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Chapter 5

Fatty Acids and Their Analogues as Anticancer Agents

Jubie Selvaraj

Additional information is available at the end of the chapter

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Abstract

Recent research supports the beneficial effects of dietary polyunsaturated fatty acids (PUFAs) on inhibiting tumour development. Long-chain fatty acids modulate the tumour cell response to chemotherapeutic drugs. Investigators recently claimed high dietary intake of omega-6 polyunsaturated fatty acids such as linoleic acid especially in association with a low intake of omega-3 polyunsaturated fatty acids such as docosahexaenoic acid to increase risks for cancers of the breast, colon and possibly prostate. In addition to these facts, a number of investigations have demonstrated that a modified fatty acid analogues are promising molecules in cancer prevention and have potential in the treatment of cancer. Although billions of dollars have been spent on research and development on anticancer drugs, the disease remains uncontrolled. It is expected that anticancer agents preferentially kill tumour cells without causing adverse effects on normal cells. But this is rarely achieved with the existing cancer therapy. Hence, polyunsaturated fatty acids have come under the category of nutraceuticals/functional foods; their exploration in the treatment of cancer may be considered as safe. This chapter describes the effects of long-chain fatty acids and their analogues in cancer chemotherapy.

Keywords: fatty acids, cancer, PUFA, fatty acid synthase, omega-3

1. Introduction to fatty acids

Plants, animals and microbes generally contain even number of carbon atoms in straight chains, with a carboxylic group at one end and double bonds with *cis* configuration on the another end. The chain length of the common fatty acids varies between 14 and 22, but on occasions can span between 2 and 36 or even more in animal tissues. Fatty acids found in animal tissues have one to six double bonds, whereas those in algae have up to five bonds. Higher plants rarely have more than three, whereas microbial fatty acids occasionally have more than one. The fatty acids, which are derived from triglycerides or phospholipids, have a chain of

4–28 carbons. Fatty acids, which are not attached to other molecules, are known as free fatty acids which on breakdown yield large quantities of ATP. Many cell types use either glucose or fatty acids for this purpose. In particular, heart and skeletal muscle prefer fatty acids [1].

Fatty acids may be monounsaturated, polyunsaturated or saturated (**Figure 1**). They help in moving oxygen through the blood stream to all parts of the body, aid cell membrane development and strengthen the organs and tissue. They also help in healthy skin and prevent early ageing and more importantly help rid the arteries of cholesterol build-up.

2. Types of fatty acids

2.1. Saturated fatty acids

Saturated fatty acids are straight-chain compounds with 14, 16 and 18 carbon atoms. The most abundant saturated fatty acids found in animal and plant tissues are esterified with odd- and even-numbered homologues with 2–36 carbon atoms. A list of common saturated fatty acids together with their trivial names and shorthand designations is given in **Table 1**.

2.2. Monoenoic fatty acids

Monoenoic fatty acids are straight-chain fatty acids containing 10–30 carbon atoms with one *cis*-double bond. The double bond can be in different positions and this is specified in the systematic nomenclature in relation to the carboxyl group (**Table 2**).

2.3. Polyunsaturated fatty acids

Polyunsaturated fatty acids (PUFAs) are fatty acids which contain multiple double bonds and are subdivided into families according to their derivation from specific biosynthetic precursors. In each instance, the families contain between two and six *cis*-double bonds separated

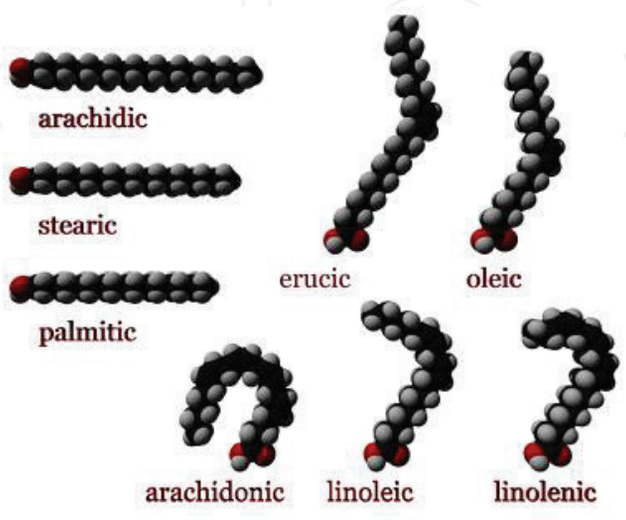


Figure 1. Naturally occurring fatty acids.

S. no.	Systematic name	Shorthand designation	Trivial name
1.	Ethanoic	2:0	Acetic
2.	Butanoic	4:0	Butyric
3.	Hexanoic	6:0	Caproic
4.	Octanoic	8:0	Caprylic
5.	Nonanoic	9:0	Pelargonic
6.	Decanoic	10:0	Capric
7.	Undecanoic	11:0	–
8.	Dodecanoic	12:0	Lauric
9.	Tridecanoic	13:0	–
10.	Tetradecanoic	14:0	Myristic
11.	Pentadecanoic	15:0	Myristic
12.	Hexadecanoic	16:0	Palmitic
13.	Heptadecanoic	17:0	Margaric
14.	Octadecanoic	18:0	Stearic
15.	Nonadecanoic	19:0	Margaric
16.	Arachidic	20:0	Eicosanoic
17.	Heneicosanoic	21:0	–
18.	Docosanoic	22:0	Behenic
19.	Tetracosanoic	24:0	Lignoceric

Table 1. Saturated fatty acids of general formula $CH_3(CH_2)_n$ COOH.

by single methylene\ groups, and have the same terminal structure [2]. A list of some of the important PUFAs is presented in **Table 3**.

2.4. Branched-chain and cyclopropane fatty acids

Branched-chain fatty acids, which occur widely in nature, are present as minor components except in bacteria, where they appear to replace unsaturated fatty acids functionally. The branch consists of a single methyl group, either on the penultimate (*iso*) or on the antepenultimate (*anteiso*) carbon atoms [3, 4].

2.5. Oxygenated and cyclic fatty acids

A large number of hydroperoxy, hydroxyl and epoxy fatty acids (eicosanoids) are formed enzymatically as intermediates in the biosynthesis of prostanoids. A large number of hydroxy fatty acids occur in seed oils, and the best known of these is ricinoleic acid which is the principle constituent of castor oil. Polyhydroxy fatty acids are present in plant cutins, shellacs and many seed oils.

S. no.	Systematic name	Shorthand designation	Trivial name
1.	*cis*-9-Tetradecenoic	14:1(n-5)	Myristoleic
2.	*cis*-9-Hexadecenoic	16:1(n-7)	Palmitoleic
3.	*trans*-3-Hexadecenoic	–	–
	cis-6-Octadecenoic	18:1(n-12)	Petraselenic
4.	*cis*-9-Octadecenoic	18:1(n-9)	Oleic
5.	*cis*-11-Octadecenoic	18:1(n-7)	*cis*-Vaccenic
6.	*trans*-11-Octadecenoic	–	Elaidic
7.	*cis*-9-Eicosenoic	20:1(n-11)	Gadoleic
8.	*cis*-11-Octadecenoic	18:1(n-9)	Gondic
9.	*cis*-13-Docosenoic	22:1(n-9)	Erucic
10.	*cis*-15-Tetracosenoic	24:1(n-9)	Nervonic

Table 2. Monoenoic fatty acids of general formula $CH_3(CH_2)mCH=CH(CH_2)nCOOH$.

2.6. Omega-3 and omega-6 fatty acids

The biological fatty acids are of different lengths, the last position is labelled as *omega* (ω). *Omega-3* fatty acids are long-chain polyunsaturated fatty acids (18–22 carbon atoms) with the first of many double bonds beginning with the third carbon atom. However, *omega-6* fatty acids have the first of many double bonds beginning with the sixth carbon atom. Alpha-linolenic acid (ALA) and linoleic acid (LA) are the parent compounds of the omega-3 family and omega-6 family of fatty acids, respectively.

S. no.	Systematic name	Shorthand designation	Trivial name
1.	9,12-Octadecadienoic*	18:2(n-6)	Linoleic
2.	6,9,12-Octadecatrienoic	18:3(n-6)	γ-Linolenic
3.	8,11,14-Eicosatrienoic	18:3(n-6)	Homo-γ-linolenic
4.	5,8,11,14-Eicosatetraenoic	20:4(n-6)	Arachidonic
5.	4,7,10,13,16-Eicosapentaenoic	20:5(n-6)	–
6.	9,12,15-Octadecatrienoic	18:3(n-6)	α-Linolenic
7.	5,8,11,14,17-Eicosapentaenoic	20:5(n-3)	EPA
8.	7,10,13,16,19-Docosapentaenoic	22:5(n-3)	–
9.	4,7,10,13,16,19-Docosahexaenoic	22:5(n-3)	DHA
10.	5,8,11-Eicosatrienoic	20:3(n-9)	Mead's acid

*The double bond configuration in each instance is *cis*.

Table 3. Polyunsaturated fatty acids of general formula $CH_3(CH_2)m(CH=CHCH_2)x(CH_2)$ n COOH.

Although the International panel of lipid experts says the ideal ratio of *omega-3* to *omega-6* essential fatty acids is approximately 1:1, still we follow the ratio 20:1 in our diet [5]. Long-chain polyunsaturated fatty acids cannot be formed *de novo* but can be synthesized from the essential fatty acids like linoleic acid and alpha-linolenic acid. These two essential fatty acids are desaturated and lengthened progressively by microsomal enzyme systems to form highly unsaturated, long-chained fatty acids such as arachidonic acid and docosahexaenoic acid (DHA). The *omega-3 and omega-6* fatty acids are not interconvertible. Dietary fish and fish oil supplements are a direct source of *omega-3* fatty acids and dietary oils have large quantity of *omega-6* fatty acids [6].

3. Polyunsaturated fatty acids as anticancer agents

Yonesawa and co-workers carried out the inhibitory effect of conjugated eicosapentaenoic acid (cEPA) on mammalian DNA polymerase and topoisomerase activities and human cell proliferation. They found that the inhibitory effect of cEPA was stronger than that of the non-conjugated EPA and suggested the therapeutic potential of cEPA as a leading anticancer compound that poisons mammalian DNA polymerase (POLS) [7]. The work carried by *Unduri* revealed the tumouricidal and antiangiogenic actions of gamma-linolenic acid (GLA) and its derivatives. It was found that GLA being an endogenous naturally occurring molecule had no significant side effects [8]. Paul *et al.* reported that the long-chain eicosapentaenoic acid (EPA) and docosahexaenoic acids (DHA) have been consistently shown to inhibit the proliferation of breast and prostate cancer cell lines *in vitro* and to reduce the risk and progression of these tumours in animal experiments. Many investigations revealed that the above-said fatty acids inhibit cyclooxygenase-2 and the oxidative metabolism of arachidonic acid (AA) to PGE_2. EPA and DHA also have been shown to inhibit lipoxygenase which metabolizes AA to hydroxyl eicosatetraenoic acids and leucotrienes which suppress apoptosis, stimulate angiogenesis and stimulate tumour cell division (**Figure 2**). Further, they explained that the n-3 PUFAs potentially affect carcinogenesis by specific mechanisms [9]. These mechanisms are as follows: (1) alteration of the response of immune system to cancer cells through the suppression of arachidonic acid (AA, 20:4n-6)-derived eicosanoid biosynthesis; (2) alteration of metabolism, cell growth and differentiation; (3) alteration of oestrogen metabolism, which leads to reduced oestrogen-stimulated cell growth; (4) alteration of free radicals and productivity; and (5) alteration of the mechanisms involving insulin sensitivity and membrane fluidity. Interest in the use of supplementary omega-3-fatty acids to reduce the risk of cancer and other chronic-debilitating conditions, including cardiovascular disease and cognitive impairment, stems from several long-standing avenues of registration [9, 10]. Furthermore, the anticancer activity of fatty acids is well evidenced by Helmut *et al*. in experimental and human studies, which summarize that a high intake of omega-3 PUFAs and monounsaturated fatty acids is protective in breast, colon and prostate cancers [11].

The author and her research group isolated methyl gamma linolenate (**GLA-ME**) (**1**) from *Spirulina platensis* and the compound showed strong cytotoxicity against A-549 cells [13] when compared with the standard drug Rutin. Rutin is a bioflavanol which is a well-established

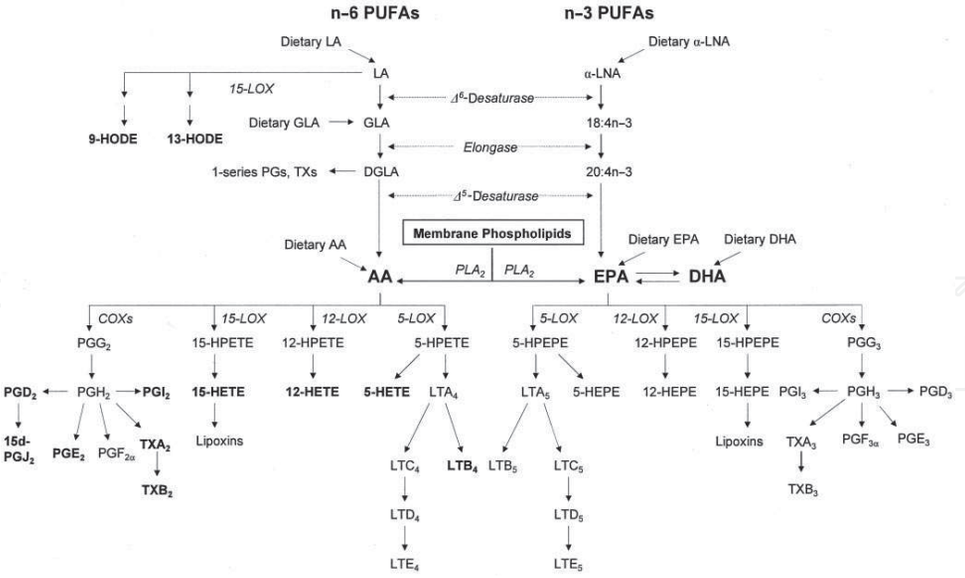
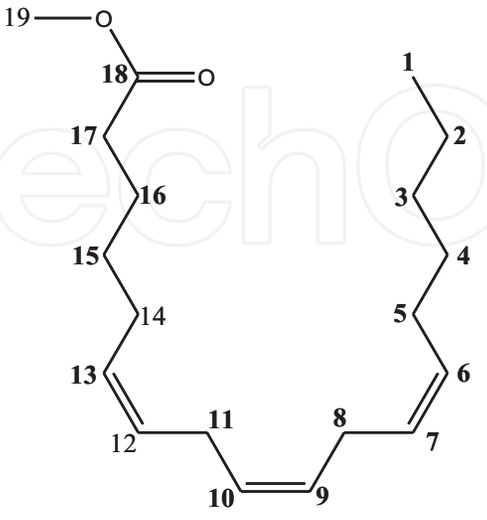


Figure 2. Overview of the metabolism of n-6 and n-3 polyunsaturated fatty acids (PUFAs) into eicosanoids involved in inflammation and carcinogenesis [12].

promising anticancer agent, and its mechanism may be due to the induction of apoptosis [14]. The comparative results are given in **Figure 3** and **Table 4**, respectively. The probable mechanism may be due to the induction of apoptosis of tumour cells by augmenting free radical generation. It is evidenced by the research work carried out by Unduri *et al.* [8]. They also reported that the induction of apoptosis of tumour cells by GLA is due to its action at the gene/oncogene level and by altering BCl-2 expression. Hence, it may be concluded that the cytotoxicity shown by GLA-ME may be due to the induction of apoptosis effect. However, a detailed study of this mechanism is in progress.



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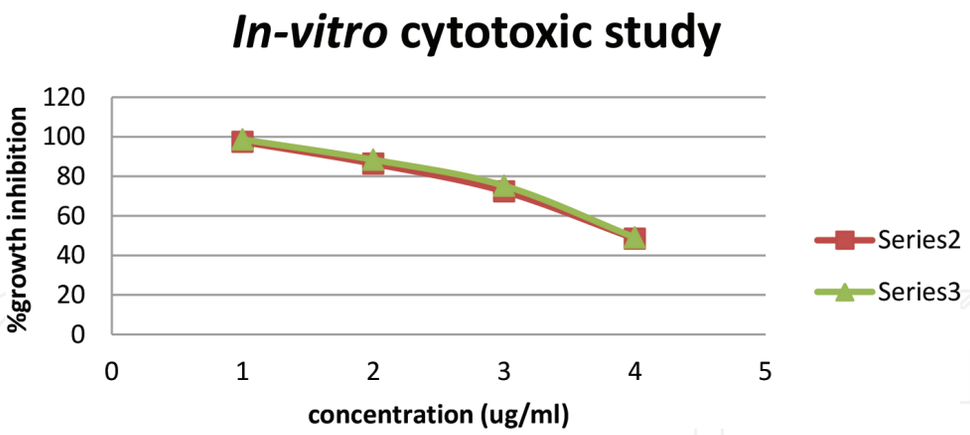


Figure 3. *In vitro* cytotoxic studies □: GLA-ME, Δ: standard rutin.

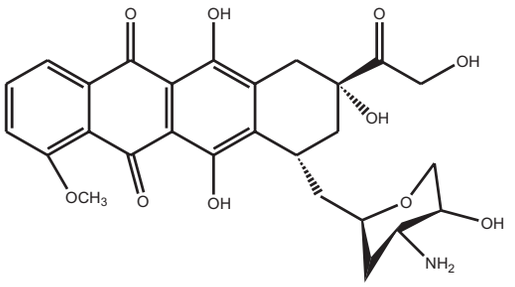
S. no.	Compound	Concentration (μM)	% growth inhibition	CTC_{50}
1.	**GLA-;ME**	3.333	97.45	0.468
2.		1.666	86.39	
3.		0.833	72.38	
4.		0.416	48.45	
5.	**Rutin**	3.333	98.65	0.442
6.		1.666	88.41	
7.		0.833	75.25	
8.		0.416	49.05	

Table 4. Determination of cytotoxicity by SRB method.

4. Polyunsaturated fatty acids as adjunct to chemotherapeutic agents

Kong and co-workers found out that gamma linolenic acid modulates the response of multi-drug-resistant K562 leukaemic cells to anticancer drugs. The study also revealed that GLA could modulate the response to anticancer drugs in P-gp overexpressing multidrug-resistant cells, which could be due to decrease P-gp expression [15]. In another study, Julie and co-workers reported that alpha linolenic acid and docosahexaenoic acid alone combined with trastuzumab reduced HER2 overexpressing breast cancer cell growth but differentially regulated HER2-signalling pathways. Their finding is different in classic mechanisms whereby n-3 PUFAs exert their effect in breast cancer. The results strongly suggest that DHA reduces growth factor receptor signalling as indicated by reductions in the phosphorylation of AKT and MAPK while the opposite effect is seen for the plant-based n-3 PUFA ALA [16]. Effenberger and co-workers synthesized novel N-acylhydrazones of doxorubicin which were derived from saturated, unsaturated and methyl or bornyl terminated fatty acids. The mode of cytotoxic action of the hydrazones was largely apoptotic. They led to a distinct long-term decrease

of bcl-2 MRNA expression, the precise apoptotic mechanism and the involvement of caspases varied for the individual cell lines and test compounds. The apoptosis of 518A2 melanoma cells treated with some compounds was characterized by an early onset of initiator caspase-9 activity. By contrast, apoptosis elicited in 518A2 or in HL-60 cells by remaining compounds was accompanied by high-initiator caspase-8 activity. The genuine slump of the bcl-2 mRNA expression may be the reason for the observed quick and steep hike of the ratio of bax mRNA to bcl-2 mRNA in 518A2 cells. Apoptosis induced by doxorubicin **(2)** and its derivatives (**3)** and (**4)** in HL-60 and 518A2 cells also proceeds with a swift and distinct loss of mitochondrial membrane potential regardless of the divergent caspase kinetics. This was a proof that fatty acid analogues are more than just lipophilic shuttle groups [17].



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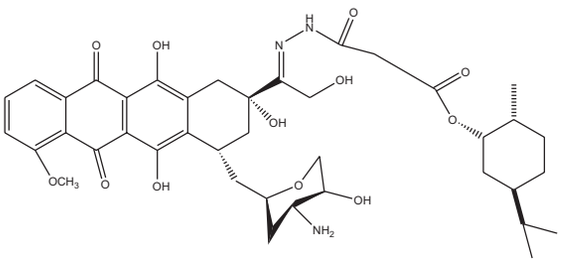

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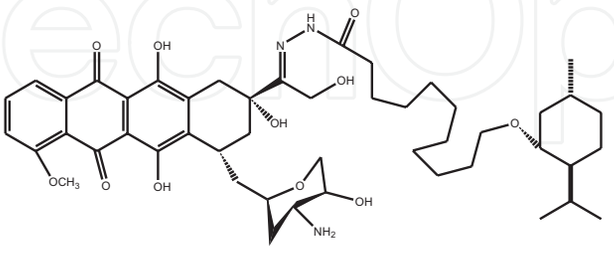

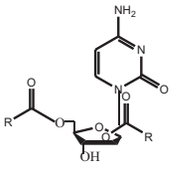

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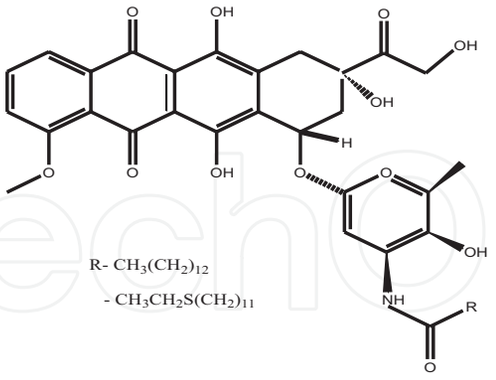
Piyali *et al.* studied the antiproliferative activity of somatostatin analogue with N-terminal acylation with long-chain fatty acids in human breast adenocarcinoma cell lines. The antiproliferative activity of the somatostatin analogue RC-160 (D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Trp-NH_2) is limited by its short serum half-life. To circumvent this limitation, fatty acids of chain lengths ranging from 4 to 18 were individually conjugated to the N-terminal residue of RC-160. Although the affinity of palmitoyl –RC-160 towards somatostatin receptors remains unaltered when compared to the –RC-160, it exhibited significantly higher antiproliferative activity on MCF-7 cells. On further increase in the lipopeptide chain, the bioactivity of lipophilized –RC-160 was reduced. Increasing the peptide hydrophobicity beyond this range reduced the bioactivity of lipophilized –RC-160. Accordingly, stearoyl –RC-160 manifested lower antineoplastic activity and receptor-binding affinity relative to palmitoyl –RC-160 and RC-160 itself. It was observed that an increase in bioactivity was manifested within an optimum range of the lipopeptide. The probable mechanisms may be alterations of the signalling pathways. Lipophilization of RC-160 with long-chain fatty acids like palmitic acid improves its stability and antiproliferative activity, thereby improving the scope of enhancing its therapeutic index [18].

5. Fatty acid analogues as anticancer agents

A number of investigations have demonstrated that a variety of modified fatty acid analogues are promising molecules in cancer prevention and have potential in the treatment of cancer. Bhupender *et al.*synthesized fatty acyl amide derivatives of doxorubicin (**5**) and evaluated their *in vitro* anticancer activities. The results indicated that the designed molecule with comparable antileukaemia activity to cytarabine with sustained release effect is possible by structure modification [19].



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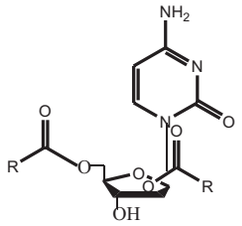
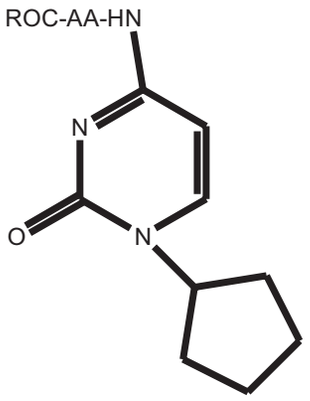


6

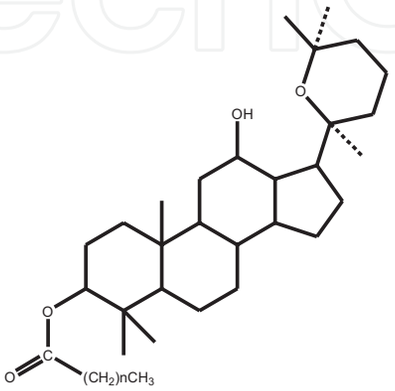
They also synthesized fatty acyl ester derivatives (**6**) of cytarabine and evaluated them for anti-leukaemia activity. Some of 2′,5′-dimyristoyl derivatives of cytarabine were found to inhibit the growth of CCRF-CEM cells [20]. Liu *et al.* reported the synthesis and antitumour evaluation of N^4 fatty acyl amino derivatives of cytarabine. The bioavailability of cytarabine is low due to its low lipophilicity. In order to improve the lipophilicity and bioavailability of cytarabine, a series of fatty acyl amino acid cytarabine analogues (**7**) were synthesized. It was found that the derivatives synthesized were more lipophilic than cytarabine. The antitumour activity determined in HL-600 and HeLa cells showed that the derivatives were more active in HeLa cells than cytarabine while most of them demonstrated similar activity to cytarbine in HL-60 cells. The length of fatty acids in the derivatives seemed to have an impact on the activity observed [21].



(7)

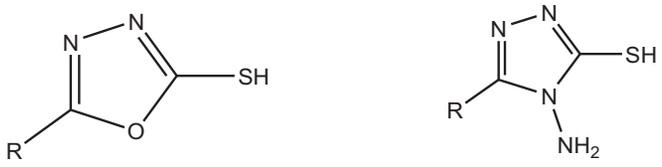
AA=Amino acids R-sugar

Zhang Chun-hong and co-workers synthesized new panaxadiol fatty acid esters (**8**) and evaluated them for their antitumour activity. Tumour cell used was Vero cell line. Positive control was 5-FU, blank was an RPMI1640 culture medium, negative control was an RPMI1640 culture medium and the solvent for drugs to be tested. The compounds show the strongest antitumour activity [22].



8

Earlier, the author of the present chapter has reported some novel fatty acid heterocyclic conjugates and their anticancer evaluation on human lung carcinoma cell lines [23, 24]. The compounds have shown comparable cytotoxicity towards human lung carcinoma cell lines. The compound (**9**), fatty acid chain substituted 1,3,4-oxadiazole showed maximum cytotoxic activity. It was observed that the presence of toxophoric –N=C-O- linkage in 1,3,4 oxadiazole nucleus may be responsible for the antitumour activity. Further, 1,3,4 oxadiazole is a good bioisostere of amide and ester functionalities with substantial improvement in biological activity in hydrogen-bonding interactions with different targets responsible for the tumour development. The 1,2,4-triazole substituted fatty acid analogues (**10**) displayed promising cytotoxicity towards human lung carcinoma cell lines. It was also observed that the length of the fatty acids plays a vital role in antitumour activity.



9 10

R-long chain fatty acids

6. Fatty acid synthase as a potential target in cancer

Human fatty acid synthase (HFAS) is a multifunctional enzyme that is essential for the endogenous synthesis of long-chain fatty acid from its precursor acetyl Co-A and malonyl Co-A (**Figure 4**). Blocking HFAS activity causes cytotoxicity [25]. The unique carboxyl terminal thioesterase (TE) domain of fatty acid chain plays a critical role in regulating the chain length of fatty acid releases. Also, the up-regulation of HFAS in a variety of cancer makes the thioesterase domain a candidate target for therapeutic treatment [26]. It was evident from the literature that the long alkyl/alkenes tail of the fatty acids can bind into the long groove tunnel site of thio-esterase domain of FAS which may be one of the factors of anticancer activities of fatty acids [27].

Employing these strategies, the author and her research group carried out the *in silico* studies on fatty acid analogues. The group designed new derivatives of stearic acid and palmitic acid and studied their *in silico*-binding affinities towards key enzyme human fatty acid synthase-thio-esterase domain (PDB code 2PX6). The literature clearly says that an identification of oncogenic antigen-519 (OA-519) from human breast carcinoma cells as FAS has made it an important diagnostic and prognostic marker for breast cancer patients [28, 29]. By superposing the scaffold structure of all our designed analogues, it is seen that these analogues bind in the same orientation and similar position in terms of the common structure, that is, long aliphatic chain (**Figure 5**). It complies with the fact that the substrate-binding site of HFAS is made up of hydrophobic groove. The docking studies revealed that there are two hydrogen-bonding interactions between the OH group of triazolo thiadiazole of

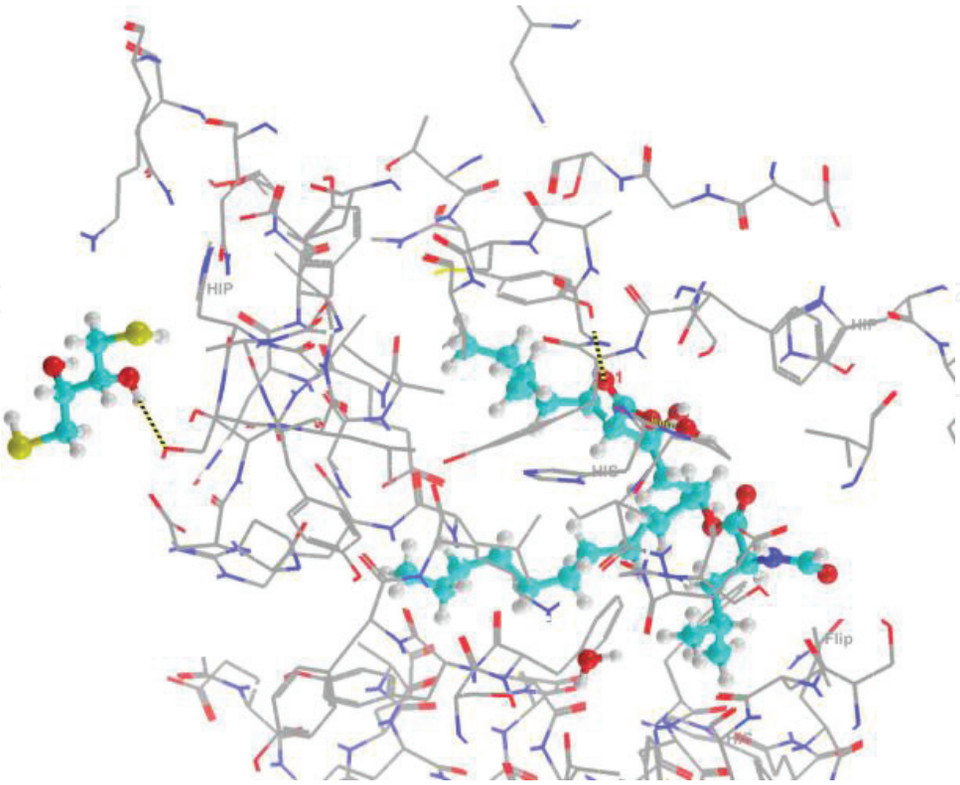


Figure 4. Human fatty acid synthase (PDB id: 2PX6).

synthesized analogues and HIS-2481 and SER-2308 residues (**Figure 6**). These interactions revealed the important binding mode, since these two residues are present in the *"catalytic triad"* of FAS-TE domain [30]. Further, the long alkyl/alkenyl chain of our synthesized analogues fits into the hydrophobic groove of the substrate-binding site. The docking pose and hydrogen-bonding interactions of one of the representative compounds are shown in **Figures 5** and **6**, respectively.

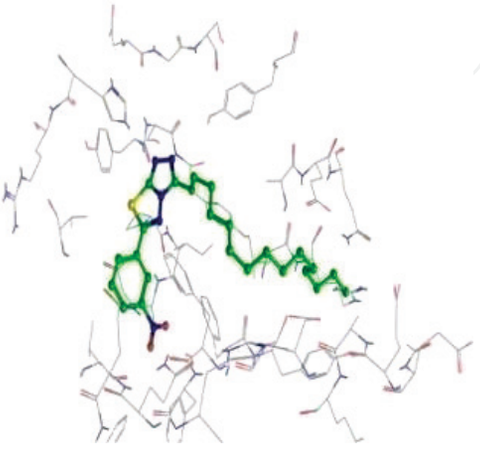


Figure 5. Docking pose.

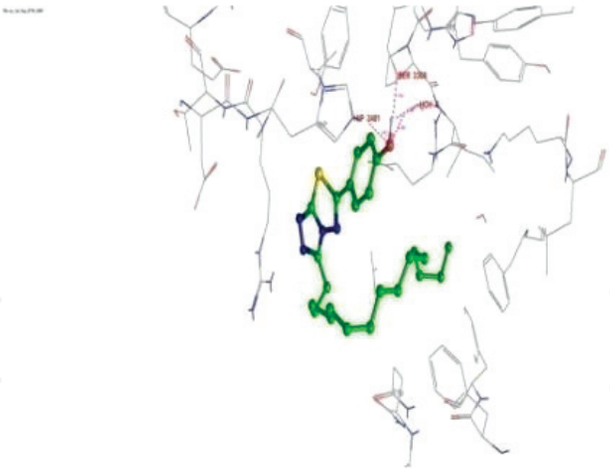


Figure 6. Hydrogen-bonding interactions.

Babak Oskouian and co-workers reported the overexpression of fatty acid synthase in $SKBR_3$ breast cancer cell line and. The objective of this study was to use a breast cancer-derived cell line, $SKBR_3$, as a model to define the underlying mechanism for overexpression of FAS in cancer cells [31]. Silva *et al.* reported a clinic pathological study of $ErbB_2$ and Ki-67 in head and neck squamous cell carcinoma (SCC) and the overexpression of fatty acid synthase enzyme. They showed FAS expression in HNSCC and pointed out ki-67 as a useful prognostic marker for these tumours [32]. Michelle Agostini *et al.* reported the proliferation of human oral squamous carcinoma cells and fatty acid synthase. FAS is overexpressed in several human cancers, such as prostate, breast, bladder, liver, lung, melanoma and oral squamous cell carcinoma [33].

7. Concluding remarks

As part of a conclusion to our discussion, the various studies have shown that fatty acids not only augment the tumouricidal action of anticancer drugs but also enhance the uptake of anticancer drugs leading to an increase in the intracellular concentration of the anticancer drugs. The omega-3 fatty acids have become adjutants to chemotherapeutic agents. Although the production of the above-said fatty acids is a big challenge, a possibility would be gradually implementing the production of these fatty acids in clinical use. Such novel uses of fatty acids in cancer therapy would provide the lipid field with a new avenue to impact public health.

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