European Journal of Pharmacology 871 (2020) 172937

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Full length article

Anticancer activities of fatty acids and their heterocyclic derivatives

Michał Jóźwiak[a], Anna Filipowska[b], Ferdinando Fiorino[c], Marta Struga[a,*]

[a] Chair and Department of Biochemistry, Medical University of Warsaw, Warsaw, Poland
[b] Department of Biosensors and Processing of Biomedical Signals, Silesian University of Technology, Zabrze, Poland
[c] Dipartimento di Farmacia Universita di Napoli "Federico II", Naples, Italy

ARTICLE INFO

Keywords:
Fatty acids
Fatty acid metabolism
Heterocyclic compounds
Hybrid molecules
Anticancer activity
Cytotoxic drugs

ABSTRACT

Traditional chemotherapy relies on the premise that rapidly proliferating cancer cells are more likely to be killed by a cytotoxic agent, but in reality, the long-standing problem of chemotherapy is the lack of tumor-specific treatments. Apart from the impact on tumor cells, the drugs' major limitation is their severe adverse side effects on normal cells and tissues. Nutritional and epidemiological studies have indicated that cancer progression is correlated with the consumption of fatty acids, but the exact mechanisms still remain unknown.

In the first part of our review, we discussed the beneficial effects of free fatty acids (saturated and unsaturated) on the progress of carcinogenesis in different tumor cell lines. We presented various mechanisms proposed in the literature, which explain the possible impact on the cells metabolism.

The second part describes modifications of different fatty acids with existing anticancer drugs and heterocyclic moieties by condensation reactions. Such conjugations increased the tissue selectivity and made chemotherapy potentially more effective and less toxic in *in vivo* and *in vitro* studies.

This fatty acid modifications, which change the activity of compounds, their uptake selectivity and alter drug delivery methods, may be the key to unlocking true medical potential of fatty acids.

1. Introduction

Fatty acids (FA) are monocarboxylic acids containing a long hydrocarbon chain. They are formed by the cleavage of fats and oils derived from natural sources such as triacylglycerols or phospholipids and, in general, can be either saturated or unsaturated. The common division of fatty acids is based on the length of their aliphatic tail: short-chain fatty acids (SCFA) are fatty acids with aliphatic tails of five or fewer carbons, medium-chain fatty acids (MCFA) contain 6-12 carbon atoms, long-chain fatty acids (LCFA) 14–20. Fatty acids which have 22 and more carbon atoms are called very long-chain fatty acids (VLFA) and are very common components of brain lipids (Beermann et al., 2003; Denise, 2017). Most naturally occurring fatty acids have an unbranched chain of an even number of carbon atoms, from 14 to 24 (Moss, Smith and D., 1995) (Table 1) (see Table 2).

Polyunsaturated fatty acids (PUFAs) are essential fatty acids (EFAs) because humans cannot desaturate the n-3 or the n-6 bond and therefore they must be obtained only from dietary sources (Tapiero et al., 2002). The difference between Omega-3 (n-3) and Omega-6 (n-6) fatty acids is the position of the first double bond in the hydrocarbon chain, either three or six carbons from the methyl end of the chain, respectively. Most n-6 fatty acid is consumed as linoleic acid (LA) mostly from vegetable oils, but some arachidonic acid (AA) is also obtained from meats (Li et al., 1998). n-3 fatty acids may also be found in vegetable oils as α-linolenic acid (LNA) and in larger amounts in fish as eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA) (Sprague et al., 2016). Both n-3 and n-6 fatty acids can be incorporated into cell membrane phospholipids resulting in disruption of membrane structure and fluidity (Takahashi et al., 1992). They also may be desaturated and elongated to fatty acids of the same series (De Gómez Dumm and Brenner, 1975), but cannot be interconverted.

Reports show that n-3 PUFAs are necessary for proper maturation of tissues and their normal physiological functioning (Clandinin et al., 1989). They also have beneficial effects on human health, such as lowering plasma triglyceride level (Harris and Bulchandani, 2006), reducing the risk of cardiovascular diseases (Casula et al., 2013; Harris et al., 2013) as well as Alzheimer's dementia (Kyle et al., 1999). PUFAs are precursors of eicosanoids, which are potent lipid mediators playing an important role in the regulation of inflammation (Alexander, 1998). Eicosanoids derived from n-3 PUFAs (e.g., EPA and DHA) have anti-inflammatory properties, whereas n-6 PUFAs derived eicosanoids (e.g., from AA) act as proinflammatory and immunoactive agents (Wall et al., 2010). They also show neuroprotective properties (Bi et al., 2019). The effect of FA on the inhibition of growth of different types of pathogens

* Corresponding author. Chair and Department of Biochemistry Medical University of Warsaw, 02-097, Warszawa, Poland.
E-mail address: marta.struga@wum.edu.pl (M. Struga).

https://doi.org/10.1016/j.ejphar.2020.172937
Received 23 August 2019; Received in revised form 8 January 2020; Accepted 13 January 2020
Available online 17 January 2020
0014-2999/

Table 1
The chemical structure of major saturated and unsaturated fatty acids.

Saturated fatty acids	
4:0 Butyric	$CH_3(CH_2)_2COOH$
5:0 Valeric	$CH_3(CH_2)_3COOH$
6:0 Caproic	$CH_3(CH_2)_4COOH$
7:0 Enanthic	$CH_3(CH_2)_5COOH$
8:0 Caprylic	$CH_3(CH_2)_6COOH$
10:0 Capric	$CH_3(CH_2)_8COOH$
12:0 Lauric	$CH_3(CH_2)_{10}COOH$
14:0 Myristic	$CH_3(CH_2)_{12}COOH$
16:0 Palmitic (PA)	$CH_3(CH_2)_{14}COOH$
17:0 Margaric	$CH_3(CH_2)_{15}COOH$
18:0 Stearic (SA)	$CH_3(CH_2)_{16}COOH$
Unsaturated fatty acids	
6:2 (2*E*, 4*E*) Sorbic	$CH_3CH{=}CHCH{=}CHCOOH$
10:1 (9*Z*) Caproleic	$CH_2{=}CH(CH_2)_7COOH$
11:1 (10*Z*) Undecylenic	$CH_2{=}CH(CH_2)_8COOH$
18:1 (9*Z*) Oleic (OA)	$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$
18:1 (9*E*) Elaidic (EA)	$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$
18:2 (9*Z*, 12*Z*) Linoleic (LA)	$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$
18:3 (9*Z*, 12*Z*, 15*Z*) α-Linolenic (LNA)	$CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$
18:3 (6*Z*, 9*Z*, 12*Z*) γ-Linolenic (GLA)	$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_4COOH$
20:3 (8*Z*, 11*Z*, 14*Z*) Dihomo-γ-linolenic acid (DGLA)	$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_6COOH$
20:4 (5*Z*, 8*Z*, 11*Z*, 14*Z*) Arachidonic (AA)	$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_3COOH$
20:5 (5*Z*, 8*Z*, 11*Z*, 14*Z*, 17*Z*) Eicosapentaenoic (EPA)	$CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_3COOH$
22:6 (4*Z*, 7*Z*, 10*Z*, 13*Z*, 16*Z*, 19*Z*) Docosahexaenoic (DHA)	$CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_2COOH$

is well known. Unmodified FA show antibacterial (Zheng et al., 2005; Urbanek et al., 2012; Bravo-santano et al., 2019) and antifungal (Liu et al., 2008; Pohl et al., 2011) activities. n-3 PUFAs are also used in chemotherapies. The key mechanism proposed for the chemosensitization or reversing multidrug chemoresistance is based on the n-3 PUFA's impact on the architecture of the cell membrane and their effect on drug uptake/efflux and transporter activity (Guffy et al., 1984) (Zijlstra et al., 1987). Furthermore, their consumption can slow the growth of tumors, by inducing the apoptotic processes in tumor cells (Chamras et al., 2002; Serini et al., 2009) or by inhibiting angiogenesis (Wen et al., 2003; Spencer et al., 2009). They also increase the efficacy of chemotherapeutic drugs and can reduce the chemotherapy or the cancer side effects (Colquhoun and Curi, 1998; Hardman, 2002; Leaver et al., 2002; Siddiqui et al., 2011), at the same time being associated with a high level of safety (Bégin et al., 1985).

FA can be used to produce pharmacologically interesting compounds through simple transformations, as they contain a hydrocarbon chain and a reactive carboxylic group. The commonly used strategy is to conjugate the lipid's carboxyl end with a hydroxyl or amine group of the drug to form a stable ester or amide linkage (Irby et al., 2017). To form lipid-drug conjugates pH sensitive conjugation hydrazone bonds are used, which decomposes efficiently at a lower pH (Wang et al., 2006). These modifications are used to increase the lipophilicity of hydrophilic drugs and to enhance their compatibility with the lipophilic cell membranes and components of drug delivery carriers (Lambert, 2000; Shao et al., 2013; Li et al., 2016). Such fatty acid-drug conjugates in the form of emulsions or micelles demonstrate several advantages including improved oral bioavailability (Borkar et al., 2015; Trevaskis et al., 2015; Bala et al., 2016) and reduced toxicity of anticancer drugs (Bradley et al., 2001), as tumor cells express enhanced uptake of natural FA as their source of energy and the supply of biochemical precursors in various processes (Sauer and Dauchy, 1992). Lipophilic prodrugs are also used to achieve extended drug release as they take part in lipid metabolism pathways and therefore can avoid hydrolysis and exhibit increased interactions with cell membranes (Chue and Chue, 2012; Tao et al., 2019). Furthermore, specific membrane proteins which activity can be modulated by changes in membrane lipid composition, emerged as potential cancer treatment therapeutic targets. Recently, a novel approach, defined as “membrane lipid therapy” emerged, and is based on the hypothesis that the use of specific lipids may alter cancer membrane composition and structure. This can disassemble the lipid raft architecture and alter the localization and activity of membrane-associated proteins, disrupting down-stream pathways that are crucial for tumor cell growth (Escribá, 2017).

Combination of FA with biologically active compounds results in novel hybrid molecules with a broad spectrum of enhanced biological activities, including antibacterial and antifungal (Kabara et al., 1972; Mod et al., 1975; Rauf and Parveen, 2005; Rauf et al., 2007) activities. FA derivatives are also associated with diverse biological properties such as antiinflammatory (Khaddaj-Mallat et al., 2016; Akagi et al., 2018) or antioxidant (Viklund et al., 2003; Akanbi et al., 2019). Literature reports revealed that a variety of modified fatty acids are promising molecules in the treatment of cancers (Morin et al., 2013; Siena et al., 2018).

Traditional chemotherapy relies on the premise that rapidly proliferating cancer cells are more likely to be killed by a cytotoxic agent, but in the reality, the long-standing problem of chemotherapy is the lack of tumor-specific treatments. Apart from the impact on tumor cells, the drugs’ major limitation is their severe adverse side effects on normal cells and tissues. This leads to high systemic toxicity and prevents the use of high drug doses that are required for effective killing of cancer cells, thus limiting antitumor efficacy (Moncevičiute-Eringiene, 2005). Therefore, exploring various drug delivery protocols and systems is a promising approach to improve the therapeutic efficacy of chemotherapy (Wang et al., 2012).

Tumor-targeting conjugates bearing cytotoxic agents can be classified into several groups based on the type of cancer recognition moieties, of which FA hybrid prodrugs have been receiving increased attention for their effectiveness in cancer chemotherapy. This review describes the utilization of various FA in tumor-targeting drugs as tumor-targeting moieties.

2. Cytostatic activity of saturated and unsaturated fatty acids

The influence of FA on carcinogenesis may occur through various mechanisms, so it is crucial to understand the role of FA in these processes. Although mostly PUFAs are recognized as anticancer dietary components, also MCFAs have been reported to perform a therapeutic

Table 2
Illustrative overview of fatty acids and their conjugates with their antitumor activity against different cell lines.

Compound	Targeted cell line	References
capric, caprylic, caproic	HTC-116, A-431, MDA-MB-231	Narayanan et al. (2015)
linoleic	KPL-1	Senzaki et al. (1998)
linoleic	Caco-2	Dommels et al. (2003)
linoleic	BT-474, A-549	Mouradian et al. (2014)
linoleic	MAC16	Hudson et al. (1993)
linoleic	DU145	Connolly et al. (1997)
γ-linolenic	GOTO, SK-N-DZ, NKP, NCG	Fujiwara et al. (1986)
γ-linolenic	LLC-WRC256	Colquhoun and Schumacher (2001)
γ-linolenic	ZR-75-1, A-549, PC-3, CCD-41SK	Bégin et al. (1985)
γ-linolenic	36B10	Vartakl et al. (1998)
docosahexaenoic	MHCC97L, SK-Mel-110	Albino et al. (2000)
docosahexaenoic	HT29	Chen and Istfan (2000)
docosahexaenoic	LNCaP, DU145, PC-3	Narayanan et al. (2005)
eicosapentaenoic	ACL-15	Iwamoto et al. (1998)
docosahexaenoic, eicosapentaenoic	Caco-2, HT-29, HCT116, LoVo, SW480	Giros et al. (2009)
docosahexaenoic, eicosapentaenoic	SW620	Bathen et al. (2008)
docosahexaenoic, eicosapentaenoic	LA-N-1	So et al. (2015)
DOX-caprylic	MSV-M	Arcamone et al. (1974)
DOX-lauric	CCRF-CEM, MDA-MB-468, SK-OV-3, HT-29	Chhikara et al. (2011)
DOX-α-linolenic	MCF-7, MDA-MB-231, HepG2	Huan et al. (2009)
DOX-α-linolenic	HepG2, MCF-7, MDA-231	Liang et al. (2014)
DOX-margaric/oleic/linoleic/α-linolenic	HL-60, 518A2, MCF-7/Topo, KB-V1/Vbl	Effenberger et al. (2010)
DOX-docosahexaenoic	L1210, B16	Wang et al. (2006)
PTX-oleic	HeLa	Lundberg et al. (2003)
PTX-conjugated linolenic	C6	Xi Yu et al. (2010)
PTX-docosahexaenoic	M109, HT-29	Bradley et al. (2001)
PTX-docosahexaenoic/linoleic/α-linolenic	A121, DLD-1	Kuznetsova et al. (2006)
ara-C-myristic	CCRF-CEM	Chhikara et al. (2010)
ara-C-capric, ara-C-myristic, ara-C-stearic	HL-60, HeLa	Liu et al. (2009)
ara-C-elaidic	L1210, BCLO, L4A6, Bara-C	(A M Bergman et al., 2004)
GEM-elaidic	CP-4126	Bergman et al. (2011)
GEM-conjugated linolenic	MCF-7	Tao et al. (2012)
GEM-docosahexaenoic	MCF-7, MB-MDA-231, HepG2, Bel-7402, A549, SCG-7901, H22	Li et al. (2014)
CP-capric	PC-3, U373-MG, LoVo, A549, MCF-7	Azéma et al. (2009)
CP-sorbic/oleic/elaidic	SW480, SW620, PC3, HaCaT	Chrzanowska et al. (2020)
1,3,4-oxadiazol-2-thione-caproleic, 1,2,4-triazol-3-thione-caproleic, 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine-caproleic	Hep3B, MCF-7, HeLa, PBMC	(A. Ahmad et al., 2017)
piperazine-(C10–C24) saturated FA	PC-3, NUGC-3, MDA-MB-231, ACHN, HTC-15, NCI–H23	Yang et al. (2011)
1,3,4-oxadiazol-2-thiol-γ-linolenic/stearic, 1,2,4-triazol-3-thiol-γ-linolenic/stearic	A549	Jubie et al. (2012)
pyrrolidine-oleic/linoleic	U251, MCF-7, OVCAR-3, NCI-ADR/RES, 786-0, NCI–H460, PC-3, HaCaT	Santos et al. (2015)
1-ethyl-6-fluoro-7-(fatty amido)-1,4-dihydro-4-oxoquinoline-3-carboxylate-(C6,C8,C12,C15,C16,C18) saturated FA/undecylenic/oleic	DU145, A549, SKOV3, MCF-7, IMR-90	Venepally et al. (2016)
dimethoxy tryptamine-(C4,C6,C8,C12,C14,C16,C18) saturated FA/undecylenic/oleic	A549, PC-3, MDA-MB-231, HepG2, HUVEC	Venepally et al. (2017)
alloxanthoxyletin-(C3,C6,C8,C12,C14,C16,C8) saturated FA/oleic/α-linolenic/conjugated linolenic/docosahexaenoic	HTB-140, A549, HaCaT	Jóźwiak et al. (2019)

role.

The medicinal value of goat milk is primarily attributed to fatty acids, which constitute about 15% of the total fatty acid content, namely capric (C10:0), caprylic (C8:0) and caproic (C6:0) acids (Pal et al., 2011; Bhattarai, 2014). Yamasaki et al. showed that 3 mM caprylic acid failed to inhibit migration and invasion of bladder cancer cells, despite the reduce of cell proliferation (Yamasaki et al., 2014). Additionally, Jansen et al. reported that intake of saturated fatty acids contained in dairy products, including caprylic, capric and caproic acids, were found to increase the risk of pancreatic cancer (Jansen et al., 2014).

Although previously mentioned papers indicate the lack of anticancerous properties of caprylic acid, Narayanan et al. *in vitro* studies confirm, that capric, caprylic and caproic acids inhibit the proliferation of human colorectal carcinoma (HTC-116), human skin epidermoid carcinoma (A-431) and human mammary gland adenocarcinoma (MDA-MB-231), cells exerting significant anticancer activity (Narayanan et al., 2015).

A number of studies have shown that intake of dietary n-3 PUFAs may play a role in the prevention of the development of different types of cancers and have described the underlying mechanisms of their action (Sauer et al., 2000; Gerber, 2012). A broad spectrum of mechanisms concerning cell's metabolism or chemosensitization have been proposed and investigated recently, including the alteration in gene regulation or cell signalling (Baracos et al., 2004; Allam-Ndoul et al., 2017), modulation of cellular proliferation (Guo et al., 2017) and differentiation (Bianchini et al., 2012) or induction of apoptosis (Sun et al., 2017). PUFAs can also increase the drug transport across the cell membrane, altering membrane fluidity by incorporation phospholipids into the cell membrane (Corsetto et al., 2012). They also take part in the

generation of reactive oxygen species (ROS) (Zhu et al., 2018).

A survey of the literature reveals that DHA can trigger cell cycle arrest in metastatic hepatocellular carcinoma (MHCC97L) cells (Yee-Ki Lee et al., 2010) and in metastatic melanoma (SK-Mel-110) cells (Albino et al., 2000). The n-3 fatty acids DHA and EPA have an cytotoxic effect on colorectal cancer (cancer cell lines: Caco-2, HT-29, HCT116, LoVo, SW480 and SW620), at least partly due to their proapoptotic activity (Bathen et al., 2008; Giros et al., 2009). Chen & Istfan suggest that the mechanism is based on down-regulation of one of cell the death regulating factors, namely Bcl-2, which is in part mediated by increased lipid peroxidation and was shown in colonic HT-29 cancer cells, (Chen and Istfan, 2000). In addition, PUFAs stimulate generation of reactive oxygen species (ROS) which activates caspases and the cleavage of Bid, a death agonist member of the Bcl-2 family. This leads to the release of cytochrome c from mitochondria into the cytosol and ultimately activates apoptosis (Das, 2004). Similar caspase-dependent apoptosis induced by DHA was described by Serini et al. in metastatic melanoma (WM266-4) cells (Serini et al., 2012).

So et al. concluded in their studies that DHA and EPA exhibit a growth-inhibitory effect on human neuroblastoma cells (LA-N-1) by triggering cell cycle arrest at the G_0/G_1 phase and activation of the intrinsic-pathway induced apoptosis. In addition, DHA and EPA exerted little, if any, direct cytotoxic effect on normal murine and human cell lines (So et al., 2015).

Zheng et al. performed a comprehensive meta-analysis of 21 independent prospective cohort studies and found that dietary intake of marine n-3 PUFA was associated with a 14% risk reduction of breast cancer (Zheng et al., 2013). Other studies also confirmed that n-3 PUFA intake is linked with a reduced risk of breast cancer cell as shown in *in vivo* studies with breast cancer cell lines (MCF-7, KPL-1, MDA-MB-231) or in a case-control study (Kim et al., 2009; Liu and Ma, 2014). Similar effects of n-3 PUFA dietary supplementation on the development of tumor were observed in regarding to prostate gland cancer (Koralek et al., 2006; Aucoin et al., 2017) and pancreatic cancer (Wigmore et al., 1996; Hidaka et al., 2015).

In addition to the antiproliferative effect on tumor growth, n-3 PUFAs may also suppress the angiogenesis process. The inhibitory effect was investigated in human umbilical vein endothelial cells (HUVEC), as described by Szymczak et al. (Szymczak et al., 2008) and in a breast cancer cell line (MDA-MB-231) (Rose and Connolly, 1999). The prevention of the formation of new blood vessels not only inhibits tumor growth but also shows antimetastatic effects. The results of investigations by Iwamoto et al. showed that the number and size of liver metastatic foci of colon carcinoma cells (ACL-15) in rats were significantly inhibited in the EPA-treated group (Iwamoto et al., 1998). *In vivo* mice model studies conducted by Senzaki et al. with human breast carcinoma cells (KPL-1) resulted in lymph node metastasis in the LA and standard diet groups, but not in the PA or EPA groups (Senzaki et al., 1998). The mechanisms by which n-3 PUFA inhibits these processes are complex and not well understood, but may involve NO synthesis (Narayanan et al., 2003), the synthesis of bioactive metabolites from n-3 PUFA (Tsuji et al., 2003), or lipoxygenase-derived metabolites (Pasqualini et al., 2003).

Omega-3 PUFAs can affect cell's metabolism playing a role in signal transduction by acting as ligand of certain nuclear receptors (Calder, 2002). They may also compete with in the cyclooxygenase-2 pathway with the synthesis of eicosanoids or alter the cellular oxidative status by enhancing lipid peroxidation, which results in increased cancer cells killing (Bégin et al., 1988; Marks et al., 2000; Kokura et al., 2002). Narayan et al. suggested that DHA modulated the levels of cyclooxygenase-2 (COX-2), nuclear factor-kappaB (NF-kappaBp65), and nuclear receptors, such as PPARgamma and retinoid X receptors. The altered expression of the above molecular parameters inhibited the cell growth and induced apoptosis in three tested prostate cancer cell lines (LNCaP, DU145 and PC-3) (Narayanan et al., 2005).

In 2005, Menendez et al. described an enhancing effect of n-3 LCPUFAs on the of chemosensitivity of cancer cells by increasing peroxidative processes and regulating oncoprotein expression. The most potent PUFA that increased paclitaxel toxicity in breast cancer cell lines (MDA-MB-231), was γ-linolenic acid (GLA), followed by LNA, EPA, and DHA. The linoleic acid (LA) had no effects. Moreover, the exposure of other mammary gland carcinoma cells (BT-474 or SK-BR-3) to DHA for 24 h significantly reduced p185Her/neu oncoprotein expression compared to untreated cells (Menendez et al., 2005). Also Vibet et. al. demonstrated the decrease in glutathione peroxidase, the major antioxidant enzyme, by DHA sensitization of breast cancer MDA-MB-231 cells to doxorubicin. The proposed mechanism suggested a post-transcriptional DHA effect due to decreased protein but not mRNA level in the cell. However, the MCF-7 breast cancer cell line did not respond to DHA (Vibet et al., 2008).

In recent years, the diets' content has significantly increased in n-6 PUFAs. Excessive amounts of n-6 PUFA intake and a very high n-6/n-3 ratio (16:1 or higher), have been suggested to promote the development of many diseases such as cardiovascular diseases, autoimmune diseases and some types of cancer, whereas a low n-6/n-3 ratio have been shown to exert suppressive effects (Simopoulos, 2002). However, Williams et al. examined the association between n-3 and n-6 PUFA and prostate cancer risk. Race-specific analyses resulted in a conclusion that an increasing dietary ratio of n-6/n-3 fatty acids correlated with higher prostate cancer risk among white men, but not black men (Williams et al., 2011). Other *in vivo* and *in vitro* studies results suggest that, unlike n-3, n-6 can accelerate tumorigenesis (Bagga et al., 2002; Yang et al., 2014). In many animal and human studies the high intake of n-6 PUFAs was found to correlate with a high risk of development of different cancers: breast, prostate, and colon cancer. (Pot et al., 2008; Hart et al., 2009; Thiebaut et al., 2009). Therefore the ratio of n-6 to n-3 is suggested to be a predictor for cancer progression. In addition, Marventano et al. stated, after reviewing evidence from human studies of n-3 and n-6 PUFA intake, a general positive effect of n-3 PUFAs intake on tumor inhibition, but suggested that the role of n-6 PUFAs on human health needs to be better assessed in order to clearly identify beneficial or harmful effects (Marventano et al., 2015).

The enhanced carcinogenesis effect of n-6 PUFAs has been attributed to the metabolism and cell signalling properties of arachidonic acid (AA, C20:4 n-6) (Abel et al., 2014). Yarla et al. critically discussed the possible utility of natural products as preventive and therapeutic antitumor agents by targeting the AA pathway, which has been found to have involvement in cancer initiation, promotion and progression. (Yarla et al., 2016). The deregulation or disturbance of AA conversions has been connected to a large number of disorders, indicating the need for tight control over the AA metabolism as an important factor in controlling cellular proliferation and apoptosis, and therefore cancer cell survival (McCarty and DiNicolantonio, 2018). High levels of n-6-derived prostaglandins and/or a high level of COX2 have been reported in many human cancers (Dannenberg et al., 2001). Most results indicate a correlation between COX-catalyzed AA peroxidation and its metabolites, e.g. PGE2, and cancer development. This includes breast (MCF-7, MDA-MB-231) (Li et al., 2013), colon (LS-174T, Caco-2) (Dommels et al., 2003; Habbel et al., 2009), prostate cancer (PC-3) (Yang et al., 2012) and the human cervical carcinoma cell lines (KB-3-1) (Das and Madhavi, 2011). However, the data available do not provide a complete explanation and contain a number of discrepancies. Sakai et al. concluded in their review, based on the revised publications, that AA exposure is not associated with increased breast and prostate cancer risk (Sakai et al., 2012).

Increasing evidence suggests that the n-6 PUFAs, such as linoleic acid (LA), γ-linolenic acid (GLA), and dihomo-γ-linolenic acid (DGLA), can show antitumor effects, and thus may constitute dietary components which prevent cancer development and help in the therapy (Xu and Qian, 2014).

LA stimulates *in vitro* cell proliferation in the human breast cancer cell line (BT-474) and the human lung cancer cell line (A549)

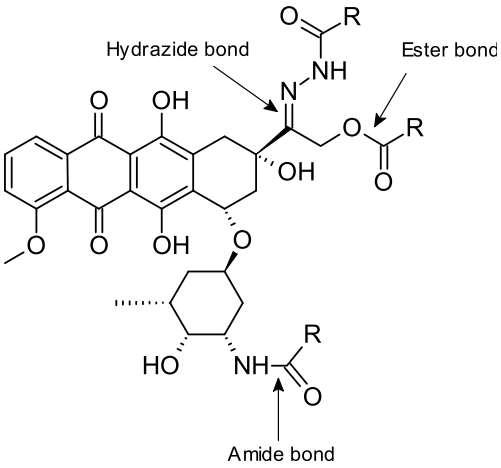

Fig. 1. Molecular structure of doxorubicin conjugates.

(Mouradian et al., 2014) and promotes colon (MAC16) and prostate (DU145) tumor growth and development in animal models (Hudson et al., 1993; Connolly et al., 1997). On the other hand, Dommels et al. concluded that a high dose of LA inhibits proliferation of the colon cancer cell line (Caco-2) (Dommels et al., 2003) and shows a protective effect against cancer development (Horrobin and Ziboh, 1997). Pro- and anticancer properties of LA are due to fact that LA is converted into various n-6 PUFAs in the following way: LA is converted into GLA by Δ-6 desaturase (D6D), followed by a two-carbon chain elongation by elongase to become DGLA. Finally it is de-saturated by Δ-5 desaturase (D5D) to form AA (Xu and Qian, 2014). Therefore, the various effects of LA on cancer growth may derive from a combination of effects of the products of its metabolism.

GLA is also associated with both *in vitro* and *in vivo* anticancer activities. Fujiwara et al. described the antitumor effect of GLA acid on 4 cultured human neuroblastoma cells (GOTO, SK-N-DZ, NKP, NCG) (Fujiwara et al., 1986) and the rat carcinosarcoma cell line (LLC-WRC256) *in vivo* (Colquhoun and Schumacher, 2001). The cytotoxic effect of GLA shows high selectivity towards cancer cells. Cell incubation with GLA caused selective apoptosis in human breast cancer (ZR-75-1), lung cancer (A549), prostatic cancer (PC-3), and astrocytoma (36B10) cell lines without affecting normal cells (Bégin et al., 1985; Vartakl et al., 1998; Das, 2006).

3. Cytostatic activity of fatty acids modified by anticancer drugs or heterocyclic compounds

FA conjugates of cytotoxic agents constitute a rather unexplored group of antitumor agents. Modifications of existing anticancer drugs by conjugating them with a targeting moiety may increase the tissue selectivity and can potentially make chemotherapy more effective and less toxic. Many studies describe the positive impact of saturated and unsaturated fatty acids used to modify different heterocyclic molecules on the compound's tumor cell targeting selectivity and cytotoxic efficacy, showing a decreased cytotoxic effect against normal cell lines at the same time (Liang et al., 2014; Jóźwiak et al., 2019; Mielczarek-Puta et al., 2019; Chrzanowska et al., 2020). In addition, fatty acids enhance the antitumor drugs' effectiveness demonstrated in many *in vivo* and *in vitro* studies (G. Ahmad et al., 2017).

The PUFA component of a drug conjugate can improve the transport of the drug, as it can bind to human serum albumin (HSA) – the primary carrier for PUFAs in the bloodstream – to form an HSA-PUFA conjugated drug complex. The conjugation of drug to PUFAs can increase their affinity to HSA (Desai et al., 2006). This connection solubilizes the hydrophobic drug, lowers the rate of clearance, and enhances the accumulation of the drug conjugate through gp60-mediated transcytosis into the tumor interstitium (Ibrahim et al., 2002; Seitz and Ojima, 2011).

As certain PUFAs are greedily taken up by tumor cells, it is very likely that PUFA-drug conjugates would also be taken up and accumulated by the tumor cells, wherein the connecting linkage is cleaved to release the free drug (Seitz and Ojima, 2011). Data published by Bradley et al. strongly suggest that the ester bond linking DHA to the cytotoxic drug (paclitaxel) is stable in the blood stream, and its slow hydrolysis is responsible for the gradual release of the free drug *in vivo*. Improved drug stability prolongs circulation time, increasing the amount of active substance that reaches the intended target, minimizing side effects and improving the quality of chemotherapy (Bradley et al., 2001). Fracasso et al. conclude, that the slow release of paclitaxel from DHA-paclitaxel conjugate in patients approximates continuous paclitaxel infusion, which may be more active and effective than taxanes therapy (Fracasso et al., 2009).

In this section we discuss examples of fatty acid conjugations with cytotoxic drugs and heterocyclic compounds, which express higher activity in the *in vivo* or *in vitro* testing phase in relation to the activity of the starting compounds.

3.1. Doxorubicin conjugates

Doxorubicin (DOX) is an important antitumor drug that is used in the clinic. It is an agent for therapeutic treatment of leukemia and a variety of other tumors. There are at least three ways in which the structure of doxorubicin can be modified: C-3′ position (by fixing the amide bond in the reaction of the primary amine group NH_2) (Huan et al., 2009; Chhikara et al., 2011; Liang et al., 2014; Piorecka et al., 2017), C-13′ position (by forming a hydrazone linker in the reaction of a carbonyl group C═O) (Wang et al., 2006; Effenberger et al., 2010; Liang et al., 2014) and C-14' position (by forming an ester bond by a hydroxyl group OH) (Fig. 1) (Arcamone et al., 1974).

Meng-lei et al. obtained DOX and LNA conjugates and tested them *in vitro* on three cancer cell lines: human breast cancer (MCF-7, MDA-MB-231) and human liver cancer (HepG2). The calculated IC_{50} (the concentration of active substance needed to inhibit cell growth by 50%) of DOX-LNA against MCF-7 was 4.7 μM, against MDA-MB-231 was 3.1 μM, and for HepG2 – 6.8 μM. DOX used as a reference substance was characterised with higher IC_{50} values for all tested cell lines (MCF-7, MDA-MB-231 HepG2) and was equal to 8.3 μM, 10.2 μM and 14,3 μM, respectively. A decrease in the IC_{50} indicates an increase in drug toxicity, therefore the DOX–LNA conjugate was more cytotoxic than free DOX regarding to tested cancer cells (Huan et al., 2009).

Chhikara et al. synthesized amide bond linked conjugates of DOX and saturated FA containing from 6 to 18 carbon atoms. The antitumor effect of the newly obtained compounds was evaluated *in vitro* in a human leukemia cell line (CCRF-CEM), breast adenocarcinoma (MDA-MB-468), ovarian adenocarcinoma (SK-OV-3), and colon adenocarcinoma (HT-29) cell lines up to 120 h at 1 μM. The results indicated higher antiproliferative activity in colon and ovarian cell lines when compared to breast and leukemia cancer cells. The overall pattern in different cell lines showed that the lauric acid containing derivative was the most effective in *in vitro* studies (Chhikara et al., 2011).

Liang et al., conjugated DOX with either unsaturated LNA or saturated PA by a hydrazone or an amide bond (DOX-hyd-LNA, DOX-ami-LNA, DOX-hyd-PA, and DOX-ami-PA) to increase the therapeutic activity of DOX and to decrease its totoxic effect toward normal tissues. The conclusions were that the cytotoxicity of DOX-hyd-LNA on a liver cancer cell line (HepG2) and breast cancer (MCF-7 and MDA-231) cells was higher compared to that of unmodified DOX and to that of other obtained derivatives. In addition DOX-hyd-LNA exhibited less toxicity *in vitro* and *in vivo*. These results were due to higher DOX-hyd-LNA stability in serum, leading to increased distribution of DOX within tumor tissues, so a greater amount of DOX could be released inside tumor cells (Liang et al., 2014).

Doxorubicin and DHA conjugates (DHA–DOX) were synthesized by Wang et al. using a hydrazide bond. The antitumor activity was then evaluated *in vitro* against leukemia cells (L1210) and *in vivo* in experimental animal models including leukemia (L1210) and melanoma (B16) tumors. The IC_{50} values of DHA–DOX and free DOX in *in vitro* studies were 1.4 μM and 0.15 μM, respectively. In animal tumor models, DHA–DOX was significantly more efficacious than free DOX (Wang et al., 2006).

N-acylhydrazones derived by the synthesis of doxorubicin and saturated (margaric acid), unsaturated (oleic, linoleic, α-linolenic acids) FA were obtained by Effenberger et al.. All compounds were tested for anticancer activity in cells of human leukemia (HL-60), melanoma (518A2), breast (MCF-7/Topo) and cervix (KB–V1/Vbl) carcinomas. The margaric hydrazone was more cytotoxic than unsaturated FA conjugates and even three times more than DOX. In addition, the treatment of HL-60 and 518A2 cells with heptadecanoyl, linolenoyl hydrazones had an impact on the mRNA expression, resulting in the changes of Bax to Bcl-2 ratio, which is a potential molecular marker of cancer tissues and determines the susceptibility of cells to the intrinsic apoptotic pathway triggered by mitochondrial dysfunction (Effenberger et al., 2010; Khodapasand et al., 2015).

Arcamone et al. used C1–C3 carboxylic acids as well as capryloate to synthesise DOX derivatives. *In vivo* antitumor activity against mouse sarcoma derived from ascites (Sarcoma 180), murine virus induced sarcoma (MSV-M), intravenously transplanted Gross leukemia, and transplanted mammary carcinoma was evaluated in mouse models. In all the experimental settings tested, DOX capryloate was the most active compound (Arcamone et al., 1974).

3.2. Paclitaxel conjugates

Paclitaxel (PTX) is a complex taxane diterpene which was originally isolated from *Taxus brevifolia* (Wani et al., 1971). It is the active compound in Taxol®, which is one of the most effective anticancer drugs. It has been approved for the treatment of breast, ovarian, and lung cancers as well as Kaposi's sarcoma. However, PTX is not capable of crossing the blood-brain barrier to reach to a notable extent the brain tissue (Sparreboom et al., 1996). The mechanism of PTX action is based on binding to the microtubules of β-tubulin, causing the formation of parallel bundles of microtubules and inhibiting cell division at the G_2-M phase of the cell cycle (Schiff and Horwitz, 1980; Yvon et al., 1999). Due to the fact, that PTX is extensively metabolized by the liver and is usually rapidly eliminated from the circulatory system, there is a search for various modifications that would extend its half-life and improve cellular uptake, thereby potentiating the drug's therapeutic effect (Xi Yu et al., 2010). PTX can be conjugated with FA in 2′-hydroxy and 7-hydroxy positions (Fig. 2).

Paclitaxel oleate (PTX-oleate) was synthesized in the reaction of oleoyl chloride with paclitaxel by Lundberg et al.. The esterification of

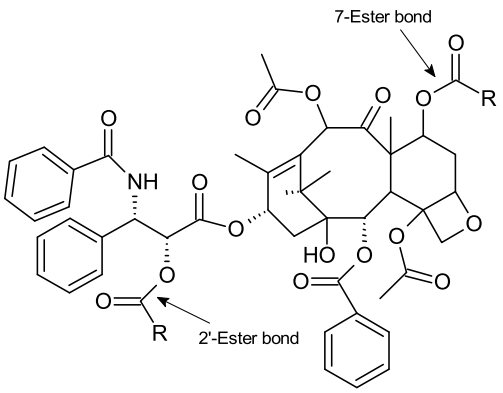

Fig. 2. Molecular structure of paclitaxel conjugates.

the 2′-hydroxyl group of paclitaxel was preferred, because of the much higher reactivity of this position compared to the 7-hydroxyl one. The conjugate demonstrated an *in vitro* cytotoxic activity against a human cervical cancer cell line (HeLa) with a significant increase in activity along with the increase of incubation time. IC_{50} for HeLa cells were 5500, 500, 150, and 100 nM for 24, 48, 72 and 96 h of incubation, respectively. In addition, the *in vitro* incubation of PTX-oleate with human plasma resulted in greater proportion found in the lipoprotein pool when compared to PTX (Lundberg et al., 2003).

Bardley et al. coupled DHA to paclitaxel at the 2′-hydroxyl position. The conjugate showed increased antitumor activity in a mice lung tumor model (M109) and in human colon (HT-29) mice implanted carcinoma when compared with PTX. The modified drug appeared to be less toxic before it was metabolized by tumor cells to the cytotoxically active free PTX form, therefore 4.4-fold higher molar doses could be delivered to mice (Bradley et al., 2001).

Bedikian et al. covalently conjugated the essential fatty acid DHA to the paclitaxel molecule (DHA-PTX) at the 2′-hydroxyl position. Preclinical studies have demonstrated increased activity of DHA-PTX compared to PTX. In the presented study, the efficacy and toxicity profiles of DHA–PTX were compared with those of dacarbazine – a structural analogue of imidazole carboxamide used as a chemotherapy drug (Bedikian et al., 2011).

Lack of efficacy of PTX against drug-resistant tumors such as colon, pancreatic, melanoma, and renal cancers is reported to be due to the overexpression of P-glycoprotein (Pgp), a transporter effluxing out hydrophobic anticancer agents including PTX. Kuznetsova et al., used PUFAs such as DHA, LA, LNA to modify second-generation toxoids: SB-T-1103, SB-T-1104, SB-T-1213, SBT-1214, SB-T-1216, and SB-T-1217 in 2′-hydroxy position. This way obtained PUFA–taxoid conjugates were assessed for their efficacy against a drug-sensitive (Pgp-) human ovarian tumor xenograft (A121) and a drug-resistant (Pgp+) human colon tumor xenograft (DLD-1) in SCID mice. While PTX was ineffective, LNA–SB-T-1213 and DHA–SB-T-1213 exhibited strong antitumor activity. LA-SB-T-1213 did not show meaningful efficacy in the same assay, which confirmed the selectiveness of drug-conjugate tumor cell targeting between n-3 PUFA (LNA, DHA) and n-6 PUFA (LA) (Kuznetsova et al., 2006).

Xi-Yu et al. synthesized conjugated linoleic acid and PTX hybrid molecule (CLA-PTX) using the hydroxyl (2′-position) group. The conjugate showed higher cellular uptake efficiency in murine glioma cells (C6) in comparison to PTX and showed lower *in vitro* cytotoxicity. The antitumor efficacy in brain tumor-bearing rats after administering CLA-PTX was significantly higher than that after giving Taxol (Xi Yu et al., 2010).

3.3. Cytarabine conjugates

Cytarabine, also known as cytosine arabinoside (ara-C), is a pyrimidine nucleoside-based anticancer drug with arabinose sugar, widely used for the treatment of leukemia. Cytarabine is predominantly used against acute myelogenous leukemia (AML) and non-Hodgkin's lymphoma (NHL), acute lymphoblastic leukemia (ALL), and erythroleukemia (Jabbour et al., 2007; Shah and Agarwal, 2008). Many research groups have been evaluating the ara-C prodrug approach using various fatty acid modifications at 2′-hydroxyl, 5′-hydroxyl and 4-amino groups of cytarabine, making the drug more lipophilic and protecting it from cytidine deaminase (Fig. 3).

Liu. et al. has used the simultaneous amino acid and fatty acid derivatization obtaining 4-amino acid (Val, Met, Tyr, Glu and Arg) and fatty acid conjugates with chain length of 10, 14 and 18 carbons. Subsequently, a direct coupling of amino acid fatty acyls derivatives and cytarabine at 4-NH_2 position was performed forming a peptide bond. The antiproliferative activity was evaluated in a human leukemia cell line (HL-60) and cervical cancer cells (HeLa), and varied depending on the type of amino acid and FA used. Methionine derivatives showed

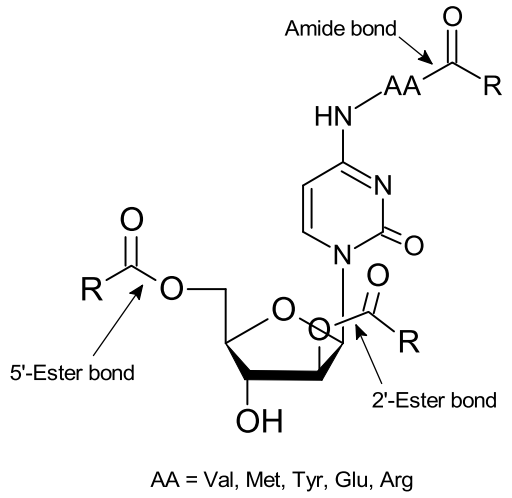

Fig. 3. Molecular structure of cytarabine conjugates.

better antiproliferative activity when compared to the other synthesized amino acid containing conjugates. Additionally, the antitumor effect decreased with the increase of carbon chain length and did not improve biological activity (Liu et al., 2009).

Fatty acid-substituted conjugates of cytarabine at 5′-hydroxyl position were characterised with significantly different properties than N4 derivatives (A. M. Bergman et al., 2004). An ester derivative of cytarabine and elaidic acid (ara-C-5′-elaidic, CP-4055) facilitated cellular accumulation and retention of ara-C in tumor cells. Unlike cytarabine, the cellular uptake of this derivative is independent on nucleoside transporters (Breistøl et al., 1999), which caused high cytotoxic effect in solid tumor and leukemia cells *in vitro* and *in vivo* (A M Bergman et al., 2004).

The cytotoxic mechanism of cytarabine involves phosphorylation of the 5′-hydroxyl group of arabinose sugar into triphosphate, therefore the effectiveness of fatty acid ester derivatives depends on the concentration of the parent drug delivered intracellularly after the ester hydrolysis and availability of the 5′-hydroxyl group for phosphorylation (Plunkett et al., 1987).

The 2′-hydroxyl position of arabinose sugar in cytarabine was also explored for functionalizing with fatty acids by Chhikara et al.. The C2′ and C5′ myristic acid substituted ara-C derivatives (ara-C-2′-myristoyl, ara-C-5′-myristoyl and ara-C-2′,5′-dimyristoyl) were synthesized and screened for their cytotoxic activity. The C5' substituted derivative was not able to inhibit the proliferation of leukemia cells (CCRF-CEM) even after 96 h at a concentration of 1 μM. 2′-Fatty acyl and 2′,5′-disubstituted derivatives of ara-C inhibited the growth of cancer cells by approximately 36–76% at a concentration of 1 μM after 96 h incubation. Enhanced cytotoxic activity of 2′,5′-disubstituted derivative after 96 h compared to that after 24 h indicates that the conjugate slowly releases cytarabine and may behave as a prodrug for sustained parent ara-C delivery, which may be beneficial for the therapy (Chhikara et al., 2010).

3.4. Gemcitabine conjugates

Gemcitabine (GEM) is a deoxycytidine analog used as chemotherapeutic drug for treatment of various solid tumors, including pancreatic cancer (Burris et al., 1997), non-small cell lung cancer, ovarian cancer and breast cancer (Hui and Reitz, 1997). It can inhibit both DNA synthesis and ribonucleotide reductase (Galmarini et al., 2002).

Modifications on GEM involve the 3′-hydroxyl, 5′-hydroxyl group and 4-amino group and thus can transform it into an ester or amide derivative (Fig. 4). Bender et al. reported that gemcitabine amides were better than the esters in terms of increased plasma half-life, since the

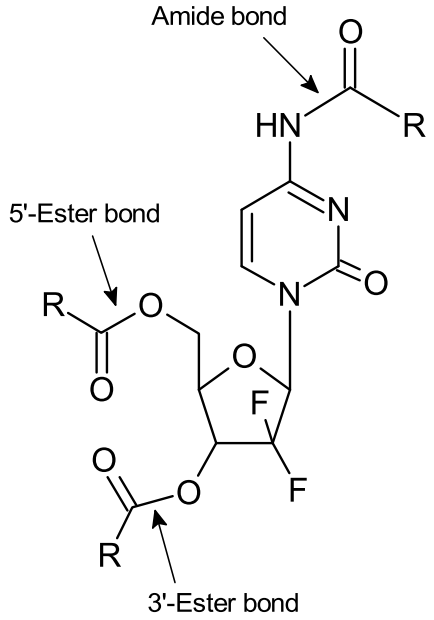

Fig. 4. Molecular structure of gemcitabine conjugates.

amides can block the site of deamination for deoxycytidine deaminase and therefore lower the metabolism of gemcitabine (Bender et al., 2009).

Immordino et al. synthesized a series of lipophilic gemcitabine prodrugs by linking the 4-amino group with valeroyl, heptanoyl, lauroyl and stearoyl acyl derivatives. Cytotoxicity of these derivatives, free or encapsulated in liposomes, was between two- and sevenfold that of GEM. Encapsulation of prodrugs in liposomes protected them from degradation in plasma, thus ensured longer plasma half-time and better intracellular release of the free drug (Immordino et al., 2004).

Bergman et al. used elaidic fatty acid to modify GEM at the 5′position by esterification. The cytotoxic activity and mechanism of action of the new lipophilic prodrug (CP-4126) was described in rodent leukemia cell lines, human leukemia and various solid tumor cell lines and xenografts. In conclusion, the gemcitabine-elaidic acid derivative showed equal antitumor activity to GEM in various xenograft models. Furthermore, oral administration compared to intraperitoneal administration resulted in equal antitumor activity (Bergman et al., 2011).

Tao et al. covalently coupled conjugated linoleic acid (CLA) to the 4-amino group of GEM to obtain CLA–GEM amide. *In vitro* tests in human breast tumor cells (MCF-7) showed an increased plasma prodrug stability and antitumor activity. The CLA–GEM conjugate was found to significantly inhibit tumor cell growth in a nucleoside transporter independent manner, in contrast to unmodified GEM. An *In vivo* pharmacokinetic study resulted in longer CLA–GEM half-life and better bioavailability compared to free GEM (Tao et al., 2012).

To enhance the drug efficacy and reduce the adverse effects Li et al. modified the N4-position of gemcitabine with DHA. The cytotoxicity of DHA, GEM and DHA-GEM was evaluated in human breast cancer cells (MCF-7 and MB-MDA-231), liver cancer (HepG2 and Bel-7402), lung cancer (A549), gastric cancer (SCG-7901) and mouse hepatoma cancer (H22) cells. The results showed that DHA-GEM had high efficacy and lower toxicity than the free GEM (Li et al., 2014).

3.5. Ciprofloxacin conjugates

Ciprofloxacin (CP) is a commonly used broad-spectrum fluoroquinolone (FQ) antibiotic with low side effects, which does not show cytotoxic effect against normal cell lines. It has been also shown to have antiproliferative and apoptotic activities in several cancer cells (Aranha et al., 2000; El-Rayes et al., 2002; Herold et al., 2002). Hussy et al.

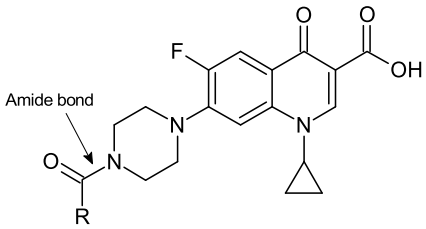

Fig. 5. Molecular structure of ciprofloxacin conjugates.

described the inhibitory effect of several FQs against mammalian DNA topoisomerases I and II and DNA polymerase and reported that CP was the most potent FQ inhibitor of all tested enzymes (Hussy et al., 1986). FA modifications of CP can be carried out only on the NH moiety in piperazine ring (Fig. 5).

Azéma et al., (2009) modified the ciprofloxacin piperazine NH group using a 5–16 carbon chain length FA and forming oxoethylalcanoate, alkoxycarbonyl, alkanoyl conjugates. The *in vitro* antitumor activity of obtained compounds and CP has been determined for prostate (PC-3), glioblastoma (U373-MG), colorectal (LoVo), lung (A549), and breast (MCF-7) human cancer cell lines. Only the amide derivative of CP and capric acid showed potent *in vitro* antitumor activity. No correlation was reported between *in vitro* antitumor activity and chain length (Azéma et al., 2009).

Chrzanowska et al., (2020) coupled ciprofloxacin (CP) with saturated and unsaturated fatty acids, and evaluated cytotoxicity, apoptosis-inducing effects and inhibition of IL-6 release in human primary (SW480) and metastatic (SW620) colon cancer, metastatic prostate cancer (PC3) and normal (HaCaT) cell lines. The oleic acid conjugate showed 13 times lower IC_{50} value (7.7 μM) for CP alone (101.4 μM) in the PC3 cell line, which was found to be the most sensitive to the presence of the obtained conjugates. The normal cell line (HaCaT) was much less sensitive to oleic acid-CP derivative and CP. The IC_{50} values were 132.5 μM and 222.1 μM, respectively.

Modification of fatty acid with heterocyclic compounds, which express none or weak cytotoxic activity, results in strong cytotoxic effect against tumor cells and weak effect against normal cell lines.

Ahmad et al. synthesized oleic acid and caproleic acid derivatives bearing 1,3,4-oxadiazol-2-thione (**a**), 1,2,4-triazol-3-thione (**b**) and 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine (**c**) moieties (Fig. 6). All compounds were tested *in vitro* for antitumor activity against three human cancer cell lines: human hepatocellular carcinoma (Hep3B), human breast adenocarcinoma (MCF-7), human cervical carcinoma (HeLa) and normal peripheral blood mononuclear cells (PBMC) by MTT assay. The results showed moderate cytotoxicity against different human cancer cell lines in range: 7.4–19.9 μM. Caproleic acid derivatives expressed higher cytotoxicity than the oleic acid ones. Cytotoxicity of starting compounds and of heterocyclic moieties was not tested in the studies (A. Ahmad et al., 2017).

Yang et al. reported the synthesis of different amide derivatives of saturated FA with different carbon chain lengths (C10–C24) and quaternary salts of piperazine (Fig. 7). Compounds were assayed towards growth inhibitory activity against six human cancer cell types: prostate

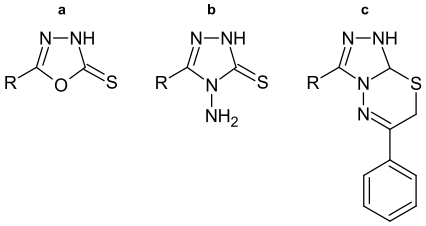

Fig. 6. Molecular structure of 1,3,4-oxadiazol-2-thione (**a**), 1,2,4-triazol-3-thione (**b**) and 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine (**c**) conjugates.

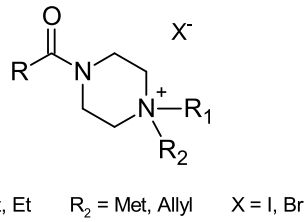

Fig. 7. Molecular structure of piperazine quaternary salts.

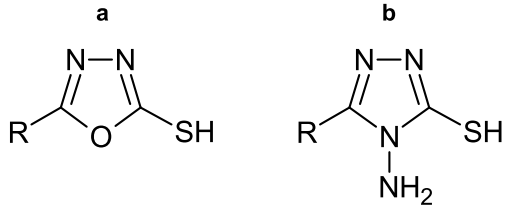

Fig. 8. Molecular structure of 1,3,4-oxadiazol-2-thiol (**a**), 1,2,4-triazol-3-thiol (**b**).

cancer (PC-3), gastric cancer (NUGC-3), breast cancer (MDA-MB-231), renal cancer (ACHN), colon cancer (HCT-15), and non-small cell lung cancer (NCI–H23). The palmitic acid derivatives exhibited the most potent inhibitory profile. For compounds with a relatively shorter or longer carbon chain (C10 or C24), the cell growth inhibition was weak, or was not observed at all, irrespective of cell type. Perifosine and NSC126188 (a piperazine alkyl derivative) were used as positive references for comparison of *in vitro* activities (Yang et al., 2011).

Jubie et al. synthesized some novel 1,3,4-oxadiazoles (**a**) and 1,2,4-triazoles (**b**) derivatives of stearic and gamma-linolenic acids (Fig. 8). Cytotoxicity of these compounds was evaluated by the growth inhibition assay in human lung carcinoma cell lines (A-549) cells *in vitro*. Conjugates of gamma-linolenic acid showed more potent cytotoxicity than stearic acid. No reference compound was used in the study. (Jubie et al., 2012).

Amides of FA (palmitic, stearic, oleic, elaidic and linoleic acids) and benzylamine derivatives: benzylamine, (R)-methylbenzylamine, (S)-methylbenzylamine as well as pyrrolidine, piperidine, morpholine were obtained by Santos et al. (Fig. 9). Antiproliferative *in vitro* study resulted in a clear structure-activity relationship in seven human cancer cell lines: glioma (U251), breast epithelial carcinoma (MCF-7), ovarian (OVCAR-3), ovarian with a phenotype of multiple drug resistance (NCI-ADR/RES), kidney (786–0), non-small cell lung cancer (NCI–H460), prostate (PC-3) as well as two normal cell lines: human keratinocyte (HaCaT) and kidney epithelial cells from the African green monkey (VERO). The presence of a five membered heterocyclic compound with unsaturated chain resulted in significantly greater antiproliferative activity when compared to saturated chain derivatives. Pyrrolidine conjugates of oleic and linoleic acids were the most effective in inhibiting cell proliferation in most of the cell lines. No information about the cytotoxic activity of pyrrolidine was provided in the paper (Santos et al., 2015).

Venepally et al. synthesized a series of novel ethyl derivatives [1-ethyl-6-fluoro-7-(fatty amido)-1,4-dihydro-4-oxoquinoline-3-carboxylate] containing an amide linkage at the C-7 position (Fig. 10). The amine group was covalently coupled with saturated FA: C6, C8, C12, C15, C16, C18 and unsaturated FA: undecylenic (C11), oleic (C18). All synthesized compounds were screened against four cancer cell lines:

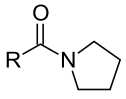

Fig. 9. Molecular structure of the most active pyrrolidine derivatives.

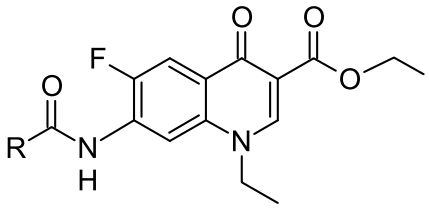

Fig. 10. Molecular structure of 1-ethyl-6-fluoro-7-(fatty amido)-1,4-dihydro-4-oxoquinoline-3-carboxylate.

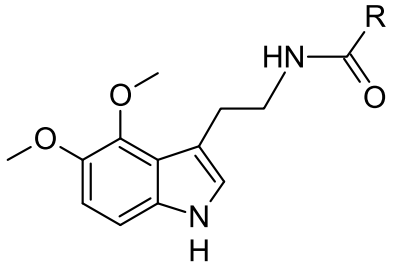

Fig. 11. Molecular structure of dimethoxy tryptamine derivatives.

human prostate (DU145), lung cancer (A549), ovarian cancer (SKOV3), breast cancer (MCF-7) and normal lung cell line (IMR-90). DOX was used as a standard positive control. The FQs derivatives with hexanoic, octanoic, lauric and myristic fatty acids exhibited promising cytotoxicity against all tested tumor cell lines with hexanoic acid derivative showing the highest one. None of intermediate compounds obtained in multistep synthesis of the final quinolone derivatives were tested for cytotoxic activity (Venepally et al., 2016).

In another work Venepally et al. obtained N-fatty acyl derivatives of saturated FA: C4, C6, C8, C12, C14, C16, C18 and unsaturated FA: undecylenic (C11:1), oleic (C18:1) and dimethoxy tryptamine (Fig. 11). Compounds were tested for antitumor activity against different human cancer cell lines: lung cancer (A549), prostate cancer (PC-3), breast cancer (MDA-MB-231), liver cancer (HepG2) and normal cell line (HUVEC). Most of derivatives showed a significant cytotoxic effect. Conjugates of butyric acid (C4) and oleic acid (C18:1) were the most promising ones (IC_{50} < 16 μM). Only final derivatives were screened for antitumor activity (Venepally et al., 2017).

Jóźwiak et al. synthesized eleven esters of alloxanthoxyletin and fatty acids (saturated: C3, C6, C8, C12, C14, C16, C18 and unsaturated: oleic, α-linolenic, conjugated linolenic and docosahexaenoic) (Fig. 12) and screened for their anticancer toxicity using tumor cell lines such as human melanoma cells (HTB-140), human epithelial lung carcinoma cells (A549) and a normal cell line – human keratinocyte line (HaCaT). Derivatives of unsaturated FA showed high cytotoxic potential against cancer cells with IC_{50} of 14.4–39.4 μM, with the compound bearing DHA acid being the most effective. The increasing level of unsaturation of the hydrocarbon chain resulted in an increased compound's activity. In addition, alloxanthoxyletin derivatives showed greater cytotoxic effects against tumor cell lines compared to normal cells (HaCaT). (Jóźwiak et al., 2019). 7-Hydroxyalloxanthyletin used as a starting compound expressed significantly lower cytotoxic activity against the

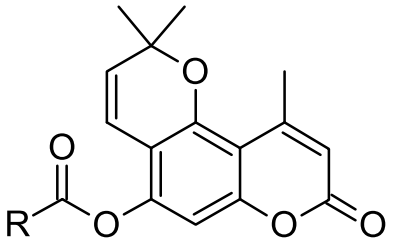

Fig. 12. Molecular structure of alloxanthoxyletin derivatives.

majority of tested tumor cell lines. It showed a cytotoxic effect against Vero cells of African green monkey (IC_{50} = 41 μg/ml), breast carcinoma MCF-7 cells (IC_{50} > 50 μg/ml), epidermoid carcinoma KB cells (IC_{50} = 48 μg/ml) and small cell lung cancer NCI–H187 (IC_{50} = 11 μg/ml) (Promsuwan and Yenjai, 2013).

4. Conclusion and perspectives

Considering saturated fatty acids, only short-carbon chain molecules show antitumor activity. There was no anticancer activity reported for saturated FA with carbon chains longer than C10. The activity for unsaturated FA increases with the elongation of the carbon chain in the molecule as well as with the level of unsaturation. Besides the number of double bonds in the molecule, the location of the double bond (n-3, n-6, n-9) has also an important impact on the activity of FA. Among unsaturated FA, long-chain polyunsaturated (PUFAs) molecules show the greatest antitumor activity. PUFAs n-3 are a more promising group compared to PUFAs n-6, as they play a role in the prevention of the development of different cancer types *in vivo* and *in vitro*. PUFAs n-6 (arachidonic acid, linoleic acid) can promote or inhibit tumor development depending on the mechanism of metabolic action induced within the cell, therefore they possible use in cancer treatment is so far controversial. Modifications of existing anticancer drugs by conjugating them with FA may increase their tissue selectivity and can potentially make chemotherapy more effective and less toxic. Improved drug stability, solubility and therefore bioavailability limits undesirable physiological interactions and prolongs circulation half-time. All this increases the amount of active substance that can reach the intended target, minimizing side effects and improving the quality of chemotherapy. Conjugates of FA with commonly used anticancer drugs express higher cytotoxicity against tumor cell lines compared to normal cell lines.

The literature review revealed that heterocyclic structures exhibit a cytotoxic activity which can be improved by the modifications with FA. The starting heterocyclic compounds, if, did not show cytotoxic effects against treated cells or exhibited significantly lower efficacy compared to the FA-heterocycle conjugate, as shown in the reviewed studies. Among the short-chain acyl derivatives, both saturated and unsaturated conjugates expressed anticancer activity. Condensation with long-chain FA resulted in a high cytotoxic effect only in case of unsaturated chains used.

Syntheses of different conjugates of existing drugs with fatty acids are well known and described in the literature. Mechanisms of action of these hybrid molecules have been tested, proving an increase of the drugs' selectivity against tumor cells. As a consequence, a lesser amount of a drug is needed to achieve the same effect in comparison to the non-modified drug.

To perform a complete evaluation of connections of fatty acids with heterocyclic compounds, further research is required, since the cytotoxicity tests for normal cell lines were not included in many studies. In most cases, the presented results were *in vivo* and *in vitro* preliminary studies conducted only on tumor cell lines. The mechanisms of cytotoxic activity of new fatty acid combinations with heterocyclic compounds are mostly unknown. Furthermore, conjugates of fatty acids with heterocyclic moieties require additional research determining the pharmacokinetics of new combinations. This may result in finding new potentially active molecules, which mechanisms of action haven't been described yet.

Although a number of fatty acid and cytostatic drugs connections have been approved and tested in phase I, II or III of the clinical trial process, e.g. taxoprexin, which is a prodrug of paclitaxel bound to the docosahexaenoic acid. Phase II studies have demonstrated favourable results with this new paclitaxel formulation in human patients with lung melanoma and other cancers (Homsi et al., 2010). However, compounds have not been introduced into treatment because their efficacy as a first-line therapy for metastatic melanoma does not exceed

that seen with other single-agent chemotherapies such as dacarbazine (Bedikian et al., 2011). Further exploration of new connections of DHA with other chemotherapy or targeted agents could be considered. Shougang et al. connects docotaxel, a currently used drug in first- or second-line lung cancer treatment, with DHA as a tumor-targeting ligand. The researchers conclude that DHA-docotaxel may exhibit a potential therapeutic effect against lung cancer metastasis to bone (Jiang et al., 2018).

In order to develop tumor specific chemotherapeutic drugs, new formulations of drug delivery systems are tested. Gulzar et al. formulated an oil-in-water nanoemulsion of a next generation taxoid DHA-SBT-1214 and evaluated its biodistribution and pharmacokinetics. The results from this study demonstrated effective encapsulation of the drug in a nanoemulsion and this nanoemulsion showed sustained plasma levels and enhanced tumor delivery relative to the solution form (G. Ahmad et al., 2017).

This FA modifications, which increase the activity and the uptake selectivity of the compounds, and alter drug delivery methods may be the key to unlocking the true medical potential of FA, in particular PUFAs.

Acknowledgements

This work was supported by the Polish National Science Centre under the grant PRELUDIUM number 2017/25/N/NZ7/01583. This work was supported by the Polish National Science Centre under the grant PRELUDIUM number 2017/25/N/NZ7/01583.

References

Abel, S., Riedel, S., Gelderblom, W.C.A., 2014. Dietary PUFA and cancer. Proc. Nutr. Soc. 73, 361–367. https://doi.org/10.1017/S0029665114000585.

Ahmad, A., et al., 2017. Synthesis and anticancer activity of long chain substituted 1,3,4-oxadiazol-2-thione, 1,2,4-triazol-3-thione and 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine derivatives. Arabian Journal of Chemistry. King Saud University 10, S3347–S3357. https://doi.org/10.1016/j.arabjc.2014.01.015.

Ahmad, G., et al., 2017. Nanoemulsion formulation of a novel taxoid DHA-SBT-1214 inhibits prostate cancer stem cell-induced tumor growth. Cancer Lett. 406, 71–80. https://doi.org/10.1016/j.canlet.2017.08.004.

Akagi, D., Hoshina, K., W, T., Conte, M.S., 2018. Drug therapy for abdominal aortic aneurysms utilizing omega-3 unsaturated fatty acids and their derivatives. Curr. Drug Targets 1309–1317. https://doi.org/10.2174/1389450118666171013101815.

Akanbi, T.O., Marshall, S.N., Barrow, C.J., 2019. Polydatin-fatty acid conjugates are effective antioxidants for stabilizing omega 3-containing bulk fish oil and fish oil emulsions. Food Chem. 301 (March), 125297. https://doi.org/10.1016/j.foodchem.2019.125297.

Albino, A.P., et al., 2000. Cell cycle arrest and apoptosis of melanoma cells by docosahexaenoic acid: association with decreased pRb phosphorylation. Cancer Res. 60, 4139–4145. Available at: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L30636596.

Alexander, J.W., 1998. Immunonutrition: the role of ω-3 fatty acids. Nutrition 14 (7–8), 627–633. https://doi.org/10.1016/S0899-9007(98)00004-5. Elsevier.

Allam-Ndoul, B., et al., 2017. A study of the differential effects of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) on gene expression profiles of stimulated thp-1 macrophages. Nutrients 9 (5), 7–10. https://doi.org/10.3390/nu9050424.

Aranha, O., Wood, D.P., Sarkar, F.H., 2000. Ciprofloxacin mediated cell growth inhibition, S/G2-M cell cycle arrest, and apoptosis in a human transitional cell carcinoma of the bladder cell line. Clin. Cancer Res. 6, 891–900.

Arcamone, F., et al., 1974. Synthesis and biological evaluation of some 14-O-acyl derivatives of adriamycin. J. Med. Chem. 17 (3), 335–337. https://doi.org/10.1021/jm00249a017.

Aucoin, M., et al., 2017. Fish-derived omega-3 fatty acids and prostate cancer: a systematic review. Integr. Cancer Ther. 16 (1), 32–62. https://doi.org/10.1177/1534735416656052.

Azéma, J., et al., 2009. 7-((4-Substituted)piperazin-1-yl) derivatives of ciprofloxacin: synthesis and *in vitro* biological evaluation as potential antitumor agents. Bioorg. Med. Chem. 17 (15), 5396–5407. https://doi.org/10.1016/j.bmc.2009.06.053. Elsevier Ltd.

Bagga, D., et al., 2002. Long-chain n-3-to-n-6 polyunsaturated fatty acid ratios in breast adipose tissue from women with and without breast cancer. Nutr. Cancer 42 (2), 180–185. https://doi.org/10.1207/S15327914NC422_5. United States.

Bala, V., et al., 2016. Lipophilic prodrugs of SN38: synthesis and *in vitro* characterization toward oral chemotherapy. Mol. Pharm. 13 (1), 287–294. https://doi.org/10.1021/acs.molpharmaceut.5b00785.

Baracos, V.E., Mazurak, V.C., Ma, D.W.L., 2004. n-3 Polyunsaturated fatty acids throughout the cancer trajectory: influence on disease incidence, progression, response to therapy and cancer-associated cachexia. Nutr. Res. Rev. 17, 177–192. https://doi.org/10.1079/nrr200488.

Bathen, T.F., et al., 2008. Omega-3 fatty acids suppress growth of SW620 human colon cancer xenografts in nude mice. Anticancer Res. 28, 3717–3724.

Bedikian, A.Y., et al., 2011. Phase 3 study of docosahexaenoic acid-paclitaxel versus dacarbazine in patients with metastatic malignant melanoma. Ann. Oncol. 22 (4), 787–793. https://doi.org/10.1093/annonc/mdq438.

Beermann, C., et al., 2003. Short term effects of dietary medium-chain fatty acids and n-3 long-chain polyunsaturated fatty acids on the fat metabolism of healthy volunteers. Lipids Health Dis. 2 (10). https://doi.org/10.1186/1476-511X-2-10.

Bégin, M.E., et al., 1985. 'Selective killing of human cancer cells by polyunsaturated fatty acids', *Prostaglandins, leukotrienes, and medicine*. Scotlands 19 (2), 177–186.

Bégin, M.E., Ells, G., Horrobin, D.F., 1988. Polyunsaturated fatty acid-induced cytotoxicity against tumor cells and its relationship to lipid peroxidation. J. Natl. Cancer Inst. 80 (3), 188–194. https://doi.org/10.1093/jnci/80.3.188. United States.

Bender, D.M., et al., 2009. Synthesis, crystallization, and biological evaluation of an orally active prodrug of gemcitabine. J. Med. Chem. 52, 6958–6961. https://doi.org/10.1021/jm901181h.

Bergman, A.M., et al., 2004. Antiproliferative activity and mechanism of action of fatty acid derivatives of arabinofuranosylcytosine in leukemia and solid tumor cell lines. Biochem. Pharmacol. 67 (3), 503–511. https://doi.org/10.1016/j.bcp.2003.09.028.

Bergman, A.M., et al., 2004. Antiproliferative activity and mechanism of action of fatty acid derivatives of arabinosylcytosine (ara-C) in leukemia and solid tumor cell lines. Nucleosides Nucleotides Nucleic Acids 23 (8–9), 1523–1526. https://doi.org/10.1081/NCN-200027735. United States.

Bergman, A.M., et al., 2011. Antiproliferative activity, mechanism of action and oral antitumor activity of CP-4126, a fatty acid derivative of gemcitabine, in *in vitro* and *in vivo* tumor models. Investig. New Drugs 29, 456–466. https://doi.org/10.1007/s10637-009-9377-7.

Bhattarai, R., 2014. Importance of goat milk. J. Food Sci. Technol. Nepal 7. https://doi.org/10.3126/jfstn.v7i0.11209.

Bi, J., et al., 2019. Neuroprotective effect of omega-3 fatty acids on spinal cord injury induced rats. Brain and behavior, e01339. https://doi.org/10.1002/brb3.1339. United States.

Bianchini, F., et al., 2012. 22:6 n-3 DHA inhibits differentiation of prostate fibroblasts into myofibroblasts and tumorigenesis. Br. J. Nutr. 108 (12), 2129–2137. https://doi.org/10.1017/S0007114512000359.

Borkar, N., et al., 2015. Lipophilic prodrugs of apomorphine I: preparation, characterisation, and *in vitro* enzymatic hydrolysis in biorelevant media. Eur. J. Pharm. Biopharm. 89, 216–223. https://doi.org/10.1016/j.ejpb.2014.12.014. Elsevier B.V.

Bradley, M.O., et al., 2001. Tumor targeting by covalent conjugation of a natural fatty acid to paclitaxel. Clin. Cancer Res. 7 (10), 3229–3238.

Bravo-santano, N., et al., 2019. Intracellular Staphylococcus aureus elicits the production of host very long-chain saturated fatty acids with antimicrobial activity. Metabolites 9 (7), 148. https://doi.org/10.3390/metabo9070148.

Breistøl, K., et al., 1999. Antitumor activity of P-4055 (elaidic acid-cytarabine) compared to cytarabine in metastatic and s.c. human tumor xenograft models. Cancer Res. 59 (12), 2944–2949.

Burris 3rd, H.A., et al., 1997. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J. Clin. Oncol.: Off. J. Am. Soc. Clin. Oncol. 15 (6), 2403–2413. https://doi.org/10.1200/JCO.1997.15.6.2403. United States.

Calder, P.C., 2002. Dietary modification of inflammation with lipids. Proc. Nutr. Soc. 61, 345–358. https://doi.org/10.1079/PNS2002166.

Casula, M., et al., 2013. Long-term effect of high dose omega-3 fatty acid supplementation for secondary prevention of cardiovascular outcomes: a meta-analysis of randomized, double blind, placebo controlled trials. Atherosclerosis Suppl. 14 (2), 243–251. https://doi.org/10.1016/S1567-5688(13)70005-9. Elsevier Ireland Ltd.

Chamras, H., et al., 2002. Fatty acid modulation of MCF-7 human breast cancer cell proliferation, apoptosis and differentiation. JNB (J. Nutr. Biochem.) 13 (12), 711–716. https://doi.org/10.1016/S0955-2863(02)00230-9.

Chen, Z.Y., Istfan, N.W., 2000. Docosahexaenoic acid is a potent inducer of apoptosis in HT-29 colon cancer cells. Prostaglandins Leukot. Essent. Fatty Acids 63 (5), 301–308. https://doi.org/10.1054/plef.2000.0218.

Chhikara, B.S., et al., 2011. Fatty acyl amide derivatives of doxorubicin: synthesis and *in vitro* anticancer activities. Eur. J. Med. Chem. 46 (6), 2037–2042. https://doi.org/10.1016/j.ejmech.2011.02.056. Elsevier Masson SAS.

Chhikara, B.S., Mandal, D., Parang, K., 2010. Synthesis and evaluation of fatty acyl ester derivatives of cytarabine as anti-leukemia agents. Eur. J. Med. Chem. 45 (10), 4601–4608. https://doi.org/10.1016/j.ejmech.2010.07.024. Elsevier Masson SAS.

Chrzanowska, A., et al., 2020. Anticancer and antimicrobial effects of novel ciprofloxacin fatty acids conjugates. Eur. J. Med. Chem. 185. https://doi.org/10.1016/j.ejmech.2019.111810.

Chue, P., Chue, J., 2012. A review of paliperidone palmitate. Expert Rev. Neurother. 12 (12), 1383–1397. https://doi.org/10.1586/ern.12.137.

Clandinin, M.T., Chappell, J.E., van Aerde, J.E., 1989. Requirements of newborn infants for long chain polyunsaturated fatty acids. Acta Paediatr. Scand. Suppl. 351, 63–71 Sweden.

Colquhoun, A., Curi, R., 1998. Effects of saturated and polyunsaturated fatty acids on human tumor-cell proliferation. Gen. Pharmacol. Vasc. Syst. 30 (2), 191–194. https://doi.org/10.1016/S0306-3623(97)00110-9. Pergamon.

Colquhoun, A., Schumacher, R.I., 2001. Gamma-Linolenic acid and eicosapentaenoic acid induce modifications in mitochondrial metabolism, reactive oxygen species generation, lipid peroxidation and apoptosis in Walker 256 rat carcinosarcoma cells. Biochim. Biophys. Acta 1533, 207–219.

Connolly, J.M., Coleman, M., Rose, D.P., 1997. 'Effects of dietary fatty acids on DU145

human prostate cancer cell growth in athymic nude mice. Nutr. Cancer 29 (2), 114–119. https://doi.org/10.1080/01635589709514611. United States.
Corsetto, P.A., et al., 2012. Chemical-physical changes in cell membrane microdomains of breast cancer cells after omega-3 PUFA incorporation. Cell Biochem. Biophys. 64 (1), 45–59. https://doi.org/10.1007/s12013-012-9365-y.
Dannenberg, A.J., et al., 2001. Cyclo-oxygenase 2: a pharmacological target for the prevention of cancer. Lancet Oncol. 2 (9), 544–551. https://doi.org/10.1016/S1470-2045(01)00488-0.
Das, U.N., 2004. From bench to the clinic: gamma-linolenic acid therapy of human gliomas. Prostagl. Leukot. Essent. Fat. Acids 70, 539–552. https://doi.org/10.1016/j.plefa.2003.12.001.
Das, U.N., 2006. Tumoricidal and anti-angiogenic actions of gamma-linolenic acid and its derivatives. Curr. Pharmaceut. Biotechnol. 7 (6), 457–466.
Das, U.N., Madhavi, N., 2011. Effect of polyunsaturated fatty acids on drug-sensitive and resistant tumor cells *in vitro*. Lipids Health Dis. 10, 159. https://doi.org/10.1186/1476-511X-10-159. BioMed Central Ltd.
Denise, F., 2017. Lippincott Illustrated Reviews: Biochemistry, seventh ed. Wolters Kluwer.
Desai, N., et al., 2006. Increased antitumor activity, intratumor paclitaxel concentrations, and endothelial cell transport of cremophor-free, albumin-bound paclitaxel, ABI-007, compared with cremophor-based paclitaxel. Clin. Cancer Res. 12 (4), 1317–1324. https://doi.org/10.1158/1078-0432.CCR-05-1634.
Dommels, Y.E.M., et al., 2003. The role of cyclooxygenase in n-6 and n-3 polyunsaturated fatty acid mediated effects on cell proliferation, PGE2 synthesis and cytotoxicity in human colorectal carcinoma cell lines. Carcinogenesis 24 (3), 385–392.
Effenberger, K., Breyer, S., Schobert, R., 2010. Modulation of doxorubicin activity in cancer cells by conjugation with fatty acyl and terpenyl hydrazones. Eur. J. Med. Chem. 45 (5), 1947–1954. https://doi.org/10.1016/j.ejmech.2010.01.037. Elsevier Masson SAS.
El-Rayes, B.F., et al., 2002. Ciprofloxacin inhibits cell growth and synergises the effect of etoposide in hormone resistant prostate cancer cells. Int. J. Oncol. 21 (1), 207–211 Greece.
Escribá, P.V., 2017. Membrane-lipid therapy: a historical perspective of membrane-targeted therapies-From lipid bilayer structure to the pathophysiological regulation of cells. Biochim. Biophys. Acta 1859 (Pt B), 1493–1506. https://doi.org/10.1016/j.bbamem.2017.04.023.
Fracasso, P.M., et al., 2009. Phase 1 and pharmacokinetic study of weekly docosahexaenoic acid-paclitaxel, Taxoprexin®, in resistant solid tumor malignancies. Cancer Chemother. Pharmacol. 63 (3), 451–458. https://doi.org/10.1007/s00280-008-0756-0.
Fujiwara, F., Todo, S., Imashuku, S., 1986. Antitumor effect of gamma-linolenic acid on cultured human neuroblastoma cells. Prostaglandins Leukot. Med. 23, 311–320.
Galmarini, C.M., Mackey, J.R., Dumontet, C., 2002. Nucleoside analogues and nucleobases in cancer treatment. Lancet Oncol. 3, 415–424.
Gerber, M., 2012. Omega-3 fatty acids and cancers: a systematic update review of epidemiological studies. Br. J. Nutr. 107 (Suppl. 2), 228–239. https://doi.org/10.1017/S0007114512001614.
Giros, A., et al., 2009. Regulation of colorectal cancer cell apoptosis by the n-3 polyunsaturated fatty acids Docosahexaenoic and Eicosapentaenoic. Cancer Prev. Res. 2 (8), 732–742. https://doi.org/10.1158/1940-6207.CAPR-08-0197. United States.
De Gómez Dumm, I.N.T., Brenner, R.R., 1975. Oxidative desaturation of α-linolenic, linoleic, and stearic acids by human liver microsomes. Lipids 10 (6), 315–317. https://doi.org/10.1007/BF02532451.
Guffy, M.M., North, J.A., Burns, C.P., 1984. Effect of cellular fatty acid alteration on adriamycin sensitivity in cultured L1210 murine leukemia cells. Cancer Res. 44 (5), 1863–1866.
Guo, Y., et al., 2017. Omega-3 free fatty acids attenuate insulin-promoted breast cancer cell proliferation. Nutr. Res. 42, 43–50. https://doi.org/10.1016/j.nutres.2017.04.008. Elsevier Inc.
Habbel, P., et al., 2009. Docosahexaenoic acid suppresses arachidonic acid-induced proliferation of LS-174T human colon carcinoma cells. World J. Gastroenterol. 15 (9), 1079–1084. https://doi.org/10.3748/wjg.15.1079.
Hardman, W.E., 2002. Omega-3 fatty acids to augment cancer therapy. J. Nutr. 132, 3508S–3512S.
Harris, W.S., Bulchandani, D., 2006. Why do omega-3 fatty acids lower serum triglycerides? Curr. Opin. Lipidol. 17 (4), 387–393. https://doi.org/10.1097/01.mol.0000236363.63840.16. England.
Harris, W.S., Dayspring, T.D., Moran, T.J., 2013. Omega-3 fatty acids and cardiovascular disease: new developments and applications. PGM (Postgrad. Med.) 125 (6), 100–113. https://doi.org/10.3810/pgm.2013.11.2717. Taylor & Francis.
Hart, C., et al., 2009. Influence of omega-6 PUFA arachidonic acid and bone marrow adipocytes on metastatic spread from prostate cancer. Br. J. Canc. 102 (2), 403–413. https://doi.org/10.1038/sj.bjc.6605481. Nature Publishing Group.
Herold, C., et al., 2002. Ciprofloxacin induces apoptosis and inhibits proliferation of human colorectal carcinoma cells. Br. J. Canc. 86, 443–448. https://doi.org/10.1038/sj/bjc/6600079.
Hidaka, A., et al., 2015. Fish, n-3 PUFA consumption, and pancreatic cancer risk in Japanese: a large, population-based, prospective cohort study. Am. J. Clin. Nutr. 102 (6), 1490–1497. https://doi.org/10.3945/ajcn.115.113597.1.
Homsi, J., et al., 2010. Phase 2 open-label study of weekly docosahexaenoic acid-paclitaxel in patients with metastatic uveal melanoma. Melanoma Res. 20 (6), 507–510. https://doi.org/10.1097/CMR.0b013e3283403ce9.
Horrobin, D.F., Ziboh, V.A., 1997. The importance of linoleic acid metabolites in cancer metastasis and in the synthesis and actions of 13-HODE. Adv. Exp. Med. Biol. 433, 291–294. https://doi.org/10.1007/978-1-4899-1810-9_61. United States.
Huan, M. lei, et al., 2009. Conjugation with α-linolenic acid improves cancer cell uptake and cytotoxicity of doxorubicin. Bioorg. Med. Chem. Lett 19 (9), 2579–2584. https://doi.org/10.1016/j.bmcl.2009.03.016. Elsevier Ltd.
Hudson, E.A., Beck, S.A., Tisdale, M.J., 1993. 'Kinetics of the inhibition of tumour growth in mice by eicosapentaenoic acid-reversal by linoleic acid', *Biochemical pharmacology*. England 45 (11), 2189–2194. https://doi.org/10.1016/0006-2952(93)90188-3.
Hui, Y.F., Reitz, J., 1997. Gemcitabine: a cytidine analogue active against solid tumors. Am. J. Health Syst. Pharm. 54 (2), 162–168. https://doi.org/10.1093/ajhp/54.2.162.
Hussy, P., et al., 1986. Effect of 4-quinolones and novobiocin on calf thymus DNA polymerase α primase complex, topoisomerases I and II, and growth of mammalian lymphoblasts. Antimicrob. Agents Chemother. 29 (6), 1073–1078.
Ibrahim, N.K., et al., 2002. Phase I and pharmacokinetic study of ABI-007, a Cremophor-free, protein-stabilized, nanoparticle formulation of paclitaxel. Clin. Cancer Res. 8 (5), 1038–1044.
Immordino, M.L., et al., 2004. Preparation, characterization, cytotoxicity and pharmacokinetics of liposomes containing lipophilic gemcitabine prodrugs. J. Control. Release 100 (3), 331–346. https://doi.org/10.1016/J.JCONREL.2004.09.001. Elsevier.
Irby, D., Du, C., Li, F., 2017. Lipid-drug conjugate for enhancing drug delivery. Mol. Pharm. 14 (5), 1325–1338. https://doi.org/10.1021/acs.molpharmaceut.6b01027.
Iwamoto, S., et al., 1998. Effects of fatty acids on liver metastasis of ACL-15 rat colon cancer cells. Nutr. Cancer 31 (2), 143–150. https://doi.org/10.1080/01635589809514694. United States.
Jabbour, E., et al., 2007. Current and emerging treatment options in chronic myeloid leukemia. Cancer 109 (11), 2171–2181. https://doi.org/10.1002/cncr.22661.
Jansen, R.J., et al., 2014. Fatty acids found in dairy, protein and unsaturated fatty acids are associated with risk of pancreatic cancer in a case-control study. Int. J. Cancer 134 (8), 1935–1946. https://doi.org/10.1002/ijc.28525.
Jiang, S., et al., 2018. Tumor targeting with docosahexaenoic acid-conjugated docetaxel for inhibiting lung cancer metastasis to bone. Oncology Letters 16 (3), 2911–2920. https://doi.org/10.3892/ol.2018.9047.
Jóźwiak, M., et al., 2019. Anticancer effects of alloxanthoxyletin and fatty acids esters – *In vitro* study on cancer HTB-140 and A549 cells. Biomed. Pharmacother. 110 (November 2018), 618–630. https://doi.org/10.1016/j.biopha.2018.12.005.
Jubie, S., et al., 2012. Synthesis and characterization of some novel quinoxaline-2,3-dione derivatives: a preliminary investigation on their activity against a human epithelial carcinoma cell line. Lett. Drug Des. Discov. 8 (4), 317–320. https://doi.org/10.2174/157018011794839385.
Kabara, J.J., et al., 1972. Fatty acids and derivatives as antimicrobial agents. Antimicrob. Agents Chemother. 2 (1), 23–28.
Khaddaj-Mallat, R., Morin, C., Rousseau, E., 2016. Novel n-3 PUFA monoacylglycerides of pharmacological and medicinal interest: anti-inflammatory and anti-proliferative effects. Eur. J. Pharmacol. 792, 70–77. https://doi.org/10.1016/j.ejphar.2016.10.038. Netherlands.
Khodapasand, E., et al., 2015. Is Bax/Bcl-2 ratio considered as a prognostic marker with age and tumor location in colorectal cancer? Iran. Biomed. J. 19 (2), 69–75. https://doi.org/10.6091/ibj.1366.2015.
Kim, J., et al., 2009. Fatty fish and fish omega-3 fatty acid intakes decrease the breast cancer risk: a case-control study. BMC Canc. 10 (216). https://doi.org/10.1186/1471-2407-9-216.
Kokura, S., et al., 2002. Enhancement of lipid peroxidation and of the antitumor effect of hyperthermia upon combination with oral eicosapentaenoic acid. Cancer Lett. 185, 139–144.
Koralek, D.O., et al., 2006. A prospective study of dietary alpha-linolenic acid and the risk of prostate cancer (United States). Cancer Causes Control 17, 783–791. https://doi.org/10.1007/s10552-006-0014-x.
Kuznetsova, L., et al., 2006. Syntheses and evaluation of novel fatty acid-second-generation taxoid conjugates as promising anticancer agents. Bioorg. Med. Chem. Lett 16 (4), 974–977. https://doi.org/10.1016/j.bmcl.2005.10.089.
Kyle, D.J., et al., 1999. 'Low serum docosahexaenoic acid is a significant risk factor for alzheimer's dementia'. Lipids 34 (1), S245. https://doi.org/10.1007/BF02562306.
Lambert, D.M., 2000. Rationale and applications of lipids as prodrug carriers. Eur. J. Pharm. Sci. 11 (Suppl. 2), 15–27. https://doi.org/10.1016/S0928-0987(00)00161-5.
Leaver, H.A., et al., 2002. Antitumour and pro-apoptotic actions of highly unsaturated fatty acids in glioma. Prostagl. Leukot. Essent. Fat. Acids 66 (1), 19–29. https://doi.org/10.1054/PLEF.2001.0336. Churchill Livingstone.
Li, D., et al., 1998. Contribution of meat fat to dietary arachidonic acid. Lipids 33 (4), 437–440. https://doi.org/10.1007/s11745-998-0225-7.
Li, F., et al., 2016. Preparation and characterization of lipophilic doxorubicin pro-drug micelles. J. Vis. Exp. 114. https://doi.org/10.3791/54338.
Li, S., et al., 2014. The targeting mechanism of DHA ligand and its conjugate with Gemcitabine for the enhanced tumor therapy. Oncotarget 5 (11), 3622–3635.
Li, Y., et al., 2013. Isoliquiritigenin induces growth inhibition and apoptosis through downregulating arachidonic acid metabolic network and the deactivation of PI3K/Akt in human breast cancer. Toxicol. Appl. Pharmacol. 272 (1), 37–48. https://doi.org/10.1016/j.taap.2013.05.031. United States.
Liang, C.H., et al., 2014. Synthesis of doxorubicin α-linolenic acid conjugate and evaluation of its antitumor activity. Mol. Pharm. 11 (5), 1378–1390. https://doi.org/10.1021/mp4004139.
Liu, B., et al., 2009. Synthesis and evaluation of anti-tumor activities of N4 fatty acyl amino acid derivatives of 1-β-arabinofuranosylcytosine. Eur. J. Med. Chem. 44 (9), 3596–3600. https://doi.org/10.1016/j.ejmech.2009.02.028. Elsevier Masson SAS.
Liu, J., Ma, D.W.L., 2014. The role of n-3 polyunsaturated fatty acids in the prevention and treatment of breast cancer. Nutrients 6, 5184–5223. https://doi.org/10.3390/nu6115184.
Liu, S., et al., 2008. Biological control of phytopathogenic fungi by fatty acids. Mycopathologia. https://doi.org/10.1007/s11046-008-9124-1.

Lundberg, B.B., et al., 2003. A lipophilic paclitaxel derivative incorporated in a lipid emulsion for parenteral administration. J. Control. Release 86 (1), 93–100. https://doi.org/10.1016/S0168-3659(02)00323-1.
Marks, F., Müller-Decker, K., Fürstenberger, G., 2000. A causal relationship between unscheduled eicosanoid signaling and tumor development: cancer chemoprevention by inhibitors of arachidonic acid metabolism. Toxicology 153, 11–26. https://doi.org/10.1016/S0300-483X(00)00301-2.
Marventano, S., et al., 2015. A review of recent evidence in human studies of n-3 and n-6 PUFA intake on cardiovascular disease, cancer, and depressive disorders: does the ratio really matter? Int. J. Food Sci. Nutr. 66 (6), 611–622. https://doi.org/10.3109/09637486.2015.1077790. Taylor & Francis.
McCarty, M.F., DiNicolantonio, J.J., 2018. 'Minimizing membrane arachidonic acid content as a strategy for controlling cancer: a review. Nutr. Cancer 70 (6), 840–850. https://doi.org/10.1080/01635581.2018.1470657. United States.
Menendez, J.A., Lupu, R., Colomer, R., 2005. Exogenous supplementation with omega-3 polyunsaturated fatty acid docosahexaenoic acid (DHA; 22:6 n-3) synergistically enhances taxane cytotoxicity and downregulates Her-2/neu (c-erbB-2) oncogene expression in human breast cancer cells. Eur. J. Cancer Prev.: Off. J. Eur. Cancer Prev. Org. (ECP) 14 (3), 263–270 England.
Mielczarek-Puta, M., Struga, M., Roszkowski, P., 2019. Synthesis and anticancer effects of conjugates of doxorubicin and unsaturated fatty acids (LNA and DHA). Med. Chem. Res. https://doi.org/10.1007/s00044-019-02443-0. Springer US.
Mod, R.R., et al., 1975. Sulfur derivatives of N,N-disubstituted amides of long chain fatty acids and their antimicrobial activities. JAOCS (J. Am. Oil Chem. Soc.) 52 (11), 455–456 United States.
Moncevičiute-Eringiene, E., 2005. Neoplastic growth: the consequence of evolutionary malignant resistance to chronic damage for survival of cells (review of a new theory of the origin of cancer). Med. Hypotheses 65 (3), 595–604. https://doi.org/10.1016/j.mehy.2005.02.033.
Morin, C., Rousseau, E., Fortin, S., 2013. Anti-proliferative effects of a new docosapentaenoic acid monoacylglyceride in colorectal carcinoma cells. Prostagl. Leukot. Essent. Fat. Acids 89 (4), 203–213. https://doi.org/10.1016/j.plefa.2013.07.004. Scotland.
Moss, G.P., Smith, P.A.S., D, T., 1995. Glossary of class names of organic compounds and reactive intermediates based on structure. Pure Appl. Chem. 67, 1307–1375. https://doi.org/10.1016/b978-0-08-021019-3.50003-1.
Mouradian, M., et al., 2014. Key roles for GRB2-associated-binding protein 1, phosphatidylinositol-3-kinase, cyclooxygenase 2, prostaglandin E2 and transforming growth factor alpha in linoleic acid-induced upregulation of lung and breast cancer cell growth. Prostaglandins Leukot. Essent. Fatty Acids 90 (4), 105–115. https://doi.org/10.1016/j.plefa.2013.12.001.Key.
Narayanan, A., et al., 2015. Anticarcinogenic properties of medium chain fatty acids on human colorectal, skin and breast cancer cells *in vitro*. Int. J. Mol. Sci. 16 (3), 5014–5027. https://doi.org/10.3390/ijms16035014.
Narayanan, B.A., et al., 2003. Modulation of inducible nitric oxide synthase and related proinflammatory genes by the omega-3 fatty acid docosahexaenoic acid in human colon cancer cells. Cancer Res. 63, 972–979.
Narayanan, N.K., Narayanan, B.A., Reddy, B.S., 2005. A combination of docosahexaenoic acid and celecoxib prevents prostate cancer cell growth *in vitro* and is associated with modulation of nuclear factor-kappaB, and steroid hormone receptors. Int. J. Oncol. 26 (3), 785–792 Greece.
Pal, U.K., et al., 2011. Quality and utility of goat milk with special reference to India: an overview. Asian J. Anim. Sci. 5, 56–63. https://doi.org/10.3923/ajas.2011.56.63.
Pasqualini, M.E., et al., 2003. Association between E-cadherin expression by human colon, bladder and breast cancer cells and the 13-HODE:15-HETE ratio. A possible role of their metastatic potential. Prostagl. Leukot. Essent. Fat. Acids 68, 9–16.
Piorecka, K., Stanczyk, W., Florczak, M., 2017. NMR analysis of antitumor drugs: doxorubicin, daunorubicin and their functionalized derivatives. Tetrahedron Lett. 58 (2), 152–155. https://doi.org/10.1016/j.tetlet.2016.11.118. Elsevier Ltd.
Plunkett, W., et al., 1987. 'Saturation of ara-CTP accumulation during high-dose ara-C therapy: pharmacologic rationale for intermediate-dose ara-C.', *Seminars in oncology*. United States 14 (2 Suppl. 1), 159–166.
Pohl, C.H., Kock, J.L.F., Thibane, V.S., 2011. Antifungal free fatty acids: a review. In: Science Against Microbial Pathogens: Current Research and Technological Advances. 1. pp. 61–71.
Pot, G.K., et al., 2008. Opposing associations of serum n-3 and n-6 polyunsaturated fatty acids with colorectal adenoma risk: an endoscopy-based case-control study. Int. J. Cancer 123, 1974–1977. https://doi.org/10.1002/ijc.23729.
Promsuwan, P., Yenjai, C., 2013. Synthesis and cytotoxicity of coumarin derivatives and nordentatin. Asian J. Chem. 25 (7), 3629–3632. https://doi.org/10.14233/ajchem.2013.13687.
Rauf, A., Parveen, H., 2005. Preparation, characterization and antimicrobial activity of fatty alkenoates. Indian J. Chem. B Org. Med. Chem. 44, 1273–1276.
Rauf, A., Sharma, S., Gangal, S., 2007. Microwave assisted efficient one-pot synthesis of solvent-free conditions and their antimicrobial activity. Arkivoc 16, 137–147.
Rose, D.P., Connolly, J.M., 1999. Antiangiogenicity of docosahexaenoic acid and its role in the suppression of breast cancer cell growth in nude mice. Int. J. Oncol. 15 (5), 1011–1015. https://doi.org/10.3892/ijo.15.5.1011. Greece.
Sakai, M., et al., 2012. Arachidonic acid and cancer risk: a systematic review of observational studies. BMC Cancer. BMC Cancer 12, 606. https://doi.org/10.1186/1471-2407-12-606.
Santos, D.S., et al., 2015. Antiproliferative activity of synthetic fatty acid amides from renewable resources. Bioorg. Med. Chem. 23 (2), 340–347. https://doi.org/10.1016/j.bmc.2014.11.019. Elsevier Ltd.
Sauer, L.A., Dauchy, R.T., 1992. The effect of omega-6 and omega-3 fatty acids on3h-thymidine incorporation in hepatoma 7288ctc perfused in situ. Br. J. Canc. 66 (2), 297–303. https://doi.org/10.1038/bjc.1992.260.
Sauer, L.A., Dauchy, R.T., Blask, D.E., 2000. Mechanism for the antitumor and anticachectic effects of n-3 fatty acids. Cancer Res. 60, 5289–5295.
Schiff, P.B., Horwitz, S.B., 1980. Taxol stabilizes microtubules in mouse fibroblast cells. Proc. Natl. Acad. Sci. U. S. A 77 (3), 1561–1565. https://doi.org/10.1073/pnas.77.3.1561.
Seitz, J., Ojima, I., 2011. Drug conjugates with polyunsaturated fatty acids. Drug Delivery in Oncology: From Basic Research to Cancer Therapy 3, 1323–1357. https://doi.org/10.1002/9783527634057.ch41.
Senzaki, H., et al., 1998. 'Dietary effects of fatty acids on growth and metastasis of KPL-1 human breast cancer cells *in vivo* and *in vitro*', *Anticancer research*. GreeceInfo 18 (3A), 1621–1627.
Serini, S., et al., 2009. Dietary polyunsaturated fatty acids as inducers of apoptosis: implications for cancer. Apoptosis 14 (2), 135–152. https://doi.org/10.1007/s10495-008-0298-2.
Serini, S., et al., 2012. DHA induces apoptosis and differentiation in human melanoma cells *in vitro*: involvement of hur-mediated COX-2 mRNA stabilization and β-catenin nuclear translocation. Carcinogenesis 33 (1), 164–173. https://doi.org/10.1093/carcin/bgr240.
Shah, M., Agarwal, B., 2008. Recent advances in management of acute myeloid leukemia (AML). Indian J. Pediatr. 75 (8), 831–837. https://doi.org/10.1007/s12098-008-0155-x.
Shao, W., et al., 2013. Carbon nanotube lipid drug approach for targeted delivery of a chemotherapy drug in a human breast cancer xenograft animal model. Biomaterials 34 (38), 10109–10119. https://doi.org/10.1016/j.biomaterials.2013.09.007. Elsevier Ltd.
Siddiqui, R.A., et al., 2011. 'Docosahexaenoic acid: a natural powerful adjuvant that improves efficacy for anticancer treatment with no adverse effects. Biofactors 37 (6), 399–412. https://doi.org/10.1002/biof.181. Netherlands.
Siena, L., et al., 2018. Electrophilic derivatives of omega-3 fatty acids counteract lung cancer cell growth. Cancer Chemother. Pharmacol. 81 (4), 705–716. https://doi.org/10.1007/s00280-018-3538-3. Germany.
Simopoulos, A.P., 2002. The importance of the ratio of omega-6/omega-3 essential fatty acids. Biomed. Pharmacother. 56, 365–379.
So, W.W., Liu, W.N., Leung, K.N., 2015. Omega-3 polyunsaturated fatty acids trigger cell cycle arrest and induce apoptosis in human neuroblastoma LA-N-1 cells. Nutrients 7, 6956–6973. https://doi.org/10.3390/nu7085319.
Sparreboom, A., et al., 1996. Tissue distribution, metabolism and excretion of paclitaxel in mice. Anti Canccer Drugs 7 (1), 78–86 England.
Spencer, L., et al., 2009. The effect of omega-3 FAs on tumour angiogenesis and their therapeutic potential. Eur. J. Cancer 45 (12), 2077–2086. https://doi.org/10.1016/j.ejca.2009.04.026. Elsevier Ltd.
Sprague, M., Dick, J.R., Tocher, D.R., 2016. Impact of sustainable feeds on omega-3 long-chain fatty acid levels in farmed Atlantic salmon, 2006-2015. Sci. Rep. 6, 21892. https://doi.org/10.1038/srep21892.
Sun, Y., et al., 2017. 'Involvement of apoptotic pathways in docosahexaenoic acid-induced benefit in prostate cancer: pathway-focused gene expression analysis using RT2 Profile PCR Array System', *Lipids in Health and Disease*. Lipids Health Dis. 16 (1), 1–8. https://doi.org/10.1186/s12944-017-0442-5.
Szymczak, M., Murray, M., Petrovic, N., 2008. Modulation of angiogenesis by ω-3 polyunsaturated fatty acids is mediated by cyclooxygenases. Blood 111 (7), 3514–3521. https://doi.org/10.1182/blood-2007-08-109934.
Takahashi, M., et al., 1992. Effect of ω3 and ω6 fatty acids on transformation of cultured cells by irradiation and transfection. Cancer Res. 52 (1), 154–162.
Tao, X., et al., 2012. Enhanced anticancer activity of gemcitabine coupling with conjugated linoleic acid against human breast cancer *in vitro* and *in vivo*. Eur. J. Pharm. Biopharm. 82 (2), 401–409. https://doi.org/10.1016/j.ejpb.2012.06.007. Elsevier B.V.
Tao, Y., et al., 2019. Exploitation of enrofloxacin-loaded docosanoic acid solid lipid nanoparticle suspension as oral and intramuscular sustained release formulations for pig. Drug Deliv. 26 (1), 273–280. https://doi.org/10.1080/10717544.2019.1580798. Taylor & Francis.
Tapiero, H., et al., 2002. Polyunsaturated fatty acids (PUFA) and eicosanoids in human health and pathologies. Biomed. Pharmacother. 56 (5), 215–222. https://doi.org/10.1016/S0753-3322(02)00193-2.
Thiebaut, A.C.M., et al., 2009. Dietary intakes of ω-6 and ω-3 polyunsaturated fatty acids and the risk of breast cancer. Int. J. Cancer 124, 924–931. https://doi.org/10.1002/ijc.23980.
Trevaskis, N.L., Kaminskas, L.M., Porter, C.J.H., 2015. From sewer to saviour - targeting the lymphatic system to promote drug exposure and activity. Nature Publishing Group, a division of Macmillan Publishers Limited. All Rights Reserved. Nat. Rev. Drug Discov. 14, 781–803. https://doi.org/10.1038/nrd4608. Available at:.
Tsuji, M., Murota, S., Morita, I., 2003. Docosapentaenoic acid (22:5, n-3) suppressed tube-forming activity in endothelial cells induced by vascular endothelial growth factor. Prostagl. Leukot. Essent. Fat. Acids 68, 337–342. https://doi.org/10.1016/S0952-3278(03)00025-5.
Urbanek, A., et al., 2012. Composition and antimicrobial activity of fatty acids detected in the hygroscopic secretion collected from the secretory setae of larvae of the biting midge Forcipomyia nigra (Diptera: Ceratopogonidae). J. Insect Physiol. 58, 1265–1276. https://doi.org/10.1016/j.jinsphys.2012.06.014.
Vartakl, S., et al., 1998. 'Gamma-Linolenic acid (GLA) is cytotoxic to 36B10 malignant rat astrocytoma cells but not to "normal" rat astrocytes'. Br. J. Canc. 77 (10), 1612–1620.
Venepally, V., et al., 2016. Synthesis of novel ethyl 1-ethyl-6-fluoro-7-(fatty amido)-1,4-dihydro-4-oxoquinoline-3-carboxylate derivatives and their biological evaluation. Bioorg. Med. Chem. Lett 26 (2), 613–617. https://doi.org/10.1016/j.bmcl.2015.11.063. Elsevier Ltd.

Venepally, V., et al., 2017. Synthesis and biological evaluation of some new N-fatty acyl derivatives of 4,5-dimethoxy tryptamine. Indian J. Chem., Sect. B 56 (5), 531–541.
Vibet, S., et al., 2008. Sensitization by docosahexaenoic acid (DHA) of breast cancer cells to anthracyclines through loss of glutathione peroxidase (GPx1) response. Free Radic. Biol. Med. 44 (7), 1483–1491. https://doi.org/10.1016/j.freeradbiomed.2008.01.009.
Viklund, F., Alander, J., Hult, K., 2003. Antioxidative properties and enzymatic synthesis of ascorbyl FA esters. JAOCS (J. Am. Oil Chem. Soc.) 80 (8), 795–799. https://doi.org/10.1007/s11746-003-0774-1.
Wall, R., et al., 2010. Fatty acids from fish: the anti-inflammatory potential of long-chain omega-3 fatty acids. Nutr. Rev. 68 (5), 280–289. https://doi.org/10.1111/j.1753-4887.2010.00287.x.
Wang, J., et al., 2012. The powerful applications of polyunsaturated fatty acids in improving the therapeutic efficacy of anticancer drugs. Expert Opin. Drug Deliv. 9 (1), 1–7. https://doi.org/10.1517/17425247.2011.618183.
Wang, Y., et al., 2006. Synthesis and preliminary antitumor activity evaluation of a DHA and doxorubicin conjugate. Bioorg. Med. Chem. Lett 16 (11), 2974–2977. https://doi.org/10.1016/j.bmcl.2006.02.066.
Wani, M.C., et al., 1971. Plant antitumor agents. VI. The isolation and structure of taxol, a novel antileukemic and antitumor agent from Taxus brevifolia. J. Am. Chem. Soc. 93 (9), 2325–2327. https://doi.org/10.1021/ja00738a045. United States.
Wen, B., et al., 2003. n-3 Polyunsaturated fatty acids decrease mucosal/epidermal reactions and enhance antitumour effect of ionising radiation with inhibition of tumour angiogenesis. Br. J. Canc. 89 (6), 1102–1107. https://doi.org/10.1038/sj.bjc.6601136.
Wigmore, S.J., et al., 1996. The effect of polyunsaturated fatty acids on the progress of cachexia in patients with pancreatic cancer. Nutrition 12 (1), S27–S30.
Williams, C.D., et al., 2011. A high ratio of dietary n-6/n-3 polyunsaturated fatty acids is associated with increased risk of prostate cancer. Nutr. Res. 31, 1–8. https://doi.org/10.1016/j.nutres.2011.01.002. Elsevier Inc.
Xi Yu, K., et al., 2010. The therapeutic efficacy of conjugated linoleic acid-Paclitaxel on glioma in the rat. Biomaterials 31 (22), 5855–5864. https://doi.org/10.1016/j.biomaterials.2010.03.079. Elsevier Ltd.
Xu, Y., Qian, S.Y., 2014. Anti-cancer activities of ω-6 polyunsaturated fatty acids. Biomed. J. 37 (3), 112–119. https://doi.org/10.4103/2319-4170.131378.Anti-cancer.
Yamasaki, M., et al., 2014. The importance of 1,2-dithiolane structure in α-lipoic acid for the downregulation of cell surface β 1-integrin expression of human bladder cancer cells. Biosci. Biotechnol. Biochem. 78 (11), 1939–1942. https://doi.org/10.1080/09168451.2014.943647. Taylor & Francis.
Yang, B., et al., 2014. Ratio of n-3/n-6 PUFAs and risk of breast cancer: a meta-analysis of 274135 adult females from 11 independent prospective studies. BMC Cancer. BMC Cancer 14, 1–14. https://doi.org/10.1186/1471-2407-14-105.
Yang, J.S., et al., 2011. Synthesis and biological evaluation of novel aliphatic amido-quaternary ammonium salts for anticancer chemotherapy: Part i. Eur. J. Med. Chem. 46 (7), 2861–2866. https://doi.org/10.1016/j.ejmech.2011.04.009. Elsevier Masson SAS.
Yang, P., et al., 2012. Arachidonic acid metabolism in human prostate cancer. Int. J. Oncol. 41, 1495–1503. https://doi.org/10.3892/ijo.2012.1588.
Yarla, S.N., et al., 2016. Targeting arachidonic acid pathway by natural products for cancer prevention and therapy. Semin. Cancer Biol. 40–41, 48–81. https://doi.org/10.1016/j.semcancer.2016.02.001. Elsevier Ltd.
Yee-Ki Lee, C., et al., 2010. The cell cycle effects of docosahexaenoic acid on human metastatic hepatocellular carcinoma proliferation. Int. J. Oncol. 36, 991–998. https://doi.org/10.3892/ijo_00000579. Abstract.
Yvon, A.M.C., Wadsworth, P., Jordan, M.A., 1999. Taxol suppresses dynamics of individual microtubules in living human tumor cells. Mol. Biol. Cell 10, 947–959. https://doi.org/10.1091/mbc.10.4.947.
Zheng, C.J., et al., 2005. Fatty acid synthesis is a target for antibacterial activity of unsaturated fatty acids. FEBS Lett. 579 (23), 5157–5162. https://doi.org/10.1016/j.febslet.2005.08.028.
Zheng, J.-S., et al., 2013. Intake of fish and marine n-3 polyunsaturated fatty acids and risk of breast cancer: meta-analysis of data from 21 independent prospective cohort studies. BMJ (Clin. Res. ed.) 346, f3706. https://doi.org/10.1136/bmj.f3706.
Zhu, S., et al., 2018. Metabolic shift induced by ω-3 PUFAs and rapamycin lead to cancer cell death. Cell. Physiol. Biochem. 48 (6), 2318–2336. https://doi.org/10.1159/000492648.
Zijlstra, J.G., et al., 1987. Influence of docosahexaenoic acid *in vitro* on intracellular adriamycin concentration in lymphocytes and human adriamycin-sensitive and -resistant small-cell lung cancer cell lines, and on cytotoxicity in the tumor cell lines. Int. J. Cancer 40 (6), 850–856. https://doi.org/10.1002/ijc.2910400625. United States.