

Antioxidative and Prooxidative Properties of Dietary Unsaturated Fatty Acids

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ABSTRACT | Unsaturated fatty acids are considered potential agents for preventing and treating cardiovascular diseases and cancer. The aim of this review is to present available data concerning the activity of unsaturated fatty acids in humans and its possible applications as antioxidants or prooxidants. Biochemical transformations of ω -9, ω -6, and ω -3 fatty acids in the human body as well as fatty acid metabolism are described. The activity of unsaturated fatty acids varies depending on the cell type and fatty acid chemical structure. They may act as antioxidants in normal cells and as prooxidants in tumor cells. Therefore, their complex and cell type-dependent mechanism of action can be used in the treatment of cancer as well as other diseases.

KEYWORDS | Cancer; Fatty acids; Lipid peroxidation; Oxidative stress

ABBREVIATIONS | AA, arachidonic acid; ALA, α -linolenic acid; CAT, catalase; COX, cyclooxygenase; DGLA, dihomo- γ -linolenic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FA, fatty acids; GPx, glutathione peroxidase; GR, glutathione reductase; LA, linoleic acid; LOX, lipoxygenase; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid

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1. INTRODUCTION

The results of clinical and epidemiological studies suggest an existing relationship between the chemical composition and quality of the diet and the risk of

many diseases, particularly cardiovascular disorders and cancer. In very industrialized and highly developed countries, the epidemic of diseases, especially cardiovascular diseases, is largely caused by poor nutrition, mainly an excessive consumption of fats

and their products that have adverse chemical composition.

The fats in the human body fulfill mainly a function of energy material and are also necessary for its proper metabolic functioning. In 1940s, Sinclair described the relationship between diet rich in mono- and polyunsaturated fatty acids (MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids) and low mortality of people with cardiovascular problems [1]. Since then unsaturated fatty acids have been considered potential agents for preventing or treating cardiovascular diseases. In 1929, George Burr and Mildred Burr showed that the unsaturated fatty acids are essential compounds for normal growth and development of animals [2]. They must be supplied in the diet because the human body is incapable of their biosynthesis, and their deficiency results in pathological conditions. These are mainly linoleic acid (C18:2 ω -6; LA), α -linolenic acid (C18:3 ω -3; ALA), and the fatty acid metabolites synthesized in the human body or supplied with the diet, such as arachidonic acid (C20:4 ω -6; AA), eicosapentaenoic acid (C20:5 ω -3; EPA), and docosahexaenoic acid (C22:6; DHA) [3]. Fatty acids (FA), in addition to their building, energetic, and reserve functions, display a high biochemical activity, including the regulation of transcription and expression of certain genes essential for the proper functioning of the metabolic processes within the cells [4]. They are important components of cellular membranes, which play a protective, anti-inflammatory, and indirectly, an antioxidant role. The cellular membrane favors physiological defense processes against free radical activity and an increased level of oxidative stress.

2. BIOCHEMICAL TRANSFORMATIONS OF FATTY ACIDS FROM FAMILIES ω -9, ω -6 AND ω -3 IN THE HUMAN BODY

Fatty acids as long-chain carboxylic acids may have no double bonds between carbon atoms (saturated fatty acids such as stearic acid), have one double bond (monounsaturated fatty acids, e.g., oleic acid), or have at least two double bonds (polyunsaturated fatty acids, e.g., linoleic acid). The combination of three molecules of fatty acids with a glycerol molecule forms a triglyceride. The type of fatty acids building such molecules determines whether a fat is

liquid or solid at room temperature. Widespread fatty acids have their common names and they are determined by the “system ω ”. It identifies the position of the double bond closest to the last (farthest from the carboxyl group) carbon, i.e., carbon ω . The ω end of the molecule is rarely changed during metabolism. From the human metabolism point of view, the most important fatty acids are ω -3 and ω -6. The structure of the acid is also alphanumeric code, e.g., linoleic acid—C18:2 ω -6, means that the acid chain contains 18 carbon atoms, and in the chain there are two double bonds, and it belongs to the family of ω -6 [5]. Fatty acids are structural compounds of phospholipids and glycolipids, which are components of biological membranes, and FA are also covalently bound to proteins and localize them in place in the membrane. Some of their derivatives are acting as hormones and intracellular cell signaling compounds. They are the source of eicosanoids physiologically, and pharmacologically active compounds known as prostaglandins, thromboxanes, lipoxins, and leukotrienes. It is believed that these are local hormones acting through G protein coupled receptors. Leukotrienes are a family of conjugated trienes and lipoxins are a family of conjugated tetraenes, produced from eicosanoids in lipoxygenase pathway in response to immunological and non-immunological stimuli [4, 6].

C20 and C22 acids, which are the precursors of highly active eicosanoids, are derived from bioconversion of linoleic acid (LA, C18:2) and α -linolenic acid (ALA, C18:3), which are subject to subsequent stages of chain elongation and the introduction of the new double bonds (desaturation process) (**Figure 1.**). LA and ALA acids must be provided with food, because the human body lacks the ability to their biosynthesis, but has the ability to their biochemical conversion. Transformation may consist of the enzymatic cleavage of two hydrogen atoms or extension of the hydrocarbon chain with two methylene groups. The fatty acid molecule elongation or desaturation takes place at the proximal carboxyl group. The macromolecule region positioned closer to the methyl group remains unchanged. These processes typically take place alternately and therefore in the human body metabolites of fatty acids with 20–22 carbon atoms and 2–6 double bonds are formed. Desaturases and elongases are localized in the lipid layer of microsomes and require zinc atoms for their activity. The rate of fatty acid change is directly dependent on $\Delta 4$, $\Delta 5$, and $\Delta 6$ desaturase activity. $\Delta 6$

| Carbohydrates (diet) | | | Dietary Essential FA | |
|-----------------------|---|--|---|---|
| Acetate | $\xrightarrow{\quad}$ $\xrightarrow{\quad}$ \downarrow | $\xrightarrow{\quad}$ \downarrow | | |
| Desaturase $\Delta 6$ | $C_{16:1}$ (ω -7) palmitoleic acid (POA) | $C_{18:1}$ (ω -9) oleic acid (OA) | $C_{18:2}$ (ω -6) linoleic acid (LA) | $C_{18:3}$ (ω -3) α -linolenic acid (ALA) |
| | | | | |
| Desaturase $\Delta 6$ | $C_{16:2}$ (ω -7) | $C_{18:2}$ (ω -9) | $C_{18:3}$ (ω -6) γ -linoleic acid (GLA) | $C_{18:4}$ (ω -3) |
| Elongase | | $C_{20:2}$ (ω -9) | $C_{20:3}$ (ω -6) dihomo- γ -linoleic acid (DGLA) | $C_{20:4}$ (ω -3) |
| Desaturase $\Delta 5$ | | $C_{20:3}$ (ω -9) | $C_{20:4}$ (ω -6) arachidonic acid (AA) | $C_{20:5}$ (ω -3) |
| Elongase | | $C_{22:3}$ (ω -9) | $C_{22:4}$ (ω -6) | $C_{22:5}$ (ω -3) |
| Desaturase $\Delta 4$ | | | $C_{22:5}$ (ω -6) | $C_{22:6}$ (ω -3) |

FIGURE 1. Scheme of biochemical transformations of ω -9, ω -6, and ω -3 fatty acids in the human body. Unsaturated fatty acids undergo subsequent stages of elongation and desaturation on the side of the closer carboxyl group. These processes usually take place alternately; therefore, in the human body metabolites of fatty acids with 20-22 carbon atoms and 2-6 double bonds are formed. The rate of conversion of fatty acids depends directly on the $\Delta 4$, $\Delta 5$, and $\Delta 6$ desaturases activity.

desaturase catalyzes the conversion of $C_{18:2}$ ω -6 to dihomogamma-linolenic acid (DGLA, ω -6 $C_{18:3}$), and $C_{18:3}$ ω -6 to stearidonic acid. $\Delta 5$ desaturase catalyzes the synthesis of arachidonic acid ω -6 $C_{20:4}$ from DGLA and eicosapentaenoic acid (EPA, ω -3 $C_{20:5}$) from stearidonic acid. On the other hand, $\Delta 4$ desaturase converts eicosapentaenoic acid (EPA) to docosahexaenoic acid (DHA, ω -3 $C_{22:6}$) [7–9].

EPA under the influence of cyclooxygenase is metabolized to prostaglandins, prostacyclin, and thromboxane (PGE_3 , PGI_3 , and TX_3), supplanted repeatedly by more active, analogous arachidonic

acid reaction products (PGE_2 , PGI_2 , and TX_2) (Figure 2). It is similar in the case of leukotrienes LTA_5 and LTE_5 , arising under the influence of lipoxygenase from EPA as compared to the LTA_4 and LTE_4 , arising from arachidonic acid [10–12].

Regulation of gene expression involving fatty acids is very complex and depends on the carbon chain length, oxidation degree, and their metabolic forms. They may directly regulate gene expression through the activation of nuclear receptors or transcription factors, or act indirectly by generation of a large pool of active lipids and activation of various cell signal-

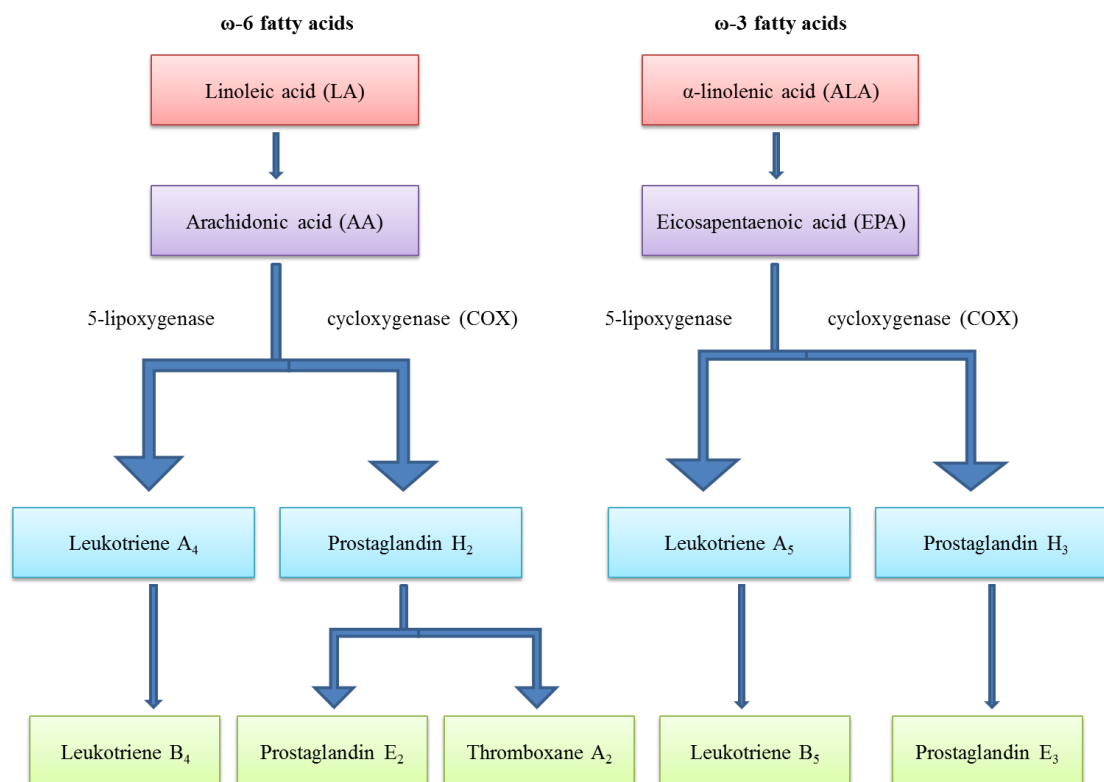


FIGURE 2. Fatty acid metabolism. Eicosapentaenoic acid is metabolized by cyclooxygenase to prostaglandins, prostacyclin, and thromboxanes (PGE₃, PGI₃, and TX₃) by displacing more active analogues of arachidonic acid (PGE₂, PGI₂, and TX₂). Likewise, LTA₅ and LTB₅ leukotrienes are produced by lipoxygenase from EPA, as compared to LTA₄ and LTB₄, synthesized from arachidonic acid.

ing cascades. Long chain fatty acids are involved in the metabolism of sugars and lipids and the activation of cell growth and differentiation. Fatty acid metabolism disorders are associated with certain diseases, e.g., cancer, inflammation, hypertension, and diabetes. Therefore, a detailed understanding of the molecular mechanisms of gene expression regulation, with the participation of specific fatty acids will allow, in the near future, more effective prevention and treatment of many diseases conditioned by disturbances in fatty acid normal biological functioning within the cell [13, 14].

However, an excessive consumption of polyunsaturated fatty acid promotes the increase in the concentration of highly reactive free radicals formed during fatty acid oxidation. This may increase the risk of the DNA structure damage and carcinogenesis,

especially when the concentration of the antioxidants is insufficient. From the consumer point of view, the unfavorable characteristics of polyunsaturated fatty acids are their unpleasant taste and odor.

3. UFA INFLUENCE ON OXIDATIVE STRESS PARAMETERS IN NORMAL AND CANCER CELLS

The influence of unsaturated fatty acids on human cells at a molecular level depends mainly on fatty acid chemical structure and cell type—they act differently in normal cell and cancer cell. In normal cells, fatty acids act usually as antioxidants; however, in cancer cells, some of them act as prooxidants through a variety of molecular mechanisms.

Fatty acids are highly energetic compounds that may influence reactive oxygen species (ROS) metabolism in many different ways. As a result of fatty acid catabolism in mitochondrion (β -oxidation and acetyl CoA degradation through the tricarboxylic acid cycle), reducing agents for redox reactions are produced. An increase in H_2O_2 formation is connected with an increase in electron efflux through the electron transport chain [15]. However, fatty acids may reduce H_2O_2 formation in mitochondrion through uncoupling proteins and adenine nucleotide translocase activation [16]. The studies of Duval et al. revealed that fatty acids reinforce antioxidant defense mechanisms against mitochondrial oxidative stress through epidermal growth factor receptor (EGFR)-dependent glutathione peroxidase (GPx) activation [17]. It has been confirmed that the activity of GPx within the cells is regulated by various physiological or pathological factors. It can be decreased by oxidative stress, selenium deficiency, adduct formation through glycation or lipoxidation, and increased by ischemia, hypertension, traumatic injury, laminar shear stress, endotoxin, obesity, and physical training. The expression of GPx gene is partially stimulated by ROS and mediated by nuclear factor- κ B (NF- κ B). But, Duval et al. have suggested that fatty acids positively influence GPx activity by signaling-dependent regulation of enzyme activity and not by gene induction [17]. It is due to the fact that GPx activity is blocked by tyrosine kinase inhibitors. Many various signaling pathways are activated by fatty acids, such as protein kinase C, phosphoinositide 3-kinase, mitogen-activated protein kinase, and EGFR. It is possible that under the influence of unsaturated fatty acids, GPx, glutathione reductase (GR), and catalase (CAT) become activated. Protein kinases activation pathway initiates signal cascade which causes an increase in antioxidative enzymes activity. Another factor, which may be responsible for the increase in antioxidative enzyme activity under the influence of unsaturated fatty acids, may be EGFR. EGFR regulates many important cell processes, such as cell migration, proliferation, and differentiation. It is probable that unsaturated fatty acids use EGFR-mediated signal transduction pathway for the activation of many metabolic functions in human cells. EGFR is a transmembrane receptor tyrosine kinase that is shared by several growth factors such as EGF, heparin-binding EGF, tumor necrosis factor- α , amphiregulin, and betacellulin. Its activity is regu-

lated by various nonspecific factors, such as UV irradiation, H_2O_2 , oxidized lipoproteins, and unsaturated fatty acids and their oxidation derivatives. EGFR dimerization, autophosphorylation of its own tyrosine residue, and stimulation of its intrinsic tyrosine kinase occur after binding of a ligand [18]. Binding sites for SH2 domains of adaptors or enzymatic proteins including phospholipase $Cy1$, GTPase-activating protein of $p21^{ras}$ (ras-GAP), SHP2, p85 subunit of phosphatidylinositol 3-kinase SHC, Nck, c-cbl, GRB2-Sos are phosphotyrosines of the C-terminal domain of EGFR. MAPK activation usually occurs through kinase cascade and $p21^{ras}$ activation, which is initiated by the activation of GRB2-Sos complex. Growth factors, hormones, cytokines, G protein-coupled receptors, and stress response can also activate MAPK and ERK (extracellular-regulated kinase) [18]. Vacaresse et al. point out that unsaturated fatty acids may activate EGFR through induction of EGFR autophosphorylation and subsequent MAPK activation. They also consider EGFR as a primary target of unsaturated fatty acids. Unsaturated fatty acids enhance the activity of protein kinase C and they also influence the activity of selected kinase cascades, that may trigger the activation of appropriate genes [19]. Activated protein kinase C acts through cell signal cascade as a catalase activator [20]. Other pathways on which catalase activity is increased by polyunsaturated fatty acids also exist. The oxidation of multiple double bonds in PUFAs by ROS is the cause of lipid peroxidation initiation process. Due to this process, a diversity of reactive aldehydes is generated and these aldehydes play an important role in modulating cell metabolism. One of these aldehydes is 4-hydroxynonenal (4-HNE) which influences cellular response to stress, resulting in an increase in the activity of antioxidant enzymes, such as catalase [21]. Considering the data obtained by Andrisic et al. in transgenic yeast, unsaturated fatty acids may cause metabolic changes leading to adaptation to oxidative stress, including an increase in catalase activity [22].

Unsaturated fatty acids influence also GSH/GSSG metabolism within normal, non-cancerous cells. Arab K. et al. have demonstrated that linoleic acid significantly induces GSH biosynthesis in fibroblasts, without upsetting redox balance in cells and without any induction of excess of lipid peroxidation [23]. It enhances the activity of enzymes connected with GSH metabolism, e.g., glutathione reductase, gluta-

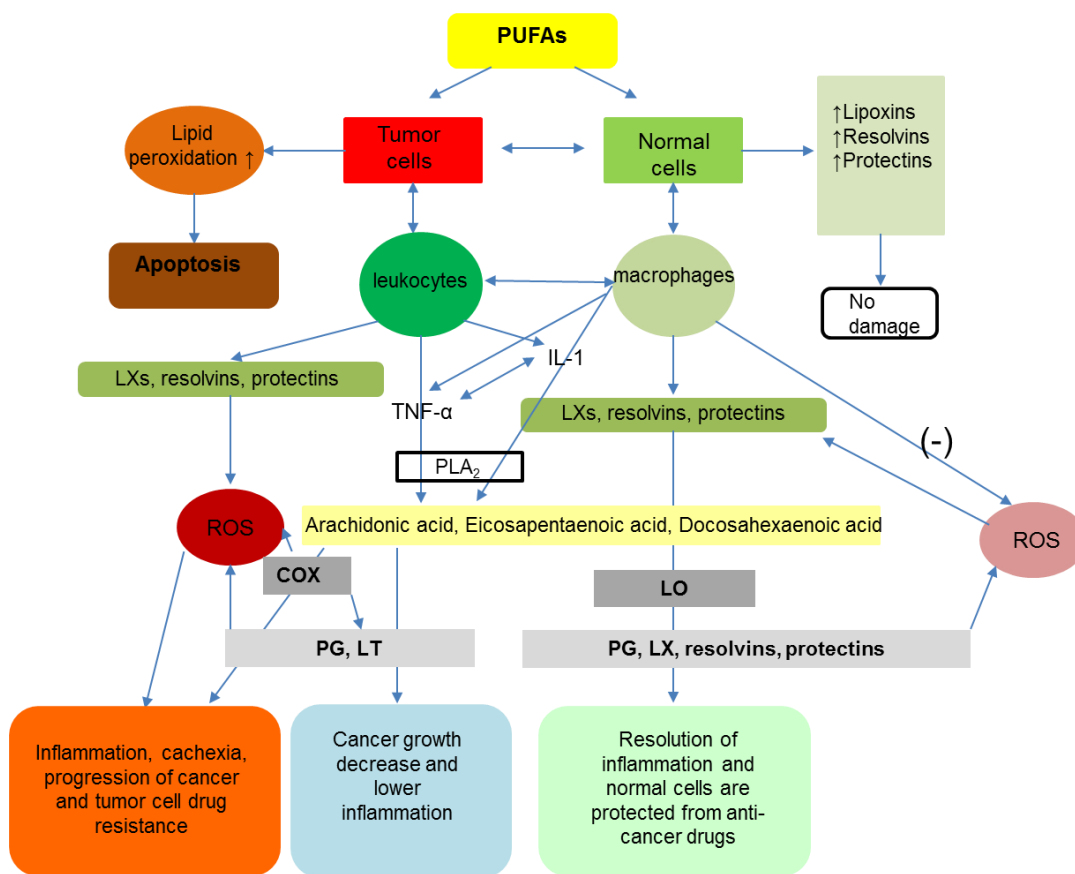


FIGURE 3. A variety of PUFA's metabolic pathways in normal and tumor cells (according to Ref. [32]). The exposure of normal cells to anticancer drugs and/or other external harmful factors such as irradiation results in an increased ROS production. As a result of this, normal cells through an enhanced activity of phospholipase A₂ synthesize from PUFAs lipoxins, resolvins, and protectins. Leucocytes and macrophages produce large amounts of IL-1 and TNF- α , which subsequently generate ROS and cause inflammation. In normal cells high amounts of lipoxins, resolvins, and protectins protect cell from apoptosis and cause no damage. However, in tumor cells leucocytes and macrophages through IL-1 and TNF- α synthesize ROS that lead to inflammation. Cancer cells supplemented with PUFAs generate free radicals, and show higher level of lipid peroxidation and apoptosis. In summary, exposure of normal cells to PUFAs results in the production of cytoprotective molecules, while exposure of cancer cells to PUFAs causes oxidative stress.

thione S-transferase, and γ -glutamylcysteinyl ligase. In normal, non-cancerous cells fatty acids stimulate an increase in GSH content, which subsequently can be connected with the decrease in lipid peroxidation and membrane protein oxidation, because GSH plays an important role in maintaining protein thiol groups in a reduced form.

Induction of cancer cell death induction is the most important factor in the therapy of cancer. Literature

data indicate that selected unsaturated fatty acids are effective anticancer agents, because they induce apoptosis and enhance the cancer cell's sensitivity to drugs, without influencing normal cells. The induction of apoptosis occurs by the increase of oxidative stress parameters. Anticancer activity of fatty acids depends mainly on their structure. Several studies indicate that ω -3 fatty acids act as anticancer agents; however, ω -6 fatty acids are pro-cancerous [24–26].

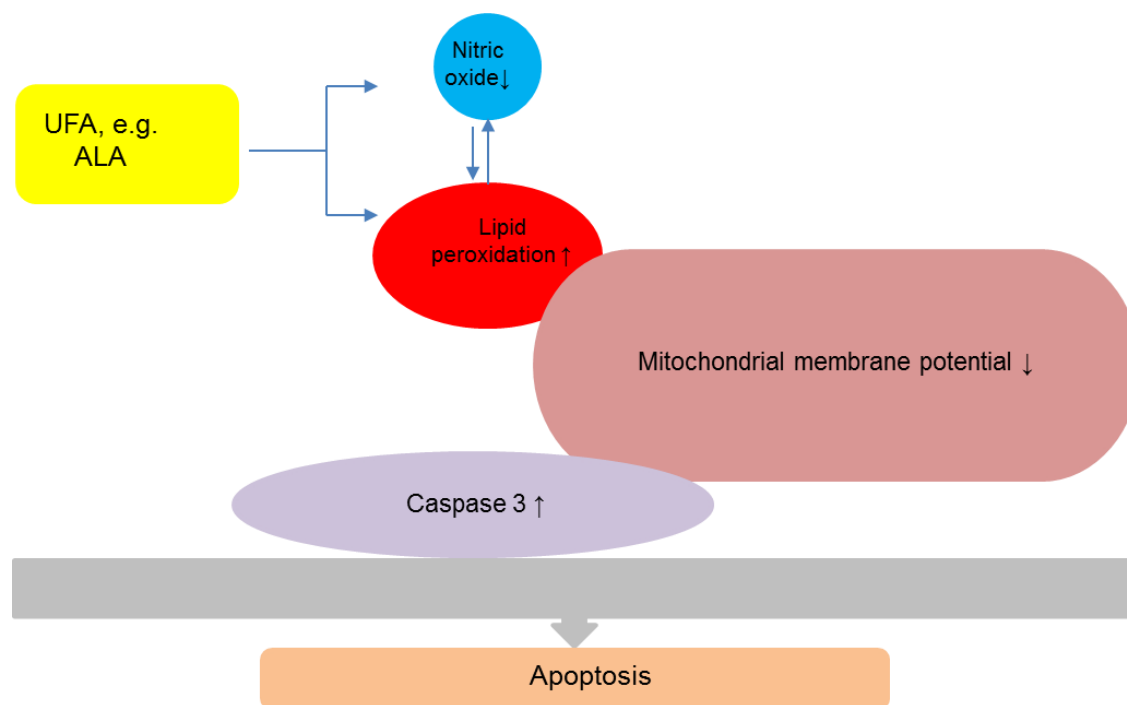


FIGURE 4. A possible mode of ALA activity in cancer cells (according to Ref. [34]). UFAs reduce nitric oxide level and increase lipid peroxidation in cancer cells. The increased lipid peroxidation in the presence of UFAs causes a decrease in nitric oxide resulting in mitochondrial membrane potential disruption and caspase 3 activation leading to apoptosis.

According to Chajes et al. the addition of PUFAs to cultured breast cancer cells causes a significant increase in the formation of conjugated dienes and lipid hydroperoxides in the cellular lipids, therefore exhibiting a tumor growth-suppressing activity [27]. The hypothesis regarding lipid hydroperoxide and cytotoxic influence of gamma-linoleic acid (GLA, omega-6 fatty acid) on human breast cancer cells has also been suggested by Gonzalez et al. [28]. An increase in cancer cell death in response to GLA connected with accelerated lipid peroxidation was observed by Takeda et al. [29]. Chajes et al. showed an inhibitory effect of ALA (alpha-linoleic acid) on the proliferation of breast cancer cells probably due, at least in part, to the formation of lipid peroxidation products. This may result from the fact that unsaturated fatty acids are metabolized by normal and tumor cells in different ways. In tumor cells treated with GLA, a significant increase in free radicals and lipid peroxides was observed, comparing to normal

cells (e.g., fibroblasts) or untreated cancer cells [30]. These results suggest that free radicals and lipid peroxides are involved in tumoricidal activity of unsaturated fatty acids and this activity varies depending on the cell type that is being tested. PUFAs produce different types of precursors, depending on cell type, with cytotoxic or cytoprotective properties. For example, as it was mentioned above, hydroperoxides formed by lipoxygenases from linoleate, linolenate, or AA are highly cytotoxic and proapoptotic in tumor cells. However, in normal cells lipoxins, resolvins, and protectins have an anti-inflammatory activity and cytoprotective properties. Observed drug resistance in tumor cells may result from an increased level of synthesis of cytoprotective molecules, such as lipoxins, resolvins, and protectins; however, this statement needs further explanations (Figure 3) [31–33].

According to Deshpande et al. ALA causes increased lipid peroxidation with a simultaneous de-

crease in nitric oxide generation in both breast and cervical cancer cell lines, which subsequently cause a decrease in cell proliferation [34]. Nitric oxide (NO) in tumor cells plays an important role in angiogenesis, cancer progression, and metastasis [35]. Results obtained by Desphane et al. indicate that ALA decreases intracellular level of NO in both breast and cervical cancer cell lines, revealing its antineoplastic potential. An increase in lipid peroxidation followed by a decrease in cell proliferation is probably also connected with changes in NO level within cancer cells. A significantly lower amount of NO in both types of cancer cell lines may be partially due to NO suppression by peroxidized products of ALA. A noticeable relationship between decreased NO levels and increased lipid peroxidation has been reported in the literature [36]. Furthermore, it should be also noticed that a high content of lipid peroxidation products under the influence of ALA results in a decrease in NO causing a disruption of the mitochondrial membrane potential and caspase 3 activation, resulting in an apoptosis process (Figure 4). Taken together, the above described data imply that ALA affects the growth and development of breast and cervical cancer cells through regulation of the level of oxidative stress parameters such as lipid peroxidation and NO generation [34].

Recently, Serinis et al. analyzed molecular targets for ω -3 PUFAs in colon inflammation and cancer. The importance of PUFAs in malignancy, whose origin is connected with the continuous inflammation was highlighted. It was suggested that ω -3 PUFAs and their oxidative metabolites could be considered as potential anticancer and anti-inflammatory agents, especially in the case of large bowel where orally administrated compounds are of major importance. During the inflammatory response analyzed, fatty acids target the epigenetic regulation of specific gene expression and alter M2 macrophage polarization. The mechanisms presented by Serinis et al. need to be further explained; however, they constitute an important contribution to unsaturated fatty acid studies [37]. It should be also mentioned that ethanolamide-derivatives of PUFAs, such as docosahexaenoyl ethanolamide (DHEA) and N-arachidonoyl-L-alanine (NALA), are proved to be potential anti-cancer agents, because of their anti-proliferative effects mediated in a cannabinoid receptor-independent manner. Park et al. observed an increase in ROS generation induced by the 5-lipoxygenase (5-LOX) pathway and

a decrease of phosphorylated Akt, in head and neck squamous cell carcinoma (HNSCC) cell lines treated with DHEA and NALA [38].

4. CONCLUSIONS

Unsaturated fatty acids play an important role in the normal growth and development of various cells and tissues. Depending on the cell type, whether it is normal or cancerous, and on their chemical structure (ω -3 or ω -6 fatty acids), they act as antioxidants or prooxidants. Recent studies, described in this review, have highlighted selected fatty acids as possible anti-cancer agents, because they induce apoptosis in cancer cells without harming normal cells. By inducing changes in oxidative stress parameters, they also enhance the drug sensitivity of cancer cells, but not normal cells. Therefore, cautious unsaturated fatty acid treatment or supplementation may be beneficial for the treatment of cancer as well as other disorders, especially cardiovascular diseases.

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