The Potential of DHA as Cancer Therapy Strategies

Subjects: Oncology

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Docosahexaenoic acid (DHA), also known as omega-3 (*n*-3) polyunsaturated fatty acid (PUFA), is a natural compound that has demonstrated pharmacological activity against several malignant neoplasms. Available cancer treatments cause side effects, affect healthy cells, reduce the quality of life of patients and may cause resistance to antineoplastics. For these reasons, the search for new therapies is continuous.

fish oil anticancer molecules in vitro experiments

1. Introduction

Cancer is a pathology with a silent onset and is characterized by the uncontrolled anticipation of malignant cells [1]. This disease affects thousands of people worldwide, and the number of new cases and deaths is growing every year [2][3]. In 2018, there were 18.1 million new cases of cancer and 9.6 million deaths [4]. In 2020, the estimated number of new cases was 19.3 million, and there were 10 million deaths [5].

In 2020, the types of cancer with the highest global incidence, considering both sexes, were breast (11.7%), lung (11.4%), colorectal (10.0%), prostate (7.3%) and stomach (5.6%), and those with the highest mortality were lung (18%), colorectal (9.4%), liver (8.3%), stomach (7.7%) and breast (6.9%) [5].

Currently, the drugs epirubicin, oxaliplatin, fluorouracil, cisplatin and capecitabine are used in cancer therapy, but they have not been internationally standardized for this treatment [6][7]. One of the principles of chemotherapy is cytotoxicity, which is the ability to kill cancer cells; however, cytotoxicity often affects healthy cells and causes side effects, which reduces the quality of life of patients. In addition, cancer is susceptible to becoming resistant to drugs [8][9][10]. Thus, finding efficient therapies to combat cancer is of great interest [11].

Docosahexaenoic acid (DHA) is an omega-3 PUFA with lipophilic characteristics [12][13]. The disposition and amount of unsaturation in DHA favor more potent biological activity and less unsaturation compared to that of other fatty acids; thus, DHA is susceptible to oxidative stress processes [14][15]. DHA helps in the prevention of cardiovascular diseases [16] and premature retinopathy [17] and promotes anti-inflammatory action [18] and anticancer activity [10].

A few years ago, some fatty acids were evaluated in the treatment of cancer, with emphasis on DHA treatments that show the potential to inhibit uncontrolled cell proliferation [18], increase the cytotoxic capacity of antineoplastic agents and which do not interfere significantly in the quality of life of people [19]. In cells, the entry of fatty acids occurs by rapid diffusion and through the support of membrane proteins, such as fatty acid transport protein (FATP), fatty acid binding proteins (FABP) and fatty acid translocase (FAT), which are also responsible for PUFA metabolism and activity [20][21][22]. In cancer cells, the modulation of these membrane receptors is high, and with the acidic tumor microenvironment, the excessive internalization of lipids in the cell and consequent development of lipid droplets inside may occur [23][24]. The accumulation of DHA inside cells can cause irreversible oxidative stress, generating ferroptosis, which consists of a type of nonapoptotic cell death that causes tissue destruction due to the biological dysfunction of proteins and cell membranes [25][26].

2. Efficiency of DHA Against Different Types of Malignant Neoplasms

Anticancer activity was observed in studies involving cell lines that were treated with DHA alone, combined with other substances, including antineoplastics, and when molecules derived from DHA were used.

One recent study on the in vitro anticancer activity of DHA was in the field of nanomedicine. In vitro experiments with DHA were associated with TS and DOX drugs transported in nanostructured lipids (NLC-DHA-TS-DOX), resulting in strongly cytotoxic cell inhibition against breast cancer (4T1 cell line) [27]. The NLC-DHA nanoparticles did not show cytotoxic activity at the tested concentration. In this 4T1 lineage, DHA was also tested [28] with DHA at concentrations of 10, 20, 30, 40 and 50 µM, and the result also did not cause cytotoxicity. This cell line was also treated with PZ and PZ-DHA, and there was no cytotoxic effect [28]. Cytotoxicity results were obtained with this cell line at concentrations of 50, 100 and 150 µM DHA at 24 h and 48 h, but at concentrations of 10 and 25 µM, there was no cytotoxic effect [29]. However, they did not observe a statistically significant result of cell inhibition at concentrations of 10, 20 and 30 µM within 72 h of treatment with DHA [30]. The studies carried out by these authors differed in terms of the type of in vitro cell viability analysis assay, treatment time and, in some cases, the concentration used.

The SUM-149 cell line was tested with DHA, PZ and PZ-DHA [30]. Statistically significant cytotoxic activity was observed after treatment with DHA and PZ-DHA at concentrations of 30, 40 and 50 µM. This cytotoxic effect was not observed by the same authors when SUM-149 cells were treated with PZ. This result demonstrates that the type of drug tested interferes with the cell inhibition effect [30]. This can also be observed on MDA-MB-231 cells within 24 h with the drug 13R,20-diHDHA, and the study did not obtain statistically significant results at any of the tested concentrations [31]. A noncytotoxic result was also observed regarding the 4-OXO-DHA molecule [32].

Studies with other DHA-derived molecules were also performed [32]. The substance 4-OH-DHA was analyzed within 96 h at a concentration of 100 µM and showed cytotoxicity in the cell lines MCF-10F, trMCF, bsMCF, MDA-MB-231 and SK-BR-3, with the exception of cytotoxic activity in the tested cell line T-47D. When the same authors

tested the substance 4-OXO-DHA, they obtained a statistically significant cytotoxicity result in all these lineages [32]. The PZ-DHA ester substance was toxic to liver cancer but not to the HP-F and RTCP10 lineages [33].

The concentration of 100 µM DHA demonstrated a cytotoxic effect in breast tumor and nontumor cell lines. This concentration was also toxic to lung [17], colorectal [20][27], prostate [19], stomach [18] and liver cell lines [33]. However, in the normal cell lines of the stomach (GES-1) [18] and liver (HP-F and RTCP10) [33], there was no statistically significant cytotoxic activity.

Cytotoxic analysis of DHA was tested comparatively with other fatty acids. In comparison with omega 3 EPA, the cytotoxic effect was shown by both substances in colorectal [34], prostate [35] and liver [33] cancer cell lines. In comparison with omega 3 (ALA), in the liver cancer cell line, only DHA was cytotoxic [33]. In comparison with omega 6 (LA), both in the colorectal cancer cell line and in the liver cancer cell line, only DHA showed cytotoxic activity that was considered statistically significant. In comparison with omega 6 (AA), in the prostate cancer cell lines, only DH was cytotoxic. In comparison with omega 9 (OA), in the liver cancer cell line, only DHA was cytotoxic. These analyses corroborate with other information, which mentioned that the disposition and quantity of unsaturation in DHA interferes with the biological activity of fatty acids [14][15].

In other studies, the cytotoxic activity of DHA alone or associated with other substances was observed. A comparison was made between DHA alone, apatinib alone and the two substances in combination [28]. The results showed that the combination of the two substances showed a synergistic effect against breast cancer. The synergistic effect was also observed in the association of nanocarried DHA with TS and DOXO in breast cancer [27], in the association of DHA with PunA in colorectal cancer [20] and with ISL in colorectal cancer [26].

The administration of DHA in cancer patients has been shown to be a coadjuvant in chemotherapy treatment. The addition of DHA in the diet, either in supplementation associated with EPA and/or proteins, helped in the process of muscle mass gain, weight maintenance, tolerance to chemotherapy and tumor shrinkage [36][37][38]. The intake of 6 g of protein, 1.1 g of EPA and 0.5 g of DHA per day is recommended to increase lean mass gain [38], and the minimum dose of 2.0 g/day of EPA + DHA can be used in clinical trials and is sufficient for tissue enrichment to occur [36].

Thus, DHA exhibits cytotoxic action against different tumor lineages and can be ingested in the diet as an adjunct to cancer treatment, within the specific concentrations presented for each type of cancer. In children, these dosages may vary to lower dosage; however, further research on the use of this drug is still needed to standardize the protocol for use in different cancer lineages.

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