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## **Anticancer Drug — Friend or Foe**

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Tuğba Taşkın-Tok and Sivakumar Gowder

Additional information is available at the end of the chapter

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### **1. Introduction**

Cancer is the third most lethal disease in the world after cardiovascular, parasitic and infectious diseases, based on reports from American Cancer Society (ACS) [1,2]. In 2011, nearly 13 million people are diagnosed with cancer and hence, cancer continues to be a great threat to people now [3]. Thus, the medical needs for cancer remain one of the most demanding areas in scientific research. Several studies have been carried out to prevent and treat cancers. Chemoprevention is defined as pharmacological intervention with synthetic or naturally occurring compounds that may inhibit or prevent carcinogenesis [4]. Cancer treatment involves surgery, radiation and drugs. Surgery-the first line of therapy, is used for early stage of cancer. Radiotherapy is most often applied in a localised setting and conjunction with surgical procedures. The last one, drugs are implemented with chemotherapy (CTX), which employs a wide group of drugs that have cytotoxic effects. The anticancer drugs inhibit cell division and proliferation and are less selectivity towards cancer cells. Thus, these drugs not only destroy cancer cells but also destroy normal cells.

In this chapter “Anti Cancer Drug: Friend or Foe” we have evaluated the beneficial and harmful effects of anticancer drugs.

### **2. Anticancer drugs — Benefical effects**

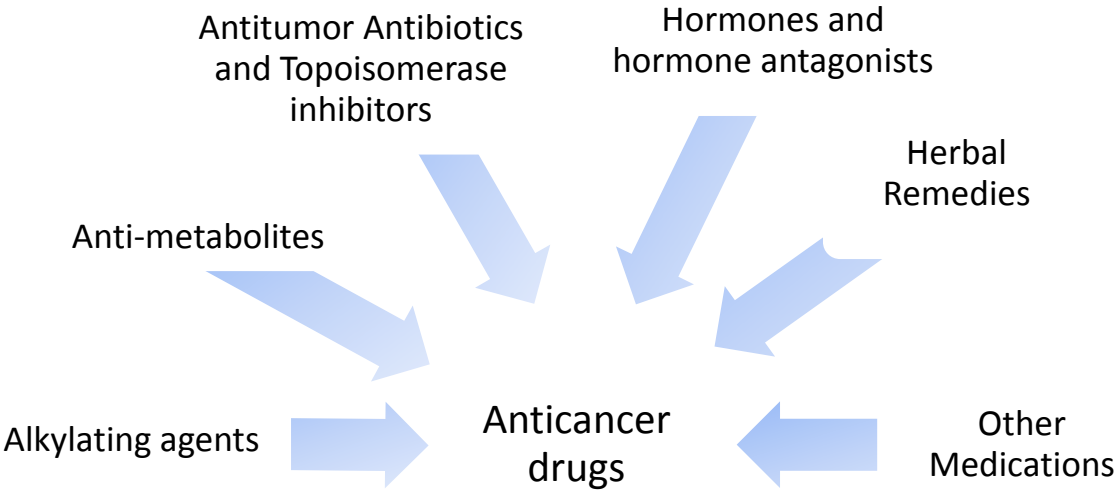
Anticancer or chemotherapy drugs are chemicals that can denature cancer cells by arresting their growth. Though anticancer drugs affect dividing cancer cells, normal cells are also affected in the course of the event. The most affected cells are:

- *bone marrow,*
- *gonads (sex organs),*

- *gastrointestinal tract*, and
- *skin (hair follicle cells)*.

In addition to the above organs, liver and kidneys (slow proliferating cells) are affected since they are the organs of metabolism or target organs of toxicity.

Today, more than 100 different drugs have been used for chemotherapy, either alone or in combination with other treatments. For several years, the most effective drugs used in chemotherapy were considered to be DNA damaging agents [5]. These drugs can be divided into different categories based on their mechanism of action. They are summarized in Figure 1.



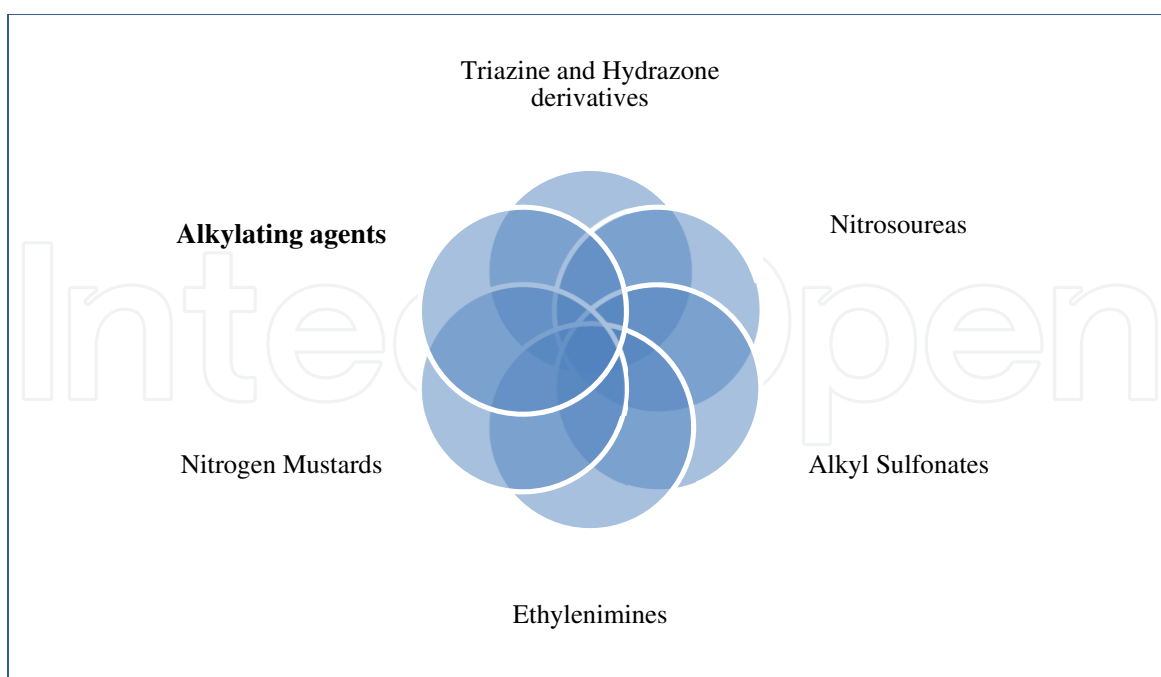
**Figure 1.** Classification of anticancer drugs.

**2.1. Alkylating agents (Figure 2)**

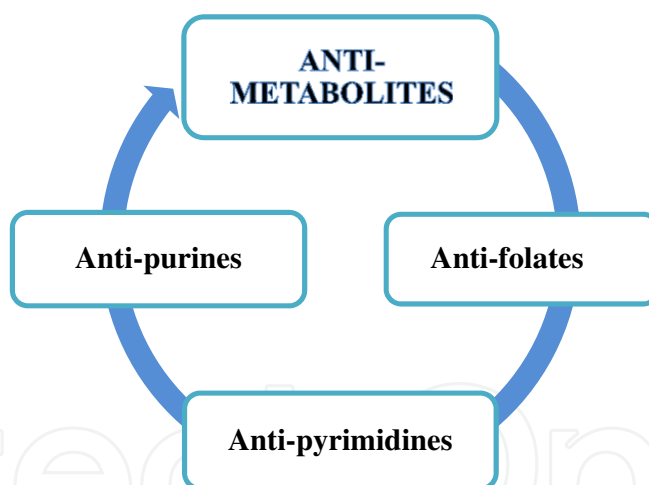
This class of drugs directly damages DNA by adding methyl or other alkyl groups onto nucleotide bases [6] and thereby inhibit their correct utilization by base pairing leading to mutation, DNA fragmentation as well as inhibition of DNA replication and transcription. They also disrupt cell respiration and intermediary metabolism by alkylation of proteins and enzymes. The anticancer drugs that contain alkylating agents are *cyclophosphamide*, *ifosfamide*, *melfalan*, and *chlorambucil*.

**2.2. Anti-metabolites (Figure 3)**

Inhibitors of DNA synthesis inhibit essential biosynthetic processes or are incorporated into DNA, RNA, proteins and other macromolecules. These drugs (Figure 3) are either structural analogues for heterocyclic bases or agents interfering with folate metabolism. DNA building blocks include heterocyclic bases and folic acid. They inhibit main steps in the formation of purine and pyrimidine bases as well as nucleotides [7]. This class of drugs includes antifolates (*methotrexate*, *pemetrexed*) [8], antipyrimidines (*5-fluorouracil*, *capecitabine*, *eniluracile*, *hydroxyurea*) [9] and antipurines (*6-mercaptopurine*, *6-thioguanine*).



**Figure 2.** Family of alkylating agents.



**Figure 3.** Anti-metabolites.

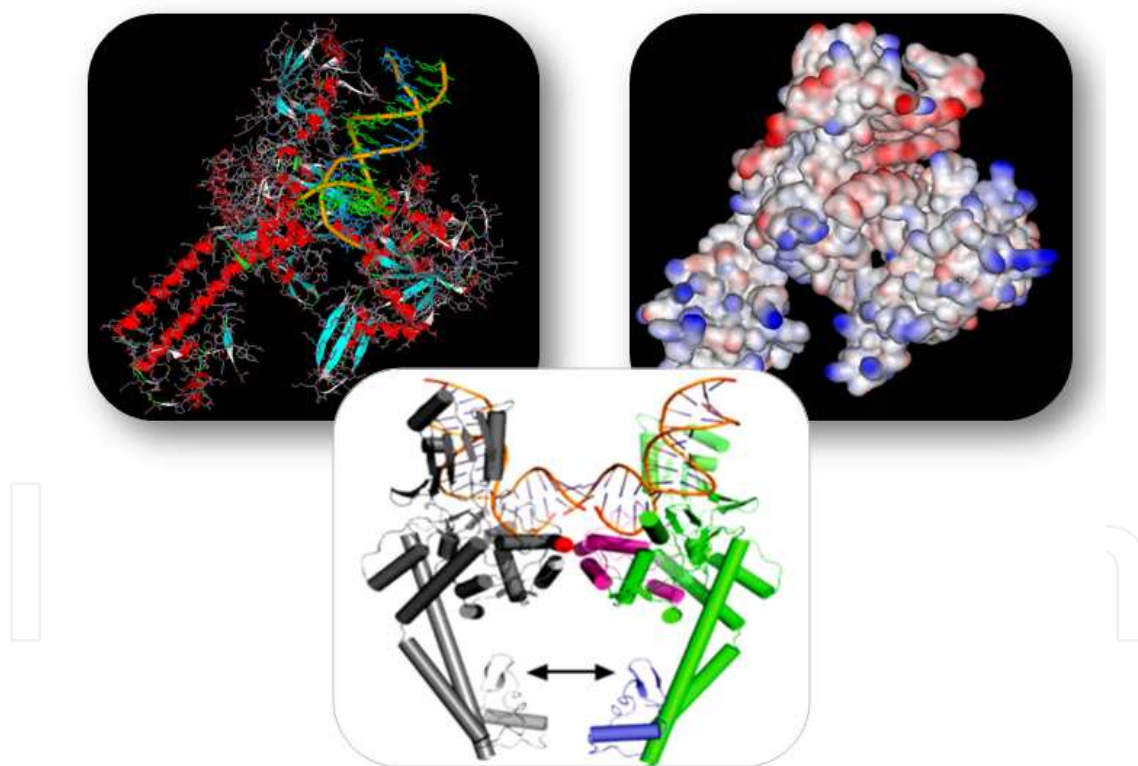
### 2.3. Antitumor Antibiotics and Topoisomerase Inhibitors

Antitumor antibiotics and topoisomerase inhibitors are obtained from the cultures of various microorganisms. Examples:

- *Doxorubicin (Adriblastina),*
- *Daunorubicin (Remember Cerubi),*
- *Bleomycin (Bleoc's),*

- *Mitomycin*,
- *Mithramycin*, and
- *Epirubicin*.

Furthermore, topoisomerase inhibitors have been used to interfere with the action of topoisomerase I and II enzymes. These enzymes regulate the changes in DNA structure which includes DNA replication, transcription, recombination, and chromatin remodelling [10-15]. The important inhibitors are *camptothecin*, *irinotecan*, *topotecan* for Topoisomerase I; *Etoposide* (VP-16), *teniposide*, *doxorubicin*, *daunorubicin*, *ellipticine* etc, for Topoisomerase II. These drugs inhibit the ability of the topoisomerase to cleave nucleic acid molecules. Although these types of drugs have important clinical efficacy, they have undesired and/or adverse effects such as drug resistance, poor bioavailability problems and myelosuppression. Furthermore, some of them lead to disruption or stabilization of DNA, so that these are also called as topoisomerase poisons. The other inhibitors of topoisomerase bind to enzyme or DNA and interrupt the catalytic activity of the enzyme and prevent the enzyme binding actions.

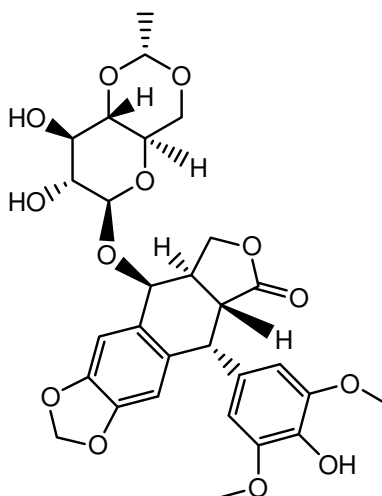


**Figure 4.** Structure of DNA-Topoisomerase II.

Bi- and ter-benzimidazole derivatives constitute a new class of DNA Topo I and II inhibitors [16-20]. In addition, a camptothecin derivative with a benzoxazole ring is shown significantly more potent than camptothecin as an inhibitor of DNA Topo I [21]. It is of the opinion that a fused ring system in the chemical structure is critical and important for the biological activity.

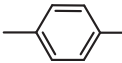
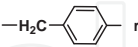
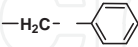
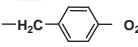
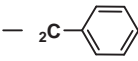
For example, 2-(4-aminophenyl)benzothiazoles, are observed by Shi et al. [22], exhibit potent anti-tumour activity against some cell lines (breast, ovarian, colon, and renal cell lines). Choi et al. [23] also synthesized a series of 2-(4-aminophenyl)benzothiazole and evaluated the Topo II inhibitory activity.

There are studies on the inhibitory effects of some novel fused heterocyclic compounds, (*benzimidazole, benzoxazole, benzothiazole, and oxazole(4,5-b)pyridine derivatives*) on eukaryotic DNA Topo II (Figure 4) in a cell-free system [24-26]. These compounds displayed more potent inhibitory activities than the reference drug etoposide (Table 1, Figure 5) [17-20]. Molecular modeling of the possible structural motifs of the fused heterocyclic compounds given in Table 1 have been studied to expose their binding mode to eukaryotic DNA topoisomerase II by molecular docking studies. The interactions involved in the anti-tumour activities of fused heterocyclic compounds lead to the rational design of novel eukaryotic DNA topoisomerase II-targeted drugs [27,28].

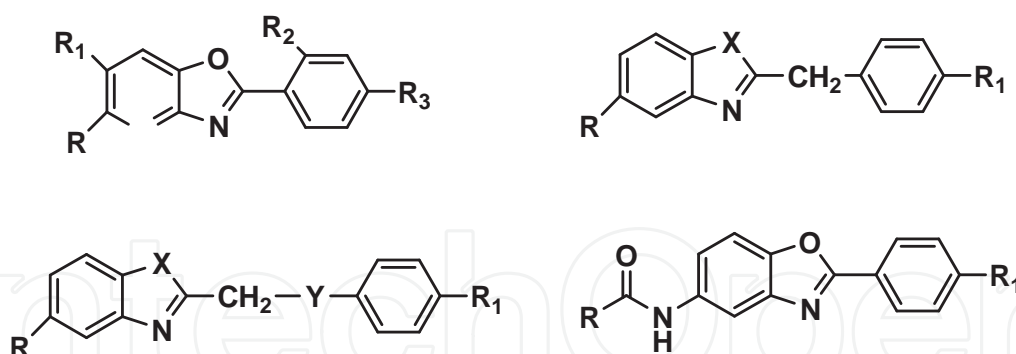


**Figure 5.** The structure of the reference drug-etoposide.

Compound	R	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	Z	IC <sub>50</sub> (μM) <sup>a</sup>
<b>1a*</b>	H	NO <sub>2</sub>	OCH <sub>3</sub>	H	CH	17
<b>1b</b>	H	CH <sub>3</sub>	F	H	CH	433.2
<b>1c*</b>	H	CH <sub>3</sub>	NO <sub>2</sub>	H	CH	18.8
<b>1d</b>	NH <sub>2</sub>	H	H	C <sub>2</sub> H <sub>5</sub>	CH	115.5
<b>1e</b>	CH <sub>3</sub>	H	CH <sub>3</sub>	CH <sub>3</sub>	CH	44.4
<b>1f</b>	Cl	H	H	C <sub>2</sub> H <sub>5</sub>	CH	NE
<b>1g</b>	CH <sub>3</sub>	H	OCH <sub>3</sub>	H	CH	433.0
<b>1h</b>	NO <sub>2</sub>	H	H	H	CH	32.4

1i	Cl	H	H	Cl	CH	NE
1j	CH <sub>3</sub>	H	H	NHCH <sub>3</sub>	CH	128.4
1k*	NO <sub>2</sub>	H	H	OC <sub>2</sub> H <sub>5</sub>	CH	22.4
1l	H	H	H	C <sub>2</sub> H <sub>5</sub>	N	45.6
1m	H	H	H	Cl	N	119.5
1n	H	H	H	C(CH <sub>3</sub> ) <sub>3</sub>	N	108.3
1p	H	H	H	CH <sub>3</sub>	N	91.2
Compound	R	R <sub>1</sub>	X		IC <sub>50</sub> (μM) <sup>a</sup>	
2a	NO <sub>2</sub>	Br	O		NE	
2b	H	OCH <sub>3</sub>	O		86.6	
2c	CH <sub>3</sub>	NO <sub>2</sub>	NH		NE	
2d	CH <sub>3</sub>	CH <sub>3</sub>	NH		101.9	
2e	CH <sub>3</sub>	NH <sub>2</sub>	NH		46.8	
Compound	R	R <sub>1</sub>	X	Y	IC <sub>50</sub> (μM) <sup>a</sup>	
3a	H	Cl	S	O	NE	
3b*	CH <sub>3</sub>	H	NH	S	27.4	
3c*	COOCH <sub>3</sub>	H	NH	S	17	
3d	H	H	NH	CH <sub>2</sub>	NE	
3e*	NO <sub>2</sub>	H	NH	O	24.8	
3f*	H	H	S	O	11.4	
Compound	R	R <sub>1</sub>			IC <sub>50</sub> (μM) <sup>a</sup>	
4a*		H			24.1	
4b		C <sub>2</sub> H <sub>5</sub>			315.1	
4c		F			206.9	
4d		H			420.1	
4e		F			420.1	
<b>Etoposide</b>					<b>21.8</b>	

**Table 1.** Eukaryotic DNA topoisomerase II inhibitory activities of novel 2,5,6-substituted benzoxazole, benzimidazole and benzothiazole(4,5-b)pyridine derivatives. [The asterisk (\*) refers to structures that are effective, according to the reference drug, *etoposide*. The small letter (a) implies that eukaryotic DNA topoisomerase II-50% inhibitory activity of the tested compounds and the reference drug, *etoposide* at the micromolar (μM) concentration of IC<sub>50</sub> values. NE: not effected].



## 2.4. Herbal remedies

*These drugs show their effects on mitosis during metaphase by preventing the formation of the spindle.*

*Etoposide VP-16 (Vepesid)*, an effective anticancer drug, is applied to treat a broad spectrum of human cancers for more than two decades. Unfortunately, its wide therapeutic application is often hindered by multidrug resistance (MDR), low water solubility and toxicity. New derivatives of benzoxazoles, benzimidazoles and related fused heterocyclic compounds, exhibited significant eukaryotic DNA topoisomerase II inhibitory activity, were synthesized and exhibited better inhibitory activity even compared with the drug etoposide (Figure 5) [27].

Other examples are:

- *Vinblastine*(Velber A),
- *Vincristine*(Oncovin),
- *Podophyllotoxin*,
- *Teniposide*(VM26-Bristol),and
- *Vindesine*(Eldisine).

## 2.5. Hormones and hormone antagonists

Hormone antagonists are used for tumors caused by hormones or hormonal imbalance. Examples:

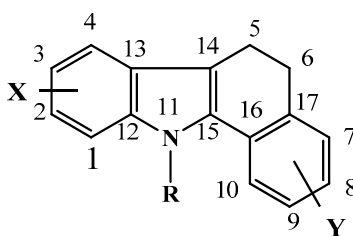
- *Glucocorticoid hormones and*
- *Estrogens.*

The endogenous estrogens in women are steroid hormones. Possible consequences of the lack of estrogen in postmenopausal women are frequently reported, including postmenopausal symptoms, increased risks of osteoporosis, coronary heart disease and Alzheimer's disease [29-33]. On the other hand, the cumulative exposure to estrogen encourages development of female reproductive cancers. Such examples include breast cancer and uterus cancer, which are found associated with hormone replacement therapy, early menarche and late menopause [34]. The contribution of estrogens in various physiological and pathological pathways



depends on the binding to estrogen receptors. It also activates transcription of estrogen responsive genes [35-38].

The anti-cancer drug *benzodihydro [α]carbazole* (BDHC), which is widely used to treat breast cancer, and for which the primary target is the human estrogen receptor (hER) [39]. This study reveals a brief introduction of BDHC therapy for breast cancer and the related mechanistic pictures of small compounds signaling through hER by using QSAR and docking methods. They were applied to understand the nature of 5,6-dihydro11-alkylbenzo [α]carbazole derivatives (Table 2) and to investigate the interactions of homolog series with binding sites on selected a-chains of human estrogen receptors (hER).



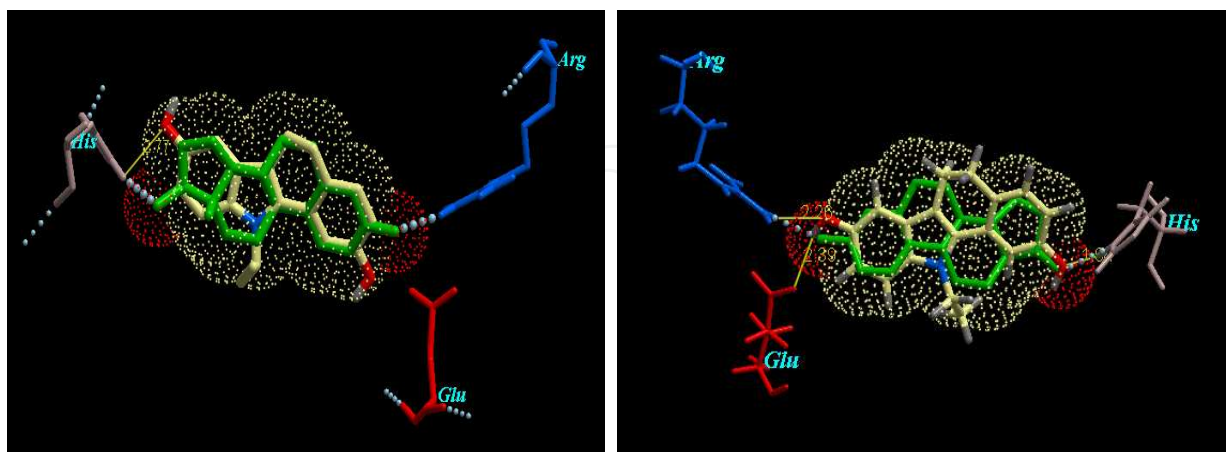
**X, Y = OH**

Compound	R	Position of		RBA <sup>a</sup>	logRBA*
		X	Y		
1	CH3	3	9	9,6	1,60
2	C <sub>2</sub> H <sub>5</sub>	3	9	30	1,10
3	C <sub>3</sub> H <sub>7</sub>	3	9	38	1,00
4	C <sub>2</sub> H <sub>5</sub>	3	8	13	1,47
5	C <sub>2</sub> H <sub>5</sub>	4	9	1,3	2,47
6	C <sub>2</sub> H <sub>5</sub>	4	8	1,9	2,30
7	C <sub>2</sub> H <sub>5</sub>	2	9	9,7	1,59
8	C <sub>2</sub> H <sub>5</sub>	2	8	0,7	2,73
9	C <sub>2</sub> H <sub>5</sub>	3		1,8	2,32
10	C <sub>2</sub> H <sub>5</sub>		8	0,06	3,80
11	C <sub>2</sub> H <sub>5</sub>		9	0,8	2,68

<sup>a</sup>Relative binding affinities (RBA) for the calf uterine estrogen receptor = ratio of molar concentrations of 17 $\beta$ -estradiol (E<sub>2</sub>) and inhibitor required to decrease the amount of bound [3H] E<sub>2</sub> by 50 %, x 100. [\*logRBA (obs.) = log1/RBA + 2.58].

**Table 2.** Relative Binding Activities (RBA) of 11-Alkyl-6,11-dihydrohydroxy-5H-benzo [a]carbazoles [39].

Furthermore, the X-ray structure of  $17\beta$ -estradiol in hER was superimposed on compound **2** and **3** on the docked structure (Figure 6).



**Figure 6.** Estradiol (green) superimposed on compound **2** and **3** in the  $\alpha$ -chain's binding site of hER. Key residues and H-bonds are shown by yellow lines and blue dotted lines.

*Other hormonal antagonists are:*

- Progestins,
- GnRH (gonadotropin releasing hormone), and
- Antiandrogens.

## 2.6. Other medicines

Medicines that are used as anticancer drugs are:

- Platinum-based drugs (cisplatin, carboplatin),
- L-Asparaginase (Crasnit's),
- Hydroxyurea (Hydrea), and
- Amsacrine (Amsidyl).

Many of the CTX drugs that are employed are naturally occurring compounds extracted from plants, while others are synthetic. Genotoxic agents bind to DNA and directly and/or indirectly affect the replication which induces the apoptosis. These agents are also divided into three important subunits-alkylating agents, intercalating agents and enzyme inhibitors. Etoposide is an enzyme inhibitor which inhibits topoisomerase II and prevents resealing of DNA that leads to cell death. However, this drug structure exhibits undesired effect for treatment of the disease. Due to this reason, different methods have been improved to evaluate the adverse effects of etoposide, the most effective and potent drug.

There are two approaches to evaluate the adverse effects of the potent drugs-first one, is synthetic way. Researchers try to find derivatives of this drug agent with the conventional

way. In the another approach, they use novel and rational drug design, discovery and development methods which are more economic and minimize time and labor by using computer models, compared with the usual conventional methods.

### 3. Harmful (or toxic) effects of anticancer drugs

An understanding of toxicity or adverse effects of anticancer compounds is important to design effective and potent drug combinations and also to interpret toxicological profile of new chemical entities. Most cytotoxic anticancer agents are evaluated at the maximum tolerated dose levels. The toxicity of these compounds is often a manifestation of their mechanism of action and their effect on growing normal cells such as *hair follicle cells*, *gastrointestinal surface epithelial cells*, and *stem cells*.

*Toxicity or adverse effects of anticancer drugs include the following:*

- Bone marrow depression due to damage for the growing stem cells causes a reduction in the white blood cell, platelet, and red cell counts. These, in turn, could cause susceptibility to infections, excessive bleeding, and anemia. In addition, certain drugs cause unique and severe bone damage, such as the osteonecrosis of the jaw associated with bisphosphonates [40].
- Damage to growing cells may cause temporary loss of hair (alopecia), skin rashes, changes in the color and texture, or loss of fingernails and toenails. These toxicities are usually reversible.
- Surface epithelial damage to the gastrointestinal tract may result in ulcers, stomatitis, difficulty in swallowing (dysphagia), vulnerability to oral infections such as candidiasis, and changes in saliva secretion. In addition, nausea, vomiting, diarrhea, or constipation occur commonly.
- Some drugs may cause kidney damage due to extensive cell destruction, purine catabolism, and deposition of urates in the renal tubules. The activity of drugs depends on the individual physiological system and the mode of renal handling of drugs.
- Cinnamaldehyde (an anticancer drug) at a dose level of 73.5 mg / kg body weight / day induced histopathological changes of kidney accompanied by increased activity of marker enzymes and an imbalance in the antioxidant status, in rats. Cinnamaldehyde induced renal damage, is due to the reactive oxygen species that formed while in the free radical scavenging reactions [41-43].
- In addition, liver damage may occur due to large blood supply. Metabolic conditions of the liver and the kidney are usually monitored for possible correlation to drug levels in the blood and dosage adjustments, since these are the major drug elimination sites or the target organs of toxicity.
- Certain symptoms and adverse effects associated with cancer could be secondary to disease progression. For example, cancer metastases to the bones could cause chronic pain due to

the proliferation of cancer cells in the bones and the associated bone remodeling and destruction. Also, tumors that compress veins, the use of central vein catheter, and relative immobility of the patient could lead to deep vein thrombosis with potential pulmonary embolism [44-46].

- Drugs such as paclitaxel and vincristine could cause peripheral neuropathy. Similarly, anthracyclines are known for rare but severe cardiotoxicity [47-49].

Thus, adverse effect and dose-limiting toxicity of anticancer compounds could be a manifestation of either their mechanisms of action or unrelated toxicities common to a given chemical entity of compounds (anthracyclines and etoposide). A close attention to monitor the emergence of known side effects of anticancer drugs, as well as those observed in the preclinical animal toxicology studies, ensures patient safety in early oncology drug clinical trials.

## 4. Conclusions and perspectives

Especially, chemotherapy has been integrated into treatment programs with surgery and radiation therapy. The major problem of the clinical efficacy in chemotherapy is because of toxicity of the anticancer drugs to the normal tissues of the body. Rapidly proliferating tissues such as bone marrow, gastrointestinal tract, hair follicle, etc are the major sites of acute toxicities. In addition, chronic and cumulative toxicities may also occur. There are measures and agents which can improve the toxicities of anticancer drugs. Furthermore, current challenges of anticancer drug development include the significant time and cost involvement, and the low success rates. These issues lead to increasing efforts of the pharmaceutical industry toward increasing the effectiveness of the drug discovery and development process to minimize failure of drug candidates at later stages of development. It also includes development of high throughput preclinical screening methods (computational molecular modeling techniques) and biological assays with greater specificity and predictability.

Increasing emphasis is being placed on developing a mechanistic understanding of the physicochemical and biological phenomena involved in drug development such as chemical structure and polymorph stability, and pharmacokinetics. The use of mathematical models to explain the mechanisms of drug degradation and predict the outcomes of formulation and process changes and scale-up is increasingly being adopted such as Quantitative Structure Activity Relationships (QSAR). This chapter summarises the beneficial and harmful (toxicity) effects of anticancer drugs and other measures adopted for its management. Proper handling of anticancer agents is the utmost importance at the earlier phase because it has an affiliation with the course of treatment and outcome of the patient in his physical, mental and social wellbeing. Because of these reasons, computer aided drug design and discovery are used to reduce the side effects of the anticancer drugs. These procedures result in effective therapeutic options for chemotherapy.

On general consideration, antioxidants (vitamins) play a significant role to ameliorate the toxicity. Thus, fruits and vegetables in the diet might protect human health from toxic effects

of drugs at certain extent [50]. While in chemotherapy, if the patients are given vitamin rich food (vegetables, fruits, etc), then toxicity of the chemotherapeutic drugs can be prevented at certain extent.

## Author details

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