxidants (Vitamin C, D, and E) on 32 typical breast cancer patients, who were considered high-risk as cancer had spread to their axillary lymph nodes. According to the findings, breast cancer metastasis did not occur in the patients after combination therapy with n-3 PUFAs and nutritional antioxidants. Additionally, none of the patients lost weight, and use of painkillers decreased as well. Therefore, it was concluded that n-3 PUFAs could increase the quality of life of the patients, while reducing the tumor size (21).

Metastasis and tumor growth could be regulated by fatty acids. The effects of direct and indirect pathways in macroenvironments on microenvironments could be the basis to determine cancer progression, which is of utmost importance in the development of new therapeutic approaches. In a research, You S. et al. proposed a new hypothesis on the effects of transition from monounsaturated to polyunsaturated fatty acids on tumor microenvironment in breast cancer. Accordingly, the transition level of n-6 PUFAs from monounsaturated increased in micro and macroenvironments, which consistent with the other studies in this regard. In addition, n-6 PUFAs were reported to induce tumorigenesis by increasing estrogen levels and inducing cell proliferation and inflammation (22).

Tumor growth is also mediated by angiogenesis activity. Angiogenesis is the process of blood vessel formation, which provides the required nutrients for cancer cells. In a study, Szymczak et al. elucidated the role of PUFAs in angiogenesis. Correspondingly, angiopoietin-2 (Ang2) and matrix metalloproteinase-9 (MMP-9) induced angiogenesis through endothelial invasion and tube formation. The obtained results also indicated that n-3 PUFAs could inhibit Ang2 and MMP-9 expression, while n-6 PUFAs had opposite effects. Moreover, the expression of Ang2 and MMP-9 was modulated by prostaglandin E2 and prostaglandin E3 in the COX pathway (23).

According to epidemiological and experimental studies, PUFAs could be involved in the development and progression of cancer. In this regard, Corsetto P. A. et al. suggested that PUFAs could mediate cell growth in breast cancer through the alteration of the physical and chemical properties of cells and membrane structure activity. Another similar research indicated that n-3 PUFAs could modify the biochemical and physical properties of the lipid rafts in the membrane, thereby leading to apoptosis (24). Furthermore, use of arachidonic acid as a PUFA mediator was reported to induce cell cycle arrest through increasing ceramide levels (25). Therefore, it could be inferred that arachidonic acid is involved in sphingolipid metabolism, which is also regulated through the induction of the COX-2 pathway (26).

According to the literature, n-3 and n-6 PUFAs have anti-inflammatory and pro-inflammatory effects, respectively (Figure 2). Inflammation is

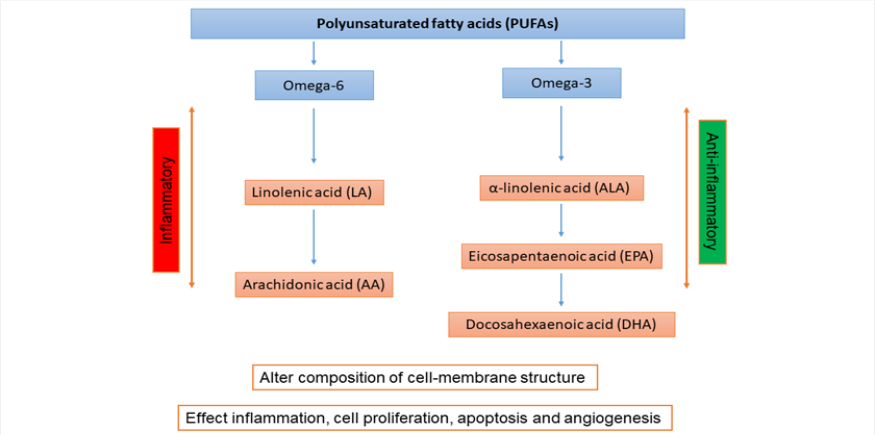

Figure 2. Regulation of Two Essential PUFAs (n-6 and n-3). (N-6 and n-3 PUFAs have contrary roles in cellular processes; N-3 PUFAs mediate anti-inflammation, apoptosis, inhibition of cell proliferation, and angiogenesis; N-6 PUFAs are involved in inflammation, cell proliferation, and angiogenesis).

critical in cancer progression since inflammatory cells regulate the tumor microenvironment through the regulation of cell proliferation, survival, invasion, and migration. These processes are maintained by several signaling pathways, such as PI3K/PTEN/AKT, Hippo/YAP, PPAR-γ/NF-κB, and COX-2.

Effect of PUFAs on Signaling Pathways

PUFAs are considered critical components to maintain homeostasis, which is a process involving several signaling pathways. Although fats are harmful to health and might induce cancer, cardiovascular diseases, and blood pressure disruption, PUFAs are considered beneficial for various organisms. PUFAs could suppress tumor progression through the inhibition of cell proliferation, migration, invasion, and metastasis, which could be regulated by several signaling pathways (Figure 3).

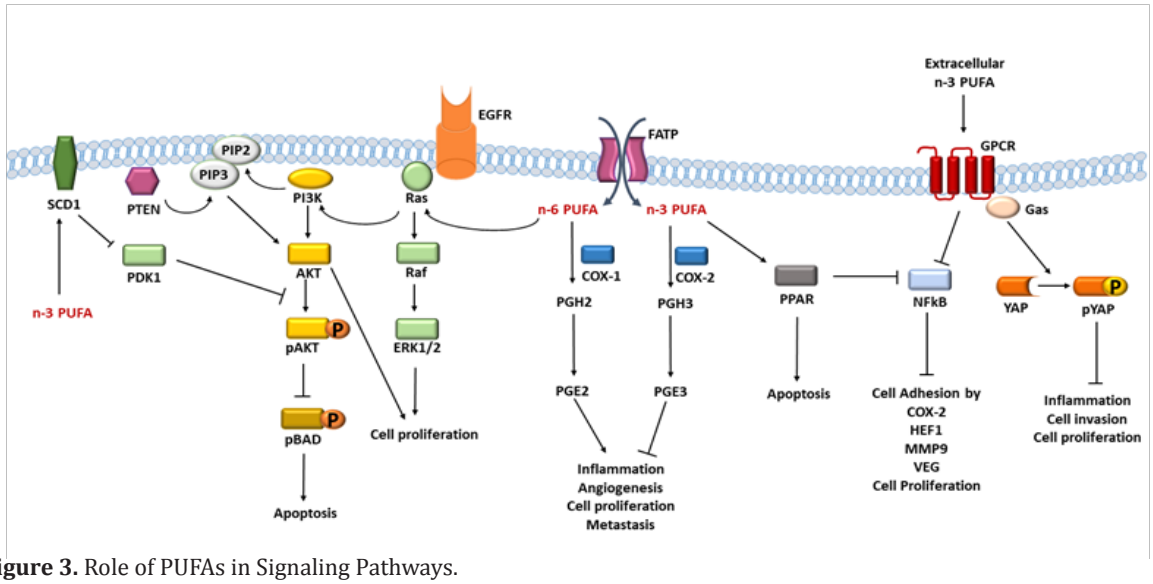

Figure 3. Role of PUFAs in Signaling Pathways.

The PI3K/PTEN/AKT pathway is essential to lipid signaling in many cancer types. This pathway mainly mediates cell growth, proliferation, and apoptosis. The epidemiological studies in this regard have demonstrated that n-3 and n-6 PUFAs affect cancer development through targeting multiple molecular pathways. For instance, Gu Z. et al. evaluated the correlations between PUFAs and the localization and signaling of AKT in prostate cancer. In the mentioned study, the arachidonic acid (AA) of n-6 PUFAs and docosahexaenoic acid (DHA) of n-3 PUFAs exerted variable effects on cancer cells. In addition, PIP3 was detected on the cell membrane of the AA-treated cells, while PIP3 was located in the cytosol of the DHA-treated cells, suggesting that the localization of PIP3 could be mediated by n-3 PUFAs. Furthermore, DHA was reported to change the location of phospho-AKT and PIP3, which inhibited the interaction of AKT and BAD, leading to the suppression of tumor growth through inducing apoptosis and inhibiting the tumor progression pathways. Therefore, it was concluded that a different family of n-3 and n-6 PUFAs could mediate the AKT pathway distinctly (27). On the same note, Yin Y. et al. confirmed the inhibition of cell proliferation via the drastic reduction of AKT, as well as metastasis through the suppression of HEF1, MMP-9, and VEG proteins in lung cancer. HEF1, MMP-9, and VEG protein levels are considered to be the main mediator in cell migration and invasion, which regulate metastasis. Use of DHA has been shown to inhibit cell invasion and migration by decreasing the expression levels of HEF1, MMP-9, and VEG proteins (28).

Syndecans (SDC-1) is a type I transmembrane protein, which mediates cell proliferation, migration, and adhesion, as well as cell-cell and cell-matrix interactions. In addition, SDC-1 is known as the main regulator of tumor microenvironment, and increased SDC-1 expression could induce apoptosis. In this regard, the findings of Edwards I. J. et al. and Hu Y. et al. demonstrated the role of PUFAs by determining the SDC-1 expression in prostate cancer. Edwards I. J. et al. determined the regulation of SDC-1 by n-3 PUFA in prostate epithelial cells, reporting that the use of n-3 PUFA could lead to the up-regulation of SDC-1. Moreover, the effects of n-3 PUFAs on SDC-1 mRNA expression level was reported to be twice more significant compared to the effects of n-6 PUFAs.

SDC-1 is a proteoglycan located on the cell membrane, which regulates growth factor signaling and cell-cell interaction. Treatment with n-3 PUFAs could results in the increased level

of SDC-1 through the activation of peroxisome proliferator-activated receptor (PPARγ), which directly affects the involvement of fatty acid metabolism. Another important factor in this regard is the association between SCD-1 and cellular signaling pathways since SCD-1 maintains the homeostasis of tumor microenvironment (29). In their study, Hu Y. et al. evaluated the interactions of SCD-1 and PDK1/AKT/BAD signaling with the prostate cancer cells treated with n-3 PUFAs. Accordingly, n-3 PUFA DHA could induce apoptosis through the suppression of SDC-1-dependent PDK1/AKT/BAD signaling, while the increased expression of SDC-1 could inhibit the phosphorylation of PDK1/AKT/BAD, thereby leading to apoptosis (30).

The Hippo/Yes-associated protein (YAP) pathway is known as a tumor suppressor pathway, which is controlled by G-protein-coupled receptors (GPRs). GPRs play a pivotal role in cell proliferation and invasion, as well as immune cell mediation. In a research in this regard, Zhang K. et al. examined the interactions of PUFAs and Hippo/YAP pathway in colorectal cancer cells. According to the findings, n-3 PUFAs induced the activation of the Hippo signaling pathway through gas components such as GPR40 and GPR120, which regulated GPRs. Additionally, n-3 PUFAs were reported to activate YAP phosphorylation (31).

Obesity and inflammation are among the other risk factors for tumor formation. According to the literature, the consumption of n-3 PUFAs could reduce tumorigenesis, obesity-related inflammation, and risk of cancer. The inflammation induced by obesity regulates tumor formation. In this respect, Chung H. et al. demonstrated the regulatory role of n-3 PUFAs in tumor formation in obese mice by determining the levels of the tumor necrosis factor (TNF-α) and GPRs. TNF-α induces the production of cytokines, which are the main mediator of inflammation. Furthermore, cytokines as secreted proteins are involved in cell interaction and communication. According to the results of the mentioned study, n-3 PUFAs could inhibit tumor growth with increased inflammatory cytokines and TNF-α in obese mice (32,33).

PUFAs are also used in combination therapies to improve the effects of chemotherapy through inducing the sensitivity of cancer cells. In a study, Sharaf I. A. et al. determined the levels of PPAR-γ and NF-κB in breast cancer patients after treatment with n-3 PUFAs. According to the obtained results, activation of PPAR-γ induced cell apoptosis and decreased cell proliferation in breast cancer, while NF-κB could control cell proliferation and inflammation. In the mentioned study, treatment with n-3 PUFAs along with chemotherapy could increase the PPAR -γ level and inhibit the NF-κB level (34).

In another study, Ma J. et al. demonstrated the effects of n-3 and n-6 PUFAs on the angiogenesis of gastric cancer via the COX-2 pathway. Furthermore, prostaglandin H2 (PGH2) and prostaglandin H3 (PGH3) were produced from n-6 and n-3 PUFAs, respectively, and the process was regulated via the COX-1 and COX-2 pathways. PGH2 and PGH3 were eventually converted into prostaglandin E synthase as PGE2 and PGE3, which played an opposing role in angiogenesis, inflammation, and tumorigenesis (35).

According to the literature, n-3 and n-6 PUFAs play a key role in several signaling pathways, such as the SCD-1/PDK-1/AKT/BAD, PI3K/PTEN/AKT, Hippo/YAP, PPAR-γ/NF-κB, and COX-2 pathways. These pathways mediate cellular processes, including cell proliferation, growth, adhesion, invasion, angiogenesis, metastasis, and inflammation.

PUFAs in the Clinical Studies

The pre-clinical results of in-vivo and in-vitro studies have confirmed that n-3 PUFAs could reduce cell growth and proliferation. Moreover, clinical trials have been conducted to determine the effects of PUFAs on cancer patients and changes in PUFAs on the serum of these patients.

In a study in this regard, Wuryanti S. et al. assessed the effects of PUFAs on the inflammation of an advanced cervical cancer patient undergoing radiation therapy. According to the findings, the overall survival rate of cervical cancer was approximately 40%. In the mentioned study, chemotherapy and radiation therapies were applied as the main treatment approaches for cervical cancer, and their combined application was reported to cause severe complications. On the other hand, use of n-3 PUFA instead of chemical drugs was considered to be beneficial owing to the associated pro-apoptotic and anti-inflammatory effects. In the mentioned research, the effects of n-3 PUFAs were also determined on 45 advanced cervical cancer patients undergoing radiotherapy for 12 months. According to the obtained results, PGE2 level decreased by 8.9% in the treatment group, while it increased by 28.1% in the control group. Additionally, tumor progression was reported to reduce in the treatment group. The patients received PUFA treatment with the ratio of n-6:n-3 PUFAs, and the level of PGE2 was observed to decrease in these patients. However, the reduction of PGE2 was observed to be more significant in the

patients receiving n-3 PUFAs only compared to those administered with n-6:n-3 PUFAs (36).

In another research, Murff H. J. et al. examined the association between the consumption of PUFAs and colorectal cancer development through the observation of adenomatous and hyperplastic polyp formation. According to the findings, the risk of adenomatous and hyperplastic polyps reduced in the women consuming n-3 PUFAs. However, the adenomatous and hyperplastic polyps in men and women were not affected by the consumption of n-6 PUFAs. The consumption of n-3 PUFAs by women was also observed to reduce PGE2 production, which in turn decreased the risk of colorectal cancer development through decreasing angiogenesis, inflammation, and tumorigenesis (37).

Previous findings have confirmed that PUFAs affect immune cells, as well as cancer cells, and the activation of immune cells depends on synthesized n-3 PUFAs. In a study in this regard, Sibbons C. M. determined the role of n-3 PUFAs in peripheral blood mononuclear cells (PBMCs) and Jurkat T cell leukemia cell line using an inhibitor of PUFA biosynthesized enzyme. According to the obtained results, n-3 PUFA synthesis was mediated by elongase and desaturase, which in turn affected the cell proliferation of PBMCs, leading to mitosis regulation. However, Jurkat cells were unaffected by n-3 PUFA synthesis since the elongation and desaturation processes were dysregulated in these cells (38).

According to the findings of Guartin M. H., intake of n-3 PUFAs could influence cell proliferation and inflammation and quality of life of patients with prostate cancer. In the mentioned study, the patients that were administered with n-3 PUFA monoacylglycerols were followed-up for one year every three months. The obtained results confirmed that clinical applications and quality of life could be improved by nutritional interventions (39).

Conclusion

Tumor progression starts with uncontrolled cell division. Removal of cancerous tissue and growth control of cancer cells are considered to be the main approaches to the prevention of cancer development. Some of the treatments that are commonly used for cancer include surgery, chemotherapy, and radiotherapy, which are associated with severe complications. Cancer cells gain resistant properties due to prolonged exposure to chemotherapy. As such, new therapeutic drugs have been developed for cancer treatment. PUFAs are natural therapeutic drugs, which are classified into two essential families of n-3 and n-6 PUFAs. These compounds could regulate cancer cell processes, including cell growth, proliferation, invasion, migration, metastasis, angiogenesis, and inflammatory, via signaling pathways.

The role of n-3 and n-6 PUFAs vary depending on the cancer type. For instance, n-3 PUFAs have been reported to increase PPAR-γ and NF-κB, which are the main regulators of apoptosis in breast cancer, while n-3 PUFAs regulate angiogenesis through the regulation of the COX pathway. PUFAs are also involved in other signaling pathways, including SCD-1/PDK-1/AKT/BAD, PI3K/PTEN/AKT, and Hippo/YAP, which play a key role in the other cellular mechanisms aiding in the initiation, development, and prevention of cancer. Additionally, n-3 and n-6 PUFAs are known as lipid mediators, which have a potential role in enzyme regulation for biotransformation. These data reveal a new treatment application by novel drug discovery and design (40). Furthermore, lipid-based drugs (e.g., epoxides and their derivatives), which are known as types of n-3 PUFAs, are essentially involved in the suppression of cell growth and induction of apoptosis in breast cancer cells, as well as the reduction of tumor size, as reported by the in-vivo studies in this regard.

According to the literature, lipid-based drugs provide specific targeting in addition to their use as tolerable drugs in cancer treatment (41). In a study, Serini S. et al. synthesized solid lipid nanoparticles encapsulated with n-3 PUFAs in order to inhibit cancer cell growth. According to the obtained results, the delivery efficacy of the synthesized nanoparticles increased in colorectal cancer cell lines. Moreover, the encapsulated n-3 PUFA nanoparticles were reported to suppress cell proliferation and induce apoptosis. The role of this nanoparticle in cell signaling pathways and its in-vivo applications should be determined so as to improve the use of PUFAs in cancer treatment (42).

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None.

Conflict of Interest

The authors declare no conflict of interest.

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