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Research Article

Topoisomerase – A Target For Anticancer Agents

Arun Ramachandran[1*], R. Saravanan[2], V. Sebastin[3]

[1*,2]Bharath Institute of Higher Education and Research, Chennai – 600 073, Tamil Nadu, India
[3]Department of Pharmaceutical Chemistry, Malik Deenar College of Pharmacy, Seethangoli, Kasaragod, Kerala, India

[*]**Correspondence :-**Associate Prof. Arun Ramachandran,
*Research Scholar, Dept. of Pharmacy, Bharath Institute of Higher Education and Research, Chennai – 600 073, Tamil Nadu, India
Associate Professor in Malik Deenar College of Pharmacy, Seethangoli, Kasaragod, Kerala, India Email id: aruncr203@gmail.com

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ABSTRACT

Topoisomerases are ubiquitous enzymes have significant roles in several critical DNA processes. Over the past few years, there has been considerable interest in DNA topoisomerases, as they were shown to be the cellular targets for several anticancer drugs. The functions of various topoisomerase enzymes related to the maintenance of DNA topology during its replication and transcription are the targets of several anticancer and antimicrobial agents. Targeting topoisomerase enzymes for cancer treatment remains a prominent focus of both fundamental and clinical oriented research. This review aimed to discuss briefly about different anticancer agents target the Topoisomerases

Keywords: DNA topoisomerases, anticancer activity

INTRODUCTION

DNA topoisomerases are ubiquitous enzymes that regulate the topology of DNA in all cells during the key cellular processes such as replication, transcription, recombination, repair and chromatin assembly. These enzymes act by introducing or removing DNA superhelical tensions, tying or untying DNA knots and catenating or decatenating circular DNA molecules. DNA topoisomerases have been isolated from both prokaryotes and eukaryotes [1-3]. There are two main types in DNA topoisomerases, Type 1 and Type II according to whether they make transient single or double stranded breaks in DNA [4]. The type I makes transient single strand break and the type II introduce transient double strand break [1-4].
There are three subtypes of type I topoisomerase Type IA, Type IB and Type IC. Type IA topoisomerases require a nick or a single-stranded region to bind to DNA. They cleave one strand of duplex DNA, covalently attach the active-site tyrosine to a 5′-phosphoryl group, and utilize the 'strand passage' mechanism to alter DNA topology. In contrast, types IB and IC topoisomerases cleave one strand of duplex DNA, covalently attach its active-site tyrosine to a 3′-phosphoryl group, and utilize the 'swivel' mechanism to relax DNA supercoils. Type II topoisomerases go through a series of large conformational changes when catalysing the reaction by the 'strand passage' mechanism. When type II topoisomerases cleave two DNA strands, they form phosphotyrosyl bonds between the two active-site tyrosines and a pair of 5′-phosphates to ensure the integrity of DNA can be restored. There are two subtypes of type II topoisomerases, type IIA and type IIB [5-10].

Topoisomerase targeting anticancer agents

Over the past few years, there has been considerable interest in DNA topoisomerases, as they were shown to be the cellular targets for several anticancer drugs. Topoisomerase-targeting anticancer drugs can be divided into two broad categories – Class I drugs and Class II drugs.
Class I drugs act by stabilizing covalent topoisomerase-DNA complexes that are the intermediates during the catalytic cycle of the enzyme. Class I drugs are also known as topoisomerase poisons because they transform the enzyme into a potent cellular toxin. Class II drugs are also known as catalytic inhibitors. This class drugs interfere with the catalytic function of the enzyme without trapping the covalent complex. Not only the anticancer agents but also certain coumarin antibiotics such as Novobiocin, Coumermycin A, Chlorobiocin and Fostriecin analogue such as Fosriecin belongs to Class II category of drugs target the topoisomerase.

Class I topoisomerase inhibitors are further grouped in to intercalative and non-intercalative agents. Intercalative agent is a group of compounds that share common structural features such as the presence of planar poly aromatic systems which bind by insertion between DNA base-pairs, with a marked preference for 5'-pyrimidine-purine-3' steps. Intercalators interact reversibly with the DNA double helix. Some acridines such as Amsacrine (m-AMSA), anthracyclines such as Doxorubicin and Daunorubicine, actinomycins such as Actinomycin D, ellipticines such as 2-methyl-9-hydroxyellipticinium acetate and certain miscellaneous agents such as Intoplicine, Mitoxan and Cisplatin are few examples for intercalative group.
Non-intercalative is family of compounds which appear to bind reversibly to double stranded DNA without intercalation between DNA base pairs. Camptothecin, a pentacyclic alkaloid and its semisynthetic derivatives such as topotecan and irinotecan, epipodophyllotoxins such as Etoposide (VP 16) and Teniposide (VM 26), isoflavodins such as Genistein, quinolone anti-bacterial agents such as Nalidixic acid, Oxolinic acid, Norfloxacin and Ciprofloxacin, and a miscellaneous agent, Azatoxin are some examples for non-intercalative group (Table 1) [3, 11-20].

Table 1: DNA topoisomerase inhibitors – divisions and some examples

Group	Sub-class	Group	Examples
Class I	Intercalative	Acridines	Amsacrine (m-AMSA)
		Anthracyclines	Doxorubicin, Daunorubicin
		Actinomycins	Actinomycin D
		Ellipticines	2-methyl-9-OH-ellipticinium acetate
		Miscellaneous	Intoplicine, Mitoxan, Cisplatin
	Non-intercalative	Alkaloids	Camptothecin, Irinotecan, Topotecan
		Epipodophyllotoxins	VP16, VM26
		Isoflavodins	Genistein
		Quinolones	Nalidixic acid, Oxolinic acid, Norfloxacin, Ciprofloxacin
		Miscellaneous	Azatoxin
Class II		Coumarins	Novobiocin, Coumermycin A, Chlorobiocin
		Fostriecin analogues	Fosriecin
		Miscellaneous	Merbarone, Suramin Topostin

Drugs targeting type I topoisomerase

Camptothecin, an alkaloid obtained from a Chinese tree, *Camptotheca acuminata* selectively inhibits the eukaryotic topo I. Structure-activity studies to improve the anticancer activity and reduce the toxicity of camptothecin indicated that the six membered lactone ring was essential for anticancer activity. A number of camptothecin derivatives have been synthesized by modifying the A-ring of the parent compound. Topotecan and irinotecan are significant among them (Figure 1). These agents are given by parenteral route particularly by IV. Generally, topotecan is indicated in ovarian cancer when other therapies are failed. Irinotecan is a pro-drug (Its active metabolite is SN-38) commonly indicated for metastatic colorectal cancer when the treatment containing fluorouracil failed.

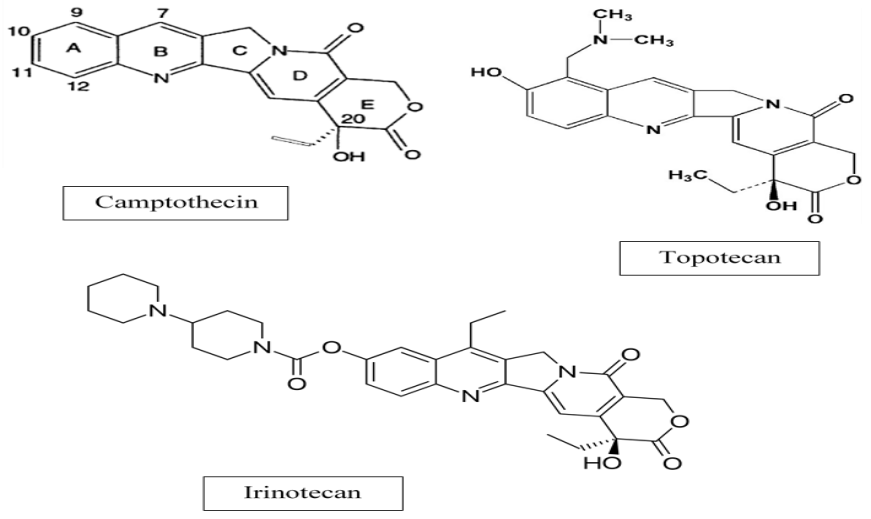

Figure 1: Chemical structure of camptothecin and its semisynthetic derivatives

Even though, camptothecins have established anticancer activity, they have a major limitation viz. they are inactivated within minutes at physiological pH by lactone E ring opening (Figure 2) [3, 21]. Recently developed derivatives such as gimatecan, belotecan and exatecan (Figure 3 [26-28]) showed improvement in solubility and clinical tolerability and able to administer by oral route, however they retain the chemical instability of camptothecins [21].

Two approaches have been taken to overcome the E ring in-stability of camptothecins. Addition of a methylene group in the E ring, limits the E ring opening but, once this happens, they become irreversibly converted to an inactive carboxylate. In the second approach, conversion of the E ring to a five-membered ring completely stabilizes the drug. These α-keto derivatives are highly potent synthetic compounds against Topo1 and in cancer cells [21-25].

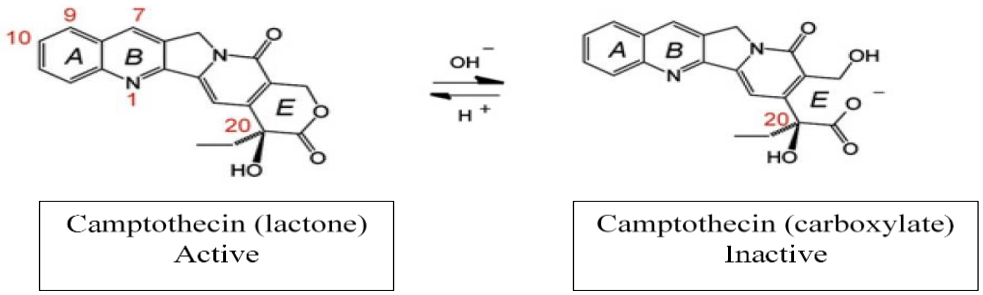

Figure 2: E-ring opening and inactivation of camptothecin

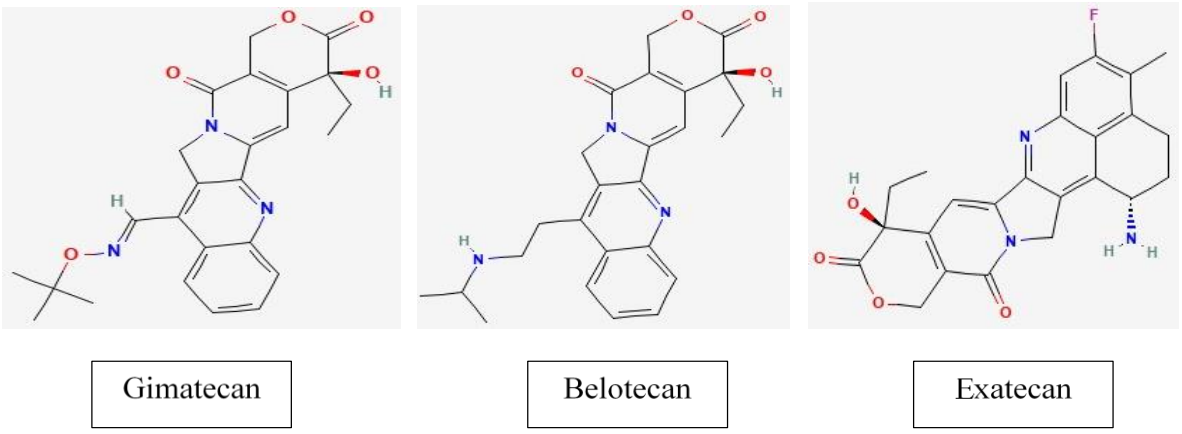

Figure 3: Some recently developed semisynthetic derivatives of camptothecin

Drugs targeting type II topoisomerase

Certain anticancer agents such as Amsacrine, Doxorubicin and Daunorubicine, Actinomycin D, 2-methyl-9-hydroxyellipticinium acetate, Intoplicine, Mitoxan, Cisplatin, Etoposide, Teniposide, Genistein, Azatoxin, Fostriecin, Merbarone and antibacterials such as Nalidixic acid, Oxolinic acid, Norfloxacin Ciprofloxacin, Novobiocin, Coumermycin A, and Chlorobiocin (Table 1) target the type II topoisomerase.

Anthracyclines, the intercalative agents are the first known class of topo II inhibitors which are initially, extracted from *Streptomyces* sp. These agents have antibiotic and antitumour activity. Doxorubicin, Daunorubicin, Epirubicin, Valrubicin and Idarubicin are some examples for clinically available agents [29, 30]. Generally, anthracyclines are used in combination with other chemotherapeutic agents. Doxorubicin and epirubicin are used to treat women after surgical resection of breast cancer with axillary lymph node involvement. Doxorubicin is also effective in the management of acute lymphoblastic and myeloblastic leukemias; Hodgkin and non-Hodgkin lymphomas; metastatic neuroblastoma, Wilms' tumour, cancers of the breast, soft tissue sarcoma, and bone sarcomas; metastatic ovarian, transitional cell bladder, thyroid, gastric, and bronchogenic carcinomas. Valrubicin administered intravesically for urinary bladder carcinoma refractory to BCG therapy in patients who are not candidates for cystectomy. Daunorubicin is effective in acute myelogenous, monocytic and erythroid lymphocytic leukemias in adults and in acute lymphocytic leukemia in children. Idarubicin is effective in the management of adult acute myeloid leukemia [29].

Anthracycline agents produce the cytotoxicity by affect the topoisomerase type IIa, IIα and IIβ by intercalation. These agents also produce the cytotoxicity by production of free radicals in iron-dependent manner. Unfortunately, this mechanism appear to be responsible for acute and chronic cardiac complications, a well-known toxicity of anthracyclines. These agents induces the production of superoxide anions and hydrogen peroxide in cardiac muscle cells leads to oxidative stress and apoptosis. Anthracyclines also disrupt the calcium

and iron levels in cardiac cells which leads to more free radical generation. Some recent studies indicated that the inhibition of topoisomerase IIβ by these agents is overexpressed in the heart also leads to cardio toxicity. Dexrazoxane, an FDA approved agent and Carvedilol, a beta blocker agent may reduce the cardio toxicity due to the inhibition of topoisomerase IIβ by anthracyclines [29, 31-37].

Anthracenedione, structurally related to anthracyclines are another one group of agents that target the topoisomerase II. Synthetic agent mitoxantrone and pixantrone belongs to this group act similarly with anthracyclines with fewer adverse effects and toxicities. Mitoxantrone is indicated for leukemia and prostate cancer. It can cross the blood brain barrier and is indicated for the reduction of frequency and intensity of multiple sclerosis relapses. Pixantrone, a novel agent is approved for the treatment of non-Hodgkin B cell lymphoma [29, 38-39].

Epipodophyllotoxin derived agents such as etoposide and teniposide are one of the important anticancer drugs target the topoisomerase II. Epipodophyllotoxin are naturally occurring substances obtained from the root of American mayapple plant, *Podophyllum peltatum* belongs to Berberidaceae family. Etoposide prevents the cell division and is particularly useful in small cell carcinoma of bronchus, lymphomas and testicular cancer. It may be used in combination with cisplatin, another one topoisomerase poison target the topoisomerase II. Teniposide is approved in patients with refractory childhood acute lymphoblastic leukemia in combination with other chemotherapy drugs [16, 29, 40, 41]. Amsacrine, an acridine group agent is a topoisomerase poison targets the topoisomerase II. The acridine ring system of the drug intercalates the DNA and contributes to its anticancer activity while the non-intercalative 4′-amino-methane-sulfon-m-anisidide (m-AMSA) headgroup imparts specificity for the DNA-topoisomerase cleavage complex [11, 29]. Structure of some topoisomerase poison are shown in Figure 4 [10, 29].

Even now several drugs targeting the topoisomerase enzymes are under evaluations. For example, recently FDA granted orphan drug status to Indotecan, a topoisomerase I inhibitor for use in patients with malignant glioma, a cancer of brain that begins in glial cell. Vosaroxin, a novel anticancer quinolone derivative targeting topoisomerase II is now under phase III clinical trial investigation for acute myelogenous leukemia Finally, continuous advancements in molecular genetics and biology have the potential to empower clinicians in tailoring treatments using anti-topoisomerase drugs for various types of cancers and infectious diseases. Finally, continuous advancements in molecular genetics and biology have the potential to empower clinicians in tailoring treatments using anti-topoisomerase drugs for various types of cancers and infectious diseases [21, 29].

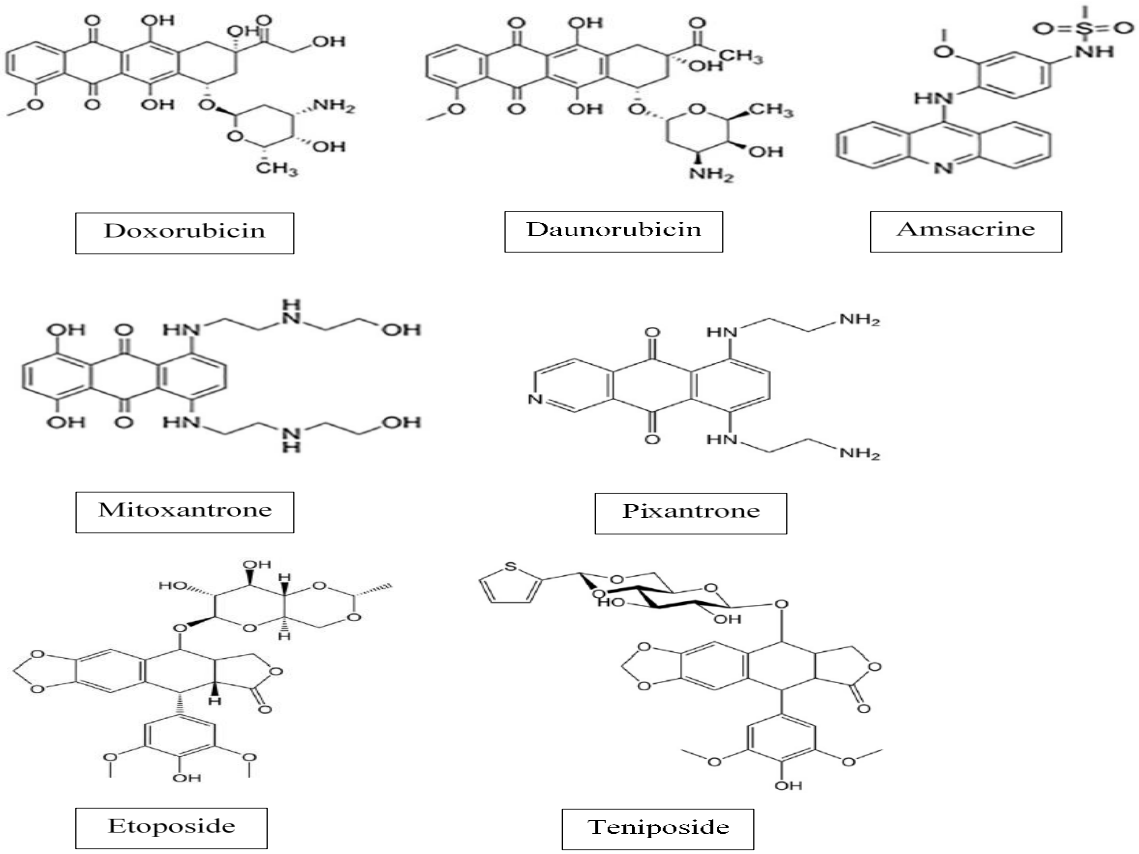

Figure 4: Structure of some topoisomerase poison

CONCLUSION

Topoisomerases are ubiquitous enzymes have significant roles in several critical DNA processes. Also, they are cytotoxic targets for many successful anticancer drugs. Even though topoisomerase IIα and IIβ are crucial for the survival of human cells and cancer chemotherapy, substantial evidences are there about its genotoxic effects and the involvement in specific leukemic chromosomal translocations. Considering the significant impact, whether positive or negative of topoisomerases on human cells, the research on these fascinating enzymes is continuing on which will generate even more prominent revelations.

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AUTHORS CONTRIBUTION
All the authors have contributed equally

CONFLICTS OF INTERESTS
Declared none

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