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REVIEW ARTICLE

Natural Compounds as Anticancer Agents Targeting DNA Topoisomerases

Chetan Kumar Jain[a], Hemanta Kumar Majumder[a,*] and Susanta Roychoudhury[b,*]

[a]*Infectious Diseases and Immunology Division, CSIR-Indian Institute of Chemical Biology, 4, Raja S.C. Mullick Road, Jadavpur, Kolkata-700032, India;* [b]*Division of Research, Saroj Gupta Cancer Centre & Research Institute, M G Road, Thakurpukur, Kolkata-700 063, India*

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Abstract: DNA topoisomerases are important cellular enzymes found in almost all types of living cells (eukaryotic and prokaryotic). These enzymes are essential for various DNA metabolic processes *e.g.* replication, transcription, recombination, chromosomal decatenation etc. These enzymes are important molecular drug targets and inhibitors of these enzymes are widely used as effective anticancer and antibacterial drugs. However, topoisomerase inhibitors have some therapeutic limitations and they exert serious side effects during cancer chemotherapy. Thus, development of novel anticancer topoisomerase inhibitors is necessary for improving cancer chemotherapy. Nature serves as a repertoire of structurally and chemically diverse molecules and in the recent years many DNA topoisomerase inhibitors have been identified from natural sources. The present review discusses anticancer properties and therapeutic importance of eighteen recently identified natural topoisomerase inhibitors (from the year 2009 to 2015). Structural characteristics of these novel inhibitors provide backbones for designing and developing new anticancer drugs.

Keywords: DNA topoisomerases, Topoisomerase inhibitors, Anticancer agents, Natural products.

1. INTRODUCTION

Since ancient times nature has been a prime source of various therapeutic molecules including anticancer agents [1, 2]. Natural compounds have diverse chemical structures and important anticancer chemotherapeutic agents such as etoposide, anthracyclines like doxorubicin (adriamycin or ADR) and daunorubicin, camptothecin derivatives like topotecan and irinotecan, paclitaxel, docetaxel, vincristine, vinblastine, mitomycin C, actinomycin D, bleomycin, and many more have been developed or derived from natural sources [1-3] camptothecin derivatives like topotecan and irinotecan, paclitaxel, docetaxel, vincristine, vinblastine, mitomycin C, actinomycin D, bleomycin, and many more have been developed or derived from natural sources [1-3]. Original natural compounds may not always serve as effective anticancer agents in therapy but they provide the skeleton to develop therapeutically effective anticancer drugs. Approximately 60% of the anticancer drugs currently used in the cancer chemotherapy have natural origin [1, 2]. Thus, nature serves as a repertoire for anticancer molecules and identification of new anticancer molecules from natural sources will help to improve cancer chemotherapy [1-3].

DNA topoisomerases are essential enzymes that control the topological state of DNA during DNA replication, transcription, recombination and chromosomal decatenation to facilitate chromosomal segregation during mitosis, as reviewed in [4-11]. Topoisomerases introduce transient single or double strand breaks in DNA and thus solve the topological problems associated with DNA metabolic processes and chromosomal decatenation during cell division, as depicted in (Fig. **1A** and **1B**), and reviewed in [4-8], single strand breaks in DNA and thus solve the topological problems associated with DNA metabolic processes and chromosomal decatenation during cell division, as depicted in (Fig. **1A** and **1B)**, and reviewed in [4-8]. In 1971, James C. Wang first discovered DNA topoisomerase enzyme in *Escherichia coli* and designated it as ω protein (topA) [10]. The ω protein was found to reduce superhelical turns in the covalently closed negatively supercoiled DNA duplex. In 1972, James J. Champoux and Renato Dulbecco discovered first eukaryotic topoisomerase enzyme and found that nuclear extracts from secondary mouse embryo cells possess an enzymatic activity of untwisting closed circular DNAs containing negative or positive superhelical turns [11]. The prokaryotic and eukaryotic enzymes were found to possess distinct mechanisms of action. They were designated as prokaryotic DNA topoisomerase I (topA) and III (topB), and eukaryotic DNA

*Address correspondence to these authors at the Division of Research, Saroj Gupta Cancer Centre & Research Institute, M G Road, Thakurpukur, Kolkata-700 063, India; Tel: +91-33-24995823; Cell: +91-9433102986; Fax: +91-33-24735197; E-mails: susantarc@gmail.com; susanta@iicb.res.in and Infectious Diseases and Immunology Division, CSIR-Indian Institute of Chemical Biology, 4, Raja S. C. Mullick Road, Jadavpur, Kolkata-700032, India; Tel: +91-33-2412 3207; Fax: +91-33-24735197;
E-mails: hkmajumder@iicb.res.in; hemantamajumder@yahoo.co.in

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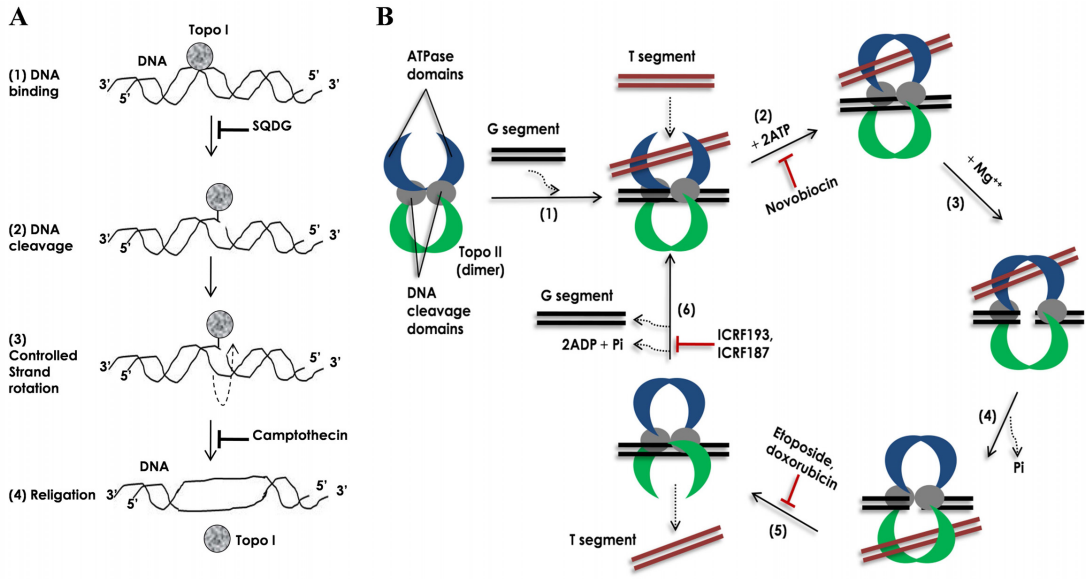

Fig. (1). Mechanisms of action for human TOP1 and TOP2 enzymes. (**A**) Mechanism of action of TOP1. (1) DNA binding: first the enzyme binds to its preferential binding site on dsDNA. (2) DNA cleavage: the enzyme then cleaves one strand of double-stranded (ds) DNA by making a nucleophilic attack and forming a transient 3'-phosphotyrosyl bond. (3) Controlled strand rotation: through the single strand break generated by the enzyme other strand of the DNA (uncleaved strand) is passed in a controlled manner. (4) Religation: the cleaved strand is religated and the enzyme is released away. (**B**) Mechanism of action of TOP2 [5, 13]. (1) DNA binding: homo-dimer of the enzyme preferentially binds to catenated, knotted and supercoiled DNA segments. Segment of dsDNA, which is cleaved during the enzymatic reaction cycle, is termed as 'G segment' ('G' for *gate*) and segment of dsDNA, which is passed through the cleaved G segment, is termed as 'T segment' ('T' for *transported*). The enzyme first binds to G segment and then to T segment. (2) ATP binding: binding of 2 ATP molecules in the ATPpase domains changes conformations of the ATP-ase domains from open to close. Novobiocin inhibits the ATP binding. (3) DNA cleavage: in the presence of Mg^{++} ions, enzyme transiently cleaves G segment DNA by making nucleophilic attack and forming two 5'-phosphotyrosyl bonds with DNA backbone. (4) Strand passage: the T segment is then passed through the cleaved G segment. (5) T segment release and religation: the T segment is then released away from the enzyme and the cleaved G segment is religated back. The religation is inhibited by etoposide and doxorubicin. (6) ATP-ase domain opening and G segment release: after release of the T segment the enzyme remains in a closed clamp form. Hydrolysis of ATP drives opening of the closed clamp releasing the G segment away and making the enzyme ready for next enzymatic reaction cycle. ATPase activity of the enzyme is inhibited by bisdioxopiperazines *e.g.* ICRF193 and ICRF187.

topoisomerase 1 (TOP1) and 2 (TOP2), as indicated in [4, 11]. In 1976, Martin Gellert and colleagues have purified DNA gyrase, an enzyme capable of introducing superhelical turns in the DNA, from *Escherichia coli* [12].

Human DNA topoisomerases are now classified into two different categories: TOP1 and TOP2, as reviewed in [4]. TOP1 transiently cleave single strand of a duplex DNA while TOP2 transiently cleave both the strand of a duplex DNA, as depicted in (Fig. **1A** and **1B**). Topoisomerases of both types are further sub-divided into four different subfamilies: TOP1A, -1B, -2A and -2B. Different enzymes in a subfamily have mechanical and structural similarities, whereas enzymes from different subfamilies are mechanically and structurally different. These enzymes have several functions: to remove DNA supercoils during transcription and DNA replication; for strand breakage during recombination; for chromosome condensation; and to disentangle intertwined DNA during mitosis [4]. Two types of topoisomerases, TOP1B and TOP2A, are present in the nucleus of mammalian cells, as depicted in (Fig. **2**), and indicated in [4, 5]. TOP2 protein has two isoforms: TOP2A and TOP2B. Enzymatic reaction cycle of topoisomerases have four common steps: (a) DNA binding: the enzyme binds to its preferential binding site on DNA, (b) DNA cleavage: nucleophilic attack on phosphodiester backbone of DNA and formation of transient 3' or 5' phosphotyrosyl bond(s), (c) controlled strand rotation or strand passage and (d) religation, as depicted in (Fig. **1A** and **1B**), and reviewed in [4, 5, 13, 14].

To facilitate rapid cell division, cancer cells require higher topoisomerase activity and indeed these enzymes have been overexpressed in numerous types of cancers [15-18]. Hence, targeting topoisomerases by small molecule inhibitors in different cancers becomes an interesting area of investigation [14, 19-23]. Till date many DNA topoisomerase inhibitors have been identified from natural sources, as reviewed in many reports regarding topoisomerase inhibitors as anticancer agents [14, 19-23]. Topoisomerase inhibitors are classified into two categories: (a) topoisomerase poisons, which inhibit either controlled strand rotation or religation, and thus stabilized covalent enzyme-DNA complexes; and (b) catalytic topoisomerase inhibitors, which inhibit DNA binding or DNA cleavage, as depicted in (Fig. **2**), and reviewed in [13, 19, 20]. For example camptothecin, an alkaloid isolated from the bark of Chinese tree *Camptotheca acuminate*, acts as DNA topoisomerase I poison, and stabilizes TOP1/DNA covalent complexes by inhibiting the religation step [19-21, 24]. Stabilization of covalent enzyme-DNA complexes by topoisomerase poisons generates DNA lesions and ultimately induces apoptosis as depicted in (Fig. **2**). Etoposide is another important topoisomerase inhibitor, which acts as a DNA topoisomerase II poison [22]. Etoposide-like fluoroquinolones, targeting both

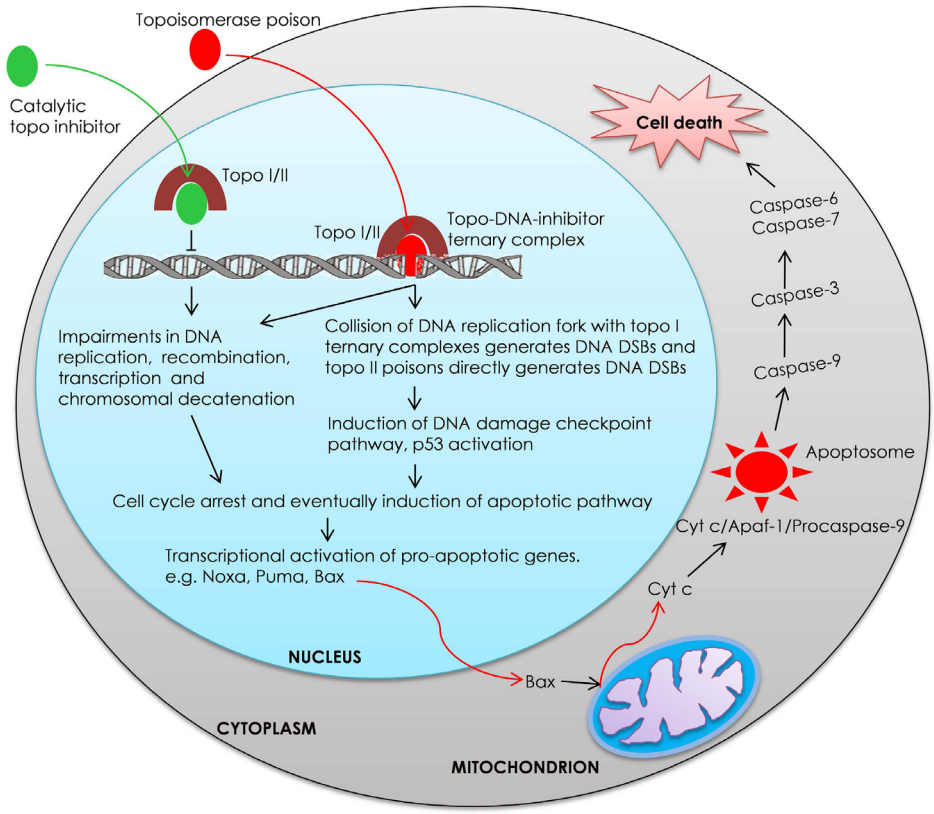

Fig. (2). Proposed model for topoisomerase inhibitor mediated cellular death. Inhibition of DNA topoisomerases by catalytic topoisomerase inhibitors or topoisomerase poisons interferes with DNA replication, recombination, transcription and decatenation, and causes DNA damage. These generate cellular stress, lead to cell cycle arrest and ultimately induce apoptotic cell death pathway.

prokaryotic DNA gyrase and DNA topoisomerase 2a (top-IV, also known as parC and parE), inhibit enzymatic religation of broken DNA ends [5, 25, 26].

On the other hand, the catalytic topoisomerase inhibitors do not generate DNA lesions e.g. betulinic acid, a naturally occurring pentacyclic triterpenoid, catalytically inhibits TOP1 and TOP2 enzymes [27-29]. Catalytic inhibitors of TOP2A are known to induce G_2 cell cycle arrest by the activation of decatenation checkpoint pathway [30]. Cells with defective decatenation checkpoint pathway fail to arrest the cell cycle in G_2 phase and enter into M phase with catenated and under-condensed chromosomes resulting into impaired mitosis and eventually cell death [31]. Hence, catalytic inhibitors of TOP2A are also promising agents for targeting decatenation checkpoint defective cancer cells during cancer chemotherapy [32]. Since camptothecin derivatives and other DNA topoisomerase inhibitors have been extensively discussed in several review articles for their anticancer activities, therefore in this review we will discuss recently identified (from the year 2009 to 2015) natural topoisomerase inhibitors with anticancer properties.

2. DNA TOPOISOMERASES IN NORMAL AND CANCER CELLS

Since the human total genomic DNA is over 3 billion base pairs, which amount to ~ 3 meters (nearly 10 ft.) and is far greater than the ability of cell to accommodate it, the multiple mechanisms leading to DNA compaction into chromatin architecture were evolved, as reviewed in [5]. DNA topoisomerases play critical roles in chromosome compaction by working with the adenosine triphosphate (ATP)-binding-cassette ATP-hydrolases (ABC ATP-ases, also known as structural maintenance of chromosomes [SMC] proteins), as reviewed [5, 33]. SMC proteins and topoisomerases co-localize as part of the protein network that helps stabilizing long-range contacts between chromosomal segments. During DNA strand synthesis, topoisomerases are required to relieve the positive supercoiling that arises from DNA unwinding mediated by replicative helicases [34, 35]. Similarly to DNA replication, RNA transcription induces changes in DNA topology since a moving RNA polymerase produces a localized positive supercoiling ahead of the transcription [9, 36-43].

Topoisomerases have been linked to specific transcriptional events, such as the activation or repression of particular promoters, and nucleosome remodeling [38-45]. For example, inactivation of TOP1B in *Saccharomyces cerevisiae* leads to a specific acetylation and methylation of histones thereby increasing the transcription of telomere-proximal genes [5, 45]. The presence or absence of DNA topoisomerase Iβ (top1B) activity can influence nucleosome disassembly and assembly at the certain gene promoter regions in *Schizosaccharomyces pombe* [4, 5, 9, 38, 46]. Eukaryotic TOP1B has been implicated in the control of gene expression through an associated kinase activity, which is reported to phosphorylate splicing factors (*e.g.* serine and/or arginine-rich proteins), thus regulating their localization and enhancing their activity [5, 35, 47-49]. TOP1B -mediated phosphorylation of splicing proteins can be negatively regulated

by the presence of poly (ADP-ribose), a substrate for poly (ADP-ribose) polymerase (PARP), as indicated in [5, 50]. In addition, DNA cleavage and the subsequent binding of PARP1 appear to be necessary to recruit high mobility group (HMG) factors (*e.g.* HMGB1 or HMGB2), leading to a stimulated transcription, as reviewed in [5, 50]. The mechanism of transcription coactivation by TOP1 was found to be dependent on basal transcription factor II (TFII) members (TFIIA and TFIID), which trigger formation of the RNA polymerase II pre-initiation complex at the specific promoters [37]. A camptothecin-mediated DNA cleavage assay demonstrated the recruitment of TOP1 to the template by TFIID [50]. Inhibition of TOP1 can cause the induction of c-JUN expression in leukemia cells, suggesting its additional role in the control of transcription [51]. TOP2B associates with the promoter regions of genes that are regulated by retinoic acid receptor elements in human acute promyelocytic leukemia cells [52]. Furthermore, TOP1 interacts with the splicing factor ASF/SF2 by which it promotes the maturation of RNA through suppressing the formation of R-loops (RNA-DNA hybrids) and prevents collision between transcription bubble and replication fork [46-48]. DNA topoisomerases are also essential for embryonic development in mammals [53]. In humans, TOP1 and TOP2 proteins bind to the regions of the pre-replicative complex in cells during the M, early G1, and G1/S phases of the cell cycle to control the firing of replication origins [37, 54, 55].

Genome instability is one of the hallmarks of cancer cells [28]. Chromosomal decatenation (the unlinking of the components of a ring or chain structure of DNA) checkpoint is critical for chromatin untangling, and is defective in cancer cells. DNA topoisomerase IIα (TOP2A) plays an important role during chromosomal decatenation [4]. As a consequence of cellular DNA replication in the S phase, catenated sister chromatids are formed [4, 30]. In order to allow proper chromosomal condensation and segregation chromatid catenations must be removed prior to onset of M phase [30]. In the G_2 phase of cell cycle TOP2A decatenates chromosomal DNA [4, 30]. The process of chromosomal decatenation is monitored by a G_2 phase checkpoint, named as decatenation checkpoint [30, 56]. Decatenation checkpoint delays entry into mitosis until all the chromosomes have been decatenated [30, 56]. Recent studies have shown that TOP2A is essential for the signaling of decatenation checkpoint [57, 58]. Luo and coworkers showed that TOP2A undergoes phosphorylation at the Serine-1524 position during the checkpoint activation [58]. The phosphorylated form of TOP2A interacts with and recruits MDC1 (mediator of DNA damage checkpoint protein-1) at the chromatin. This interaction between TOP2A and MDC1 is essential for the efficient activation of decatenation checkpoint [58]. Accumulating evidence shows that the decatenation checkpoint is defective in different types of cancer cells including lung cancer, leukemia, melanoma, colon cancer and bladder cancer, as described elsewhere [31, 59-62].

The gene encoding DNA topoisomerase IIα, *TOP2A*, is commonly amplified or deleted in human cancer cells. Abnormal alterations in the expression levels of *TOP2A*, its copy number variations, and its epigenetic modifications may have a critical role for genome instability in human cancers [63-68]. Eukaryotic DNA topoisomerase proteins are subjects to numerous post-translational modifications (PTMs) that can alter their localization and activities at various stages in the cell cycle [69-74]. Thus far, four types of the DNA topoisomerase-specific PTMs have been observed: phosphorylation, acetylation, sumoylation and ubiquitylation [69-74]. In the case of poisoned topoisomerases that are trapped on DNA, modification by sumoylation and ubiquitylation in response to DNA damage appears to target these enzymes for processing and degradation [75, 76].

3. TOPOISOMERASE INHIBITORS IN CURRENT CHEMOTHERAPY OF CANCER

So far, the semisynthetic derivatives of plant alkaloid camptothecin, topotecan (Hycamtin) and irinotecan (Camptosar, Campto) (Fig. **3A**, **3B** and **3C**), are only drugs targeting TOP1 approved by US Federal Drug Administration [19]. Topotecan and irinotecan are used in the chemotherapy of glioblastoma, sarcomas, ovarian, recurrent small cell lung, colorectal, and cervical cancers. But the uses of topotecan and irinotecan are limited due to their associated side effects and opening of α-hydroxylactone E-ring at physiological pH. Several modified camptothecin derivatives have been prepared but the α -hydroxylactone E-ring instability still remains a major drawback for their clinical use [19, 21].

On the other hand, many TOP2 targeting drugs are currently used in the cancer chemotherapy e.g. etoposide (VP-16), daunorubicin, doxorubicin (adriamycin), mitoxantrone and ICRF187 (Dexrazoxane), as depicted in (Fig. **4**). TOP2 poisons are effective anticancer agents, however their use is limited due to the associated side effects, *e.g.* etoposide treatment often induces therapy related secondary malignancies and anthracyclins, such as daunorubicin and doxorubicin, show severe cardiotoxicity, as indicated in [77-79]. Daunorubicin, discovered from the *Streptomyces sp.* soil bacteria, is used primarily for the treatment of acute leukemia and neuroblastoma in human patients [19]. Whereas doxorubicin is used for the treatment of breast cancer, sarcomas, some types of leukemia, lymphomas, multiple myeloma and thyroid cancer [19]. Etoposide is extensively used for the treatment of variety of cancers including lung cancer, testicular cancer, lymphoma, some types of leukemia, glioblastoma multiforme, Kaposi's and Ewing's sarcomas [19]. Mitoxantrone is used for the treatment of prostate cancer, acute leukemia and breast cancer [79]. ICRF187 (Dexrazoxane), which is a catalytic TOP2 inhibitor, is administered with anthracyclins to reduce their cardiotoxicity [19]. Novobiocin is another clinically important TOP2 catalytic inhibitor, which inhibits ATP binding to the enzyme (Fig. **1B** and **4F**), as described in [5].

4. NOVEL TOPOISOMERASE INHIBITORS, WHICH ARE UNDER CLINICAL DEVELOPMENT

The chemical instability of camptothecin and its derivatives has been a major problem for their clinical use; therefore many non-camptothecin TOP1 inhibitors have been developed, as reviewed in [19]. Two families of such non-camptothecin inhibitors of TOP1 are under clinical development [19]. One family of such compounds is indenoisoquinolines and two of the indenoisoquinoline derivatives, indotecan (LMP400) and indimitecan (LMP776) are currently in clinical trials (Fig. **3D** and **3E**) [19]. These derivatives were developed by the National Cancer Institute (National Institute of Health, MD, USA) and Purdue University (West Lafayette, Indiana, USA) and are licensed to Linus Oncology (Miami, FL, USA). The indenoisoquinolines

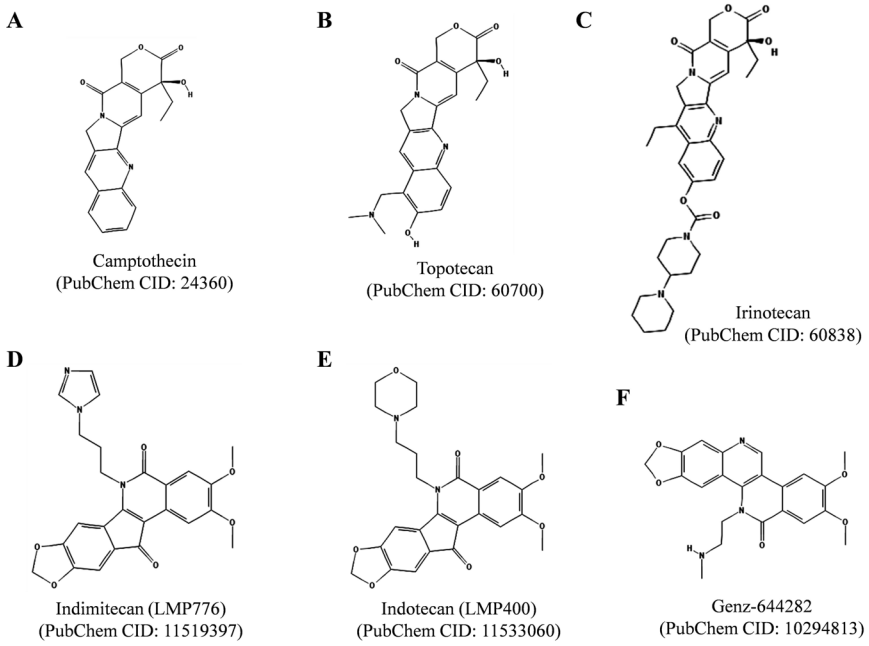

Fig. (3). Chemical structures of clinically important TOP1 inhibitors. Camptothecin (CPT) derivatives topotecan and irinotecan are clinically approved anticancer agents while indimitecan, indotecan and Genz-644282 are under clinical development. The structures were adopted from PubChem database. Respective PubChem CIDs are provided within the parentheses.

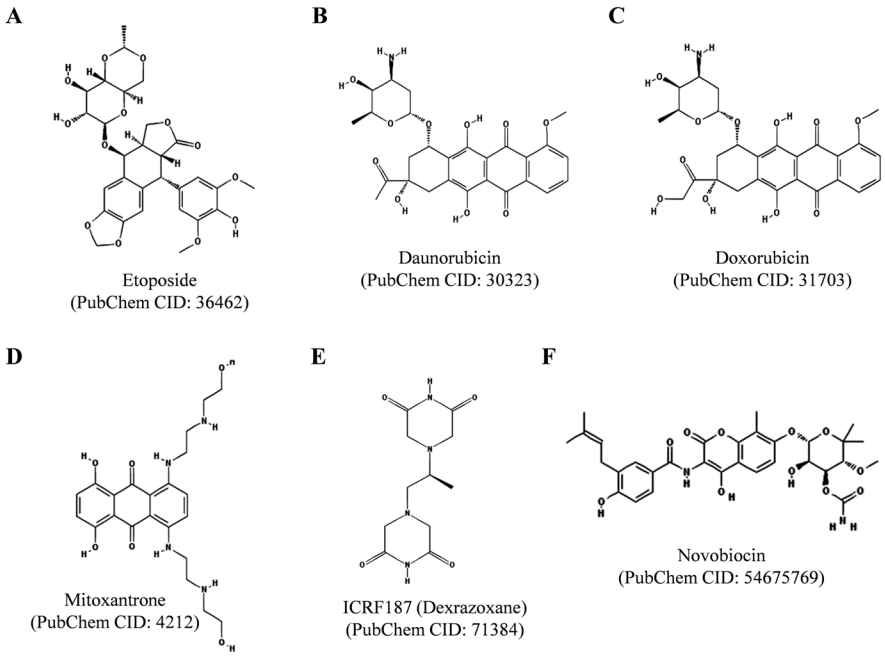

Fig. (4). Chemical structures of clinically important TOP2 inhibitors. The structures were adopted from PubChem database.

induced protein-linked DNA breaks, which persisted longer after drug removal than those produced by camptothecin and its derivatives; therefore they may assist in overcoming multidrug drug resistance [19, 80]. Another TOP1 inhibitor of non-camptothecin nature is 8, 9-dimethoxy-5- (2-N-methylaminoethyl)-2, 3-methylenedioxy-5H-dibenzo[c, h] [1, 6] naphthyridin-6-one (also known as Genz-644282; SAR402674), as depicted in (Fig. **3F**), and described in [19, 81]. Genz-644282 was found to be more potent than camptothecins against cancer cells in cell proliferation and colony forming assays *in vitro* and showed equal or superior anti-tumor activity in human tumor xenorafts in mice *in vivo* compared with standard drugs [19, 81]. Genz-644282 is currently under phase I clinical trial.

On the other hand, four TOP2 poisons, F14512, vosaroxin, C-1311, and R(+)XK469, are under clinical development (Fig. **5**). F14512 is currently in phase I clinical trials on adult acute myeloid leukemia patients [19, 22, 82]. F14512 contains an epipodophyllotoxin moiety linked with a

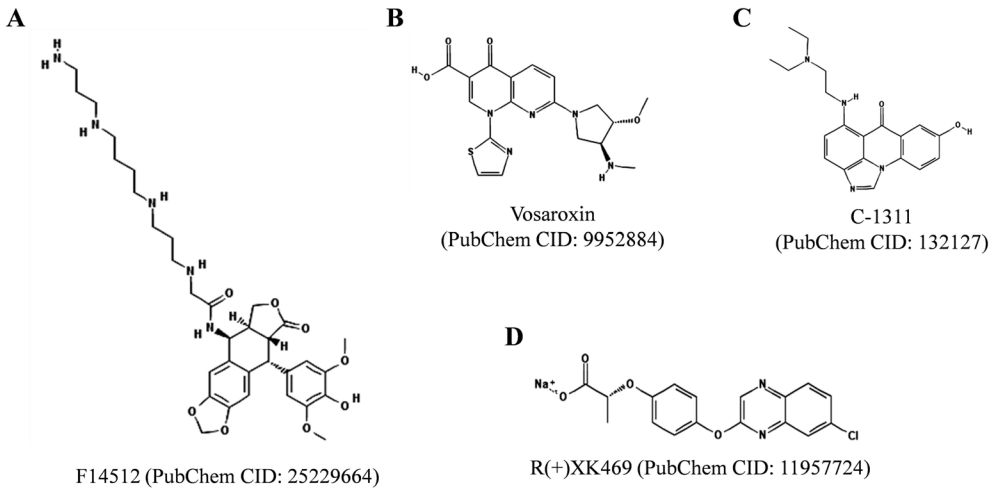

Fig. (5). Chemical structures of TOP2 inhibitors under clinical development. The structures were adopted from PubChem database.

spermine side chain by a glycine linker [19, 22, 82]. The spermine side chain facilitates cellular uptake and accumulation of F14512 in the cancer cells expressing polyamine transport system. F14512 forms more persistent ternary TOP2-drug-DNA covalent complex than etoposide and exhibits a more superior antitumor activity of F14512 *in vivo* than etoposide. F14512 has been reported to exhibit *in vivo* synergistic anti-leukemic effects in combination with cytosine arabinoside (Ara-C), doxorubicin, gemcitabine, bortezomib, or suberoylanilide hydroxamic acid [82]. F14512 has been reported to exert synergistic effects with cisplatin and to enhance effects of ionizing radiation in head and neck squamous cell carcinomas [83]. F14512 was also found to be more effective than etoposide on pediatric glioma and neuroblastoma cell lines [84].

Vosaroxin (also known as voreloxin) is another TOP2 inhibitor under clinical development [22]. Vosaroxin intercalates into DNA, inhibits TOP2 and generates DNA single-stranded breaks (DSBs), as described in [22, 85-87]. Vosaroxin in combination with cytarabine exerts synergy on primary acute myeloid leukemia blasts. Vosaroxin has shown promising anticancer effects and a phase III clinical trial study for vosaroxin in combination with cytarabine (VALOR) for the treatment of relapsed and refractory acute myeloid leukemia has been completed by Sunesis Pharmaceuticals, Inc. (http://www.sunesis.com/patients_and_ caregivers/clinical_trials/Vosaroxin.php), as indicated in [86, 87]. C-1311 (Symadex) is water soluble, DNA intercalating iminodazoacridinone derivatve [88-91]. C-1311 poisons TOP2 and exerts potent anticancer activity. C-1311 has undergone phase I and II clinical trials, as indicated in [22, 89, 90]. Another TOP2 inhibitor in clinical development is R(+)XK469, which was developed by the National Cancer Institute (Bethesda, MD), as indicated in [92]. It was initially reported as a selective TOP2B inhibitor, however the TOP2 targeting does not solely contribute to its cytotoxic activity and the other mechanisms have also been reported [19, 22, 92].

5. RECENTLY IDENTIFIED TOPOISOMERASE INHIBITORS FROM NATURAL SOURCES

(Table **1**) lists recently identified (from the year 2009 to 2015) anti-cancer topoisomerase inhibitors from natural sources. In the following sections we shall discuss these inhibitors one-by-one.

5.1. Lamellarin D

Lamellarin D (Fig. **6A**), a hexacyclic marine alkaloid found in marine mollusk of the genus *Lamellaria* and in ascidians, was initially reported as a nuclear TOP1 poison [93, 94]. Lamellarin D was also found to directly target mitochondria and mitochondria was reported to play essential role in the lamellarin D mediated apoptosis of cancer cells [95-98]. Khiati and co-authors have recently reported that lamellarin D also inhibits mitochondrial DNA (mtDNA) topoisomerase I (TOP1MT) and stabilizes TOP1MT/mtDNA covalent complexes, supporting the role of mitochondria in lamellarin D-mediated apoptosis in cancer cells [97]. In the same study, lamellarin D was found to rapidly accumulate inside mitochondria. Lamellarin D also inhibits protein kinases and induces mitochondrial perturbations. Thus, lamellarin D inhibits growth of cancer cells in a pleiotropic mode of action, which includes: inhibition of nuclear TOP1 and TOP1MT enzymes, inhibition of protein kinases and induction of mitochondrial perturbations. These studies suggest that lamellarin D is a potent and promising anticancer agent.

5.2. Erybraedin C

Erybraedin C (Fig. **6B**) is a pterocarpan isolated from the plant *Bituminaria bituminosa,* as described elsewhere [99]. Tesauro and co-authors have reported that erybraedin C can inhibit human TOP1 enzyme by suppressing both cleavage and religation steps of the enzyme reaction [99]. The compound has been shown to induce apoptosis in two human adenocarcinoma cell lines HT29 (proficient in mismatch repair system, *MMR +/+, p53 −/−* and *BCL-2 +/+,* a cell line) and LoVo (deficient in mismatch repair system, *MMR −/−, p53 +/+* and *BCL-2 −/−),* as described in [100]. However, in both the cases to achieve complete enzyme inhibition pre-incubation of the enzyme with the compound was required. The study suggested that erybraedin C act as a catalytic TOP1 inhibitor *in vitro*.

Table 1. Recently identified topoisomerase inhibitors from natural sources.

Compound Name	Source	Target	Type of Inhibitor	References
Lamellarin D	*Lamellaria sp.*	TOP1 (nuclear and mitochondrial)	Poison	[93-98]
Erybraedin C	*Bituminaria bituminosa*	TOP1	Catalytic inhibitor	[99, 100]
Bis(2,3-dibromo-4,5-dihydroxybenzyl) ether (BDDE)	*Leathesia nana, Rhodomela confervoides, Rhodomela confervoides*	TOP1	Catalytic inhibitor	[101-103]
Thaspine	*Croton lechleri*	TOP1, TOP2	Catalytic and poison for TOP1, not studied for TOP2	[104, 105]
Evodiamine	*Evodia rutaecarpa*	TOP1, TOP2	Catalytic inhibitor	[106, 107]
Albanol A	*Morus alba*	TOP1, TOP2	Not studied	[108]
Alternariol	*Alternaria alternate*	TOP1, TOP2A, TOP2B	Poison	[110-116]
4-Hydroxyderricin	*Angelica keiskei*	TOP2	Not studied	[117, 118]
(−)-Xanthatin	*Xanthium strumarium*	TOP2A	Catalytic inhibitor	[120, 121]
Echinoside A	*Holothuria nobilis*	TOP2	Interfere with DNA binding and catalytic cycle	[122, 123]
Riccardin D	*Dumortiera hirsute*	TOP2	Not studied	[125]
Wedelolactone	*Wedelia chinensis, Eclipta prostrata*	TOP2A	Not studied	[133]
Tricitrinol B	*Penicillium citrinum*	TOP2A	Poison	[136]
Daurinol	*Haplophyllum dauricum*	TOP2A	Catalytic inhibitor	[137]
Fisetin	*Found in many fruits and vegetables*	TOP1, TOP2	Catalytic inhibitor	[142, 143, 145]
Myricetin	*Found in many fruits and vegetables*	TOP1, TOP2	Poison	[143, 145]
SQDG	*Azadirachta indica*	TOP1	Catalytic inhibitor	[151]
Plumbagin	*Plumbago Zeylanica*	TOP1	Not studied	[155]

5.3. Bis (2, 3-dibromo-4, 5-dihydroxybenzyl) Ether (BDDE)

BDDE (Fig. **6C**) is a marine bromophenol compound found in the marine algae *Leathesia nana*, *Rhodomela confervoides* and *Rhodomela confervoides*, as described in [101-103]. BDDE binds to DNA minor groove and act as a catalytic inhibitor of TOP1 enzyme without stabilizing covalent TOP1/DNA complexes [102]. BDDE exerts broad-spectrum *in vitro* anticancer activities and induces apoptosis in K562 cells via mitochondrial pathway. BDDE has also been reported to inhibit α-glucosidase activity [103].

5.4. Thaspine

Thaspine (Fig. **6D**), an alkaloid found in the cortex of South American tree *Croton lechleri*, was reported to inhibit human TOP1 and TOP2 enzymes *in vitro*, as described [104]. Thaspine was found to be effective proliferation and survival inhibitor against certain tumor cells overexpressing P-glycoprotein (PgP) or multiple drug resistance (MDR) drug efflux transporters and also shown to induce apoptosis in colon carcinoma multicellular spheroids *in vitro*, and in xenograft mouse models *in vivo*. Recently, Castelli and co-authors have reported that thaspine inhibits cleavage and religation steps of the enzymatic reaction [105]. The inhibition was found to be reversible and was enhanced upon pre-incubation. In the same study, molecular docking analysis predicted that thaspine binds in proximity of active site residues preventing the cleavage reaction while docking of with TOP1/DNA cleavable complex. These studies suggest that thaspine is a promising topoisomerase inhibitor and further chemical modifications may increase its selectivity for the inhibition type and may also increase its cytotoxic potential [105].

5.5. Evodiamine

Evodiamine is a quinazolinocarboline alkaloid (Fig. **6E**) found in Chinese medicinal plant, *Evodia rutaecarpa*. Evodiamine is known for its vaso-relaxation, anti-obesity, anticancer and anti-inflammatory activities, as described in

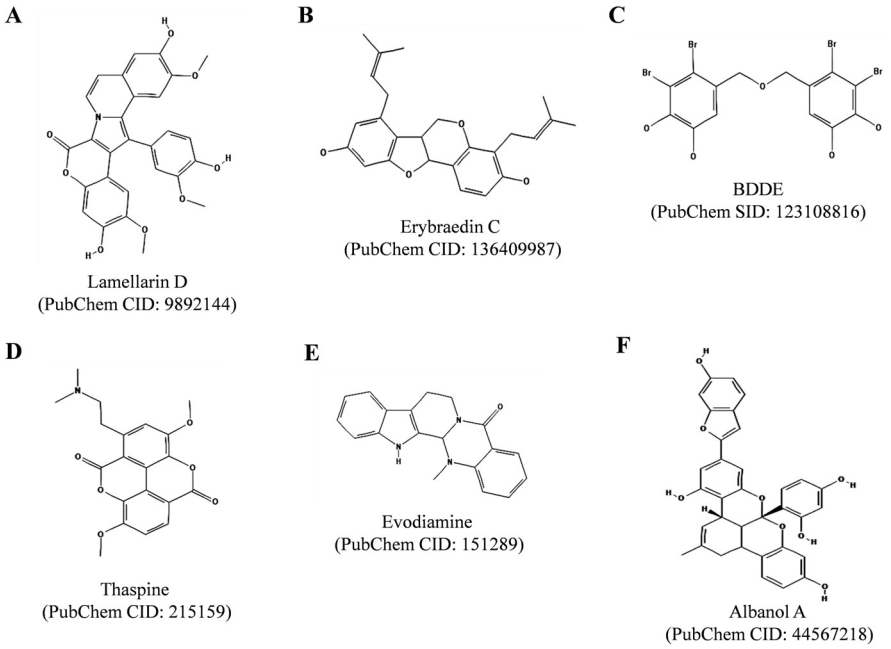

Fig. (6). Chemical structures of Lamellarin D, Erybraedin C, BDDE, Thaspine, Evodiamine and Albanol A. The structures were adopted from PubChem database.

[106]. Evodiamine was initially reported as a TOP1 poison. However, recently Pan and co-authors reported that evodiamine functions as dual catalytic inhibitor for human TOP1 and TOP2 enzymes with IC_{50} values of 60.74 and 78.81 μM, respectively [107]. Evodiamine was found to arrest cell cycle of K562 cells in G_2/M phase and exerted anti-proliferative activities against human leukemia cell lines (K562, THP-1, CCRF-CEM and camptothecin-resistant cell line CCRF-CEM/C1), as indicated in [107].

5.6. Albanol A

Albanol A (also known as mulberrofuran G, Fig. **6F**), a polycyclic compound found in the root bark of *Morus alba* (mulberry), was reported to exhibit potent antileukemic activity on human leukemia cell line, HL60 with IC_{50} value of 1.7 μM and inhibitory activity on human topoisomerase II enzyme, as described elsewhere [108]. At higher concentration (100 μM) the compound was also found to inhibit relaxation activity of TOP1 enzyme. In the same study, Albanol A was also reported to induce apoptosis in HL60 cells via stimulation of cell death receptor pathway and mitochondrial pathway through caspase-2 activation and TOP2 inhibition. Recently, Geng and co-authors reported that Albanol A also inhibits DNA replication of hepatitis B virus in HepG 2.2.15 cell line *in vitro* [109].

5.7. Alternariol

Alternariol (Fig. **7A**), a mycotoxin produced by *Alternaria alternate*, has been reported to intercalate DNA, to exert genotoxic effects and to increase rate of DNA double-strand breaks in human carcinoma cell lines, HT29 and A431, as described in [110, 111]. Alternariol inhibited *in vitro* DNA relaxation activities of TOP1, TOP2A and TOP2B enzymes and increased the DNA cleavage activity of these enzymes, suggesting that the toxin is a topoisomerase poison [111]. Alternariol treatment also stabilized covalent TOP1A/DNA complexes in cultured cells. The toxin was found to bind DNA minor groove and to preferentially target TOP2A enzyme. Fehr and co-authors have found that tyrosyl DNA phsphodiesterase 1 is involved in the repair of DNA damage caused by alternariol [112]. Solhaug and collaborators have shown that alternariol induces autophagy and senescence in RAW264.7 macrophage cells [113]. Alternariol has also been reported to induce G_2 phase cell cycle arrest in RAW264.7 macrophage cells, chinese hamster V79 lung fibroblast cells and mouse lymphoma cells [114, 115]. However, in primary porcine endometrial cells, alternariol was found to induce G_0/G_1 phase cell cycle arrest [115, 116].

5.8. 4-Hydroxyderricin

4-Hydroxyderricin (Fig. **7B**) is a prenylated chalcone found in the roots of *Angelica keiskei*. 4-Hydroxyderricin has been reported to exert cytotoxic activity against cancer cell lines and antitumor and antimetastatic activities *in vivo*, as described elsewhere [117]. Recently, Akihisa and co-authors have reported that 4-hydroxyderricin inhibits DNA relaxation activity mediated by TOP2 with IC_{50} value 21.9 μM, while failed to affect DNA relaxation activity of TOP1 enzyme [118]. In a recent study, Yasuda and co-authors have shown that 4-hydroxyderricin reduces lipopolysaccharide (LPS)-mediated production of nitric oxide (NO), inhibits LPS-induced secretion of tumor necrosis factor-alpha (TNF-α) and downregulates the expression of inducible nitric oxide synthase (iNOS, also known as NOS2) and cyclooxygenase-2 (COX-2), suggesting that 4-hydroxyderricin is a promising agent for prevention of inflammatory diseases, as well [119].

5.9. (−)-Xanthatin

(−)-Xanthatin (Fig. **7C**), a major xanthanolide present in the Cocklebur plant *Xanthium strumarium* has been reported

to stimulate caspase-independent apoptosis in human breast cancer MDA-MB-231 cells, as described elsewhere [120]. (−)-Xanthatin also inhibits catalytic activity of TOP2A enzyme, promotes DNA damage and elevates reactive oxygen species (ROS) levels, as indicated in [120]. Takeda and co-authors have concluded that inhibition of TOP2A by (−)-xanthatin triggers expression of the growth arrest and DNA-damage-inducible protein (*GADD45*)-γ mRNA and ROS production further enhances the *GADD45* γ mRNA/ GADD45 γ protein induction process leading to death of breast cancer cells [121]. Thus, (−)-xanthatin is a promising anti-breast cancer agent targeting TOP2A enzyme.

5.10. Echinoside A

Echinoside A (Fig. **7D**) is a saponin isolated from the sea cucumber *Holothuria nobilis* Selenka, as described in [122]. Li and co-authors have reported that echinoside A is a non-intercalative TOP2A inhibitor, which inhibits the non-covalent binding of TOP2A to DNA rather than inhibiting ATP-ase activity of TOP2A. Echinoside A was found to generate TOP2A-dependent DSBs. The study indicated that echinoside A is a first marine-derived TOP2A inhibitor with the saponin skeleton. Recently, Zhao and co-authors have shown that echinoside A isolated from the sea cucumber *Pearsonothuria graeffei* exerts anticancer activity on HepG2 cells by blocking cell cycle progression in G_0/G_1 phase and inducing apoptosis via mitochondrial pathway [123]. In the same study treatment of the mice bearing H22 hepatocarcinoma tumors with echinoside A reduced tumor weight, suggesting that echinoside A exerts antitumor activities *in vivo*. Echinoside A was also shown to decrease pancreatic lipase activity, increased fatty acid excretion in the feces and decreased the adipose tissue accumulation in mice A, suggesting that echinoside A exert anti-obesity activity [124].

5.11. Riccardin D

Riccardin D (Fig. **7E**), a macrocyclic bisbibenzyl compound isolated from Chinese liverwort plant *Dumortiera hirsute*, was reported to show anti-proliferative activities and to induce apoptosis in human leukemia cell lines, HL-60, K562 and multidrug resistant (MDR) counterpart K562/A02, as described elsewhere [125]. Riccardin D was found to inhibit *in vitro* DNA relaxation activity of TOP2 at the greater extent than etoposide. Treatment of K562 and K562/A02 cell lines with riccardin D decreased relaxation activities of the nuclear extracts from these cell lines. The compound induced apoptosis in the leukemic cell lines in a TOP2-dependent manner, as it had no effect on the growth of TOP2-deficient HL-60/MX2 cells. Riccardin D also decreased the expression of P-glycoprotein (P-gp) in multidrug-resistant K562/A02 cells. Besides that, riccardin D has also been reported to inhibit growth of other types of cancer cell lines via different modes of action [126-128]. Riccardin D was shown to inhibit angiogenesis in lung carcinoma cells, induce apoptosis and autophagy in osteosarcoma cells and induce DNA damage in PC-3 prostate cancer cells [126-128]. Riccardin D widely affected growth of different types of cancer cells including multidrug-resistant leukemic cells, thus the compound has marked therapeutic potential.

5.12. Wedelolactone

Wedelolactone (Fig. **7F**), a coumestan found in the plants of the Asteraceae family (*Wedelia chinensis, Eclipta prostrata*), as described elsewhere [129]. Wedelolactone has been reported to block androgen receptor function, to block the inhibitor of kappa B kinase (IKK), to induce caspase dependent apoptosis in prostate cancer cells and to inhibit RNA

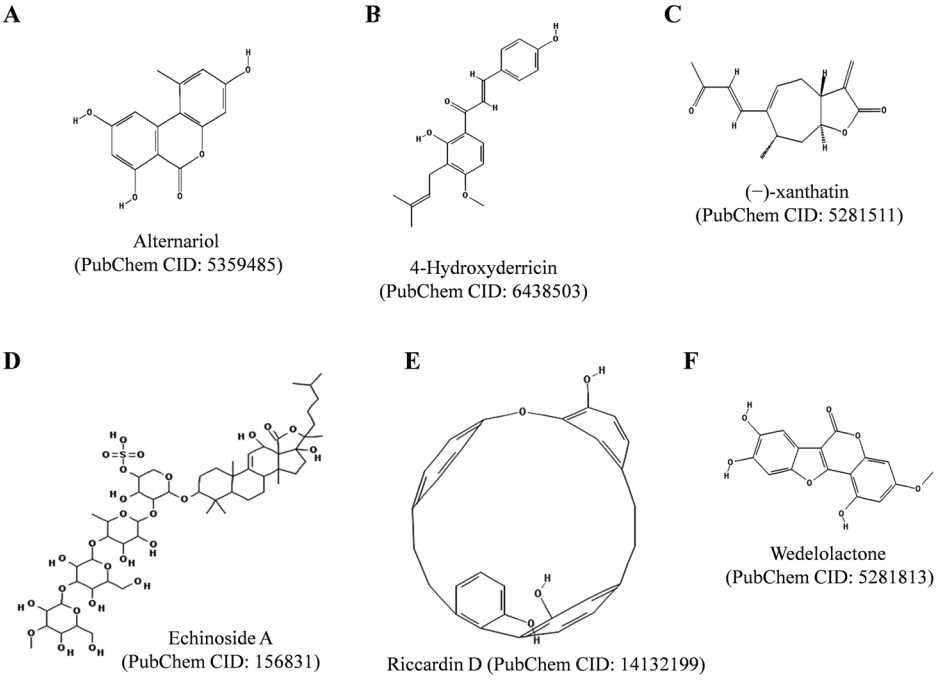

Fig. (7). Chemical structures of Alternariol, 4-Hydroxyderricin, (−)-Xanthatin, Echinoside A, Riccardin D and Wedelolactone. The structures were adopted from PubChem database.

polymerase activity of hepatitis C virus [129-132]. Benes and co-authors have found that wedelolactone inhibits DNA relaxation and decatenation activities of TOP2A enzyme [133]. They also showed that wedelolactone arrests cell cycle in S and G_2/M phases and induces DNA damage signalling in androgen receptor negative human breast cancer MDA-MB-231 cells. Wedelolactone has shown to suppresses osteoclastogenesis induced by breast cancer via decreasing AKT/mTOR signalling, thus preventing bone metastasis in breast cancer [134]. Wedelolactone also disrupts interaction between histone-lysine N-methyltransferase enzyme Enhancer of Zeste Homolog 2 (EZH2) and Polycomb protein EED, suggesting its role in pigenetic regulation of gene expression and making it a potential epigenetic drug candidate for the treatment of Polycomb Repressive Complex (PRC)-2-dependent cancer [135]. In recent years, several studies regarding the effects of wedelolactone on different cancers have been performed and the compound serves as a potential therapeutic agent [129-135].

5.13. Tricitrinol B

Tricitrinol B (Fig. **8A**), an unprecedented citrinin trimer, isolated from the volcano ash extract of the fungus *Penicillium citrinum* HGY1-5, was found to induce apoptosis in human promyelocytic leukemia HL-60 cells and human colon colorectal cancer HCT116 cells via extrinsic pathways and G_2/M cell cycle arrest, as depicted in and described in [136]. In the same study tricitrinol B was reported as intercalating TOP2A poison inducing DNA damage. Tricitrinol B mainly interferes with TOP2A mediated poststrand-passage cleavage/religation equilibrium. The compound also exerted a broad-spectrum anticancer activity *in vitro*, in seventeen different cancer cell lines.

5.14. Daurinol

Daurinol (Fig. **8B**), an arylnaphthalene lignin isolated from traditional ethnopharmacological plant *Haplophyllum dauricum* has recently reported as catalytic inhibitor of TOP2A [137]. Daurinol induced cell cycle arrest at the S-phase in HCT116 cells by enhancing the expression of cyclins E and A and by activating ATM/CHK/CDC25A pathway *in vitro*. Daurinol displayed anti-tumor effects *in vivo* in nude mice xenograft models. Daurinol treatment did not lead to significant loss in body weight and haematological parameters, while etoposide treatment led to loss in body weight and changed haematological parameters i.e. decreased white and red blood cell counts and haemoglobin concentration. Daurinol did not induce nuclear enlargement in HCT116 cells, whereas etoposide induced nuclear enlargement in HCT116 cells. Recently, Kang and co-authors reported that daurinol inhibits the ATP hydrolysis activity of TOP2A enzyme and the compound has no effect on TOP1 enzyme activity [138]. In this study anti-proliferative activity of daurinol was also studied in ovarian, small cell lung and testicular cancer cell lines. In SNU-840 human ovarian cancer cell line daurinol induced S-phase arrest, increased expression of cyclins E, A and E2F-1 and did not affect the size of nucleus while etoposide increased nuclear size. In another recent study, gene expression profile in daurinol treated HCT116 cells was studied by gene expression microarray analysis [139]. The study showed that daurinol treatment decreased expression of 18 genes involved in the mitotic spindle assembly checkpoint, including aurora kinase A (AURKA) and aurora kinase B (AURKB). Daurinol was found to exert antitumor and radio-sensitizing activities in xenograft mouse models through decreased expressions of AURKA and AURKB genes [139].

5.15. Fisetin

Fisetin (Fig. **8C**), a polyphenolic flavonoid found in many fruits and vegetables has been shown to exert antioxidant, anticancer and anti-inflammatory activities, as depicted in (Fig. **5A**), and described elsewhere [140]. Fisetin has also been reported to prevent migration and invasion of human cervical cancer cells, and micronucleus induction in human lymphoblastoid TK6 cells and promyelocytic HL60 cells *in vitro* [141, 142]. Fisetin was reported as dual catalytic inhibitor for both TOP1 and TOP2 enzymes [143]. Recently, Sahu and co-authors have reported that fisetin exerts renoprotective effects and protects kidneys from cisplatin induced nephrotoxicity in rats [140]. Fisetin pre-treatment ameliorated cisplatin induced renal impairments, histopathological alterations, and restored antioxidant and mitochondrial respiratory activities in kidney tissues. When used along with cisplatin, fisetin increases cytotoxic potential of cisplatin in human embryonic carcinoma cells, as well as the therapeutic doses of cisplatin could be minimized during cancer chemotherapy and thus toxicity caused by cisplatin could be controlled [144].

5.16. Myricetin

Myricetin (Fig. **8D**), a polyphenolic flavonoid found in many fruits and vegetables, exerts antioxidant, anticancer and anti-inflammatory properties. Myricetin acts as a dual topoisomerase inhibitor and stabilizes DNA covalent complexes with both TOP1 and TOP2 enzymes in human leukemia K562 cells [145]. Murine embryo fibroblasts lacking TOP2B were found to be resistant to myricetin induced cell death, suggesting that myricetin targets TOP2B enzyme. Besides, myricetin has also been reported to inhibit mammalian DNA polymerase and to induce G_2/M cell cycle arrest and apoptosis in human colon cancer HCT116 cells [145].

5.17. Sulfonoquinovosyl Diacylglyceride (SQDG)

SQDG (Fig. **8E**) is a member of plant sulfolipids. SQDG has been reported for its anti-leukemic, anti-bacterial and anti-viral activities [146-152]. Recently, Jain and co-authors have shown that SQDG purified from the leaves of *Azadirachta indica* catalytically inhibits human TOP1 enzyme by inhibiting DNA binding to TOP1 protein [153]. SQDG docked in the DNA binding region of TOP1 and thereby inhibited DNA binding activity of the enzyme. SQDG selectively killed acute lymphoblastic leukemia cell lines in TOP1- and tumor protein (TP) 53-dependent manner [150, 153]. In the study, SQDG was reported to generate DNA replication stress and to induce TP53-dependent apoptotic pathway in human acute lymphoblastic leukemia MOLT-4 cells [153]. SQDG treatment induced recruitment of ATR protein to the chromatin sites associated with DNA

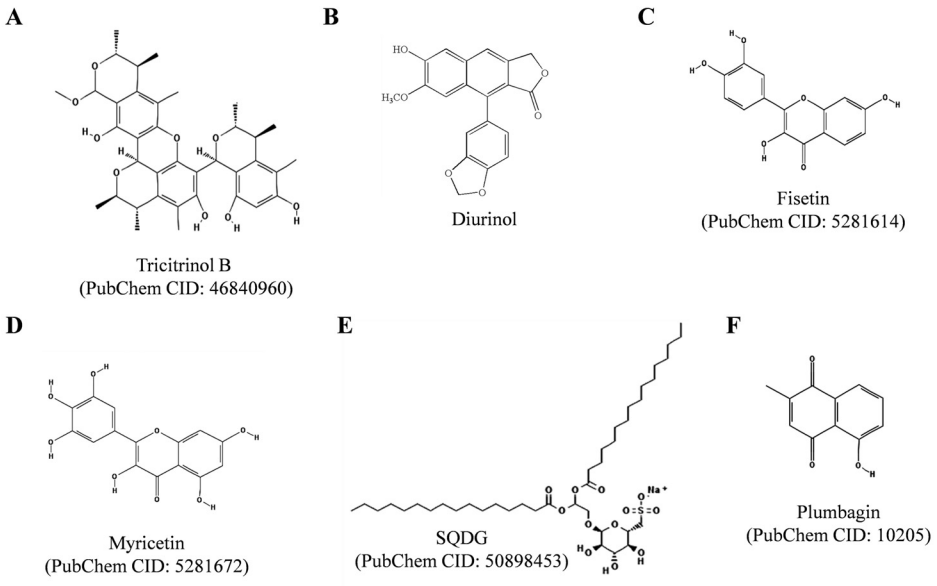

Fig. (8). Chemical structures of Tricitrinol B, Diurinol, Fisetin, Myricetin, SQDG and Plumbagin. The structures were adopted from PubChem database.

damage and arrested cell cycle at the S-phase. Downregulation of TOP1 or TP53 renders tumor cells less sensitive to SQDG, while ectopic expression of wild type TP53 protein in TP53-deficient human bone marrow chronic myelogenous leukemia (CML) K562 cells resulted in chemosensitization of tumor cells to SQDG exposure. Constant ratio combinations of SQDG with etoposide and doxorubicin were found to exert synergy on MOLT-4 cell killing. SQDG treatment delayed tumor- doubling time and reduced the expression of cell proliferation marker, Ki67, indicating *in vivo* antitumorigenic activity of SQDG. The doses of etoposide/ doxorubicin can be substantially reduced if the combination with SQDG was during acute lymphoid leukemia chemotherapy and side effects caused by these agents can also be minimized. The study also indicated that dual targeting of TOP1 and TOP2 enzymes is a promising strategy for improving chemotherapy against ALL [153].

5.18. Plumbagin

Plumbagin (Fig. **8F**) is a naphthoquinone isolated from the roots of *Plumbago zeylanica*, *Juglans regia*, *Juglans cinerea*, and *Juglans nigra* [154-160]. Plumbagin exerts anticancer, anti-bacterial, anti-fungal, anti-inflammatory and anti-oxidant properties, as reviewed in [154, 155]. In 1992, plumbagin was reported to intercalate into DNA and induce TOP2-mediated DNA cleavage *in vitro* [155]. In 2009, Chen and co-workers have reported that plumbagin and its copper complexes possess TOP1 inhibitory activities *in vitro* [156]. Copper complexes of plumbagin showed enhanced cytotoxicity and were found to be more potent TOP1 inhibitors than plumbagin. Plumbagin displays cytotoxicity against variety of cancer cell lines including breast cancer, prostate cancer, ovarian cancer, pancreatic cancer, myeloma, lung cancer, melanoma, leukemia, renal and cervical cancers [154-160]. Plumbagin was also found to display radio-sensitizing effects and to inhibit NF-κB activity in cancer cells [157, 158]. Plumbagin treatment was found to induce G_2/M cell cycle arrest and promotes apoptosis and autophagy in human tongue squamous cell carcinoma (TSCC) cells via p38 MAPK- and PI3K/AKT/mTOR-mediated pathways [159]. In another study, plumbagin was recently found to suppress epithelial to mesenchymal transition and stemness via inhibiting NRF2-mediated oxidative stress signalling pathway in TSCC cells [160].

5.19. Other Polyphenolic Compounds

Flavonoids and other polyphenolic compounds have been shown to inhibit human TOP1B through both inhibition of relaxation activity and through stabilization of the cleavable complex (poisoning), as reviewed in [19, 161, 162]. The most potent TOP1 poisons are the flavones and flavonols, whose activity is generally associated with DNA intercalation. Aqueous and methanolic extracts from *Vitis vinifera* enriched in polyphenols (caffeic acid, ferulic acid, gallic acid, protocatechuic acid and rutin) were found to act as potent inhibitors of TOP1 activity, indicating the potential mechanism for their anticancer activity [163]. These compounds also exert prooxidant activity leading to enhancement of DNA damage, which may explain their cytotoxic and apoptosis-inducing properties against cancer cells.

A flavonoid-enriched fraction isolated from the peels of Northern Spy apples was found to inhibit proliferation of human hepatocellular carcinoma HepG2 cells via a marked poisoning TOP2 catalytic activity [164]. Ellagic acid, a natural polyphenol abundant in fruits, inhibits the TOP2A and TOP2B isoforms via binding to the ATP pocket of the human DNA topoisomerase enzymes [165]. Various organic and aqueous extracts from the mulberry leaves of *Morus alba L*. (Moraceae) contained rutin, isoquercetin, and various derivatives of kaempferol and quercetin glycosides as their major constituents, as well as chlorogenic acid and caffeoylquinic acid derivatives [166]. These compounds were found to inhibit the growth of human hepatocellular carci-

noma HepG2 cells by inducing cell cycle arrest in the G2/M phase and caspase cascade-dependent apoptosis *in vitro*. Furthermore, methanolic extracts reduced the level of TOP2A, but increased the level of cyclin-dependent kinase inhibitor CDKN1B (p27Kip1).

(-)-Epigallocatechin gallate, and (-)-epigallocatechin were shown to act as redox-dependent TOP2 poisons, while quercetin, and kaempferol were traditional DNA topoisomerase poisons suggesting that structural variations might account for their mechanisms [167-171]. Epicatechin gallate (IC50 = 0.029 microM), procyanidin B2 (PB2, 4.5 microM), and resveratrol (65.7 microM), constituents of the grape cell culture (TP-4), showed the marked ability to inhibit human TOP2 catalytic activity [171, 172]. Tea phenolic compounds from *Ardisia compressa* (e.g. gallic acid, epicatechin gallate, several proanthocyanidin dimers, kaempferol, naringenin and ardisin) were shown to inhibit proliferation of human colorectal adenocarcinoma cell lines, HT-29 and Caco-2, as described in [173]. Their cytostatic effect was found to be associated with the ability to inhibit TOP2 catalytic activity.

6. THERAPEUTIC IMPORTANCE OF RECENTLY IDENTIFIED TOPOISOMERASE INHIBITORS

The novel natural topoisomerase inhibitors discussed in this review display fascinating pre-clinical features. Chemical structures of these inhibitors offer the novel skeletons to develop modified derivatives with enhanced therapeutic efficacy and target selectivity. MtDNA is essential for mitochondria, and its mutations are known to increase the risk of cancer development [174, 175]. Thus, compound like lamellarin D, which targets both TOP1MT and TOP1, may serve as important therapeutic agent to confront a mitochondrial dysfunction shown to be associated with cancers. Erybraedin C, which is equally cytotoxic for DNA mismatch repair (MMR) system-deficient and proficient cells, may be clinically important with respect to colon cancers, as MMR deficiency is well appreciated contributor to genetic instability in human colon cancers [176].

Thaspine, which was found to be effective against cells overexpressing drug efflux transporters and induced apoptosis in multicellular spheroids *in vivo*, has therapeutic importance for drug resistant solid tumors [105]. Evodiamine, albanol A and riccardin D exhibited anti-leukemic activities, and thus may serve as potential anti-leukemic chemotherapeutic agents [107, 108, 125]. Riccardin D also exerted a wide spectrum of anticancer activities [126-128]. Riccardin D exerted a cytotoxic activity on multidrug resistant (MDR) K562/A02 cells, inhibited angiogenesis in lung carcinoma cells, induced apoptosis and autophagy in osteosarcoma cells and caused DNA damage in prostate cancer cells [126-128]. (−)-Xanthatin induced GADD45 γ expression an ROS production in breast cancer cell line leading to cell death [120, 121].

Wedelolactone, another TOP2 inhibitor, kills androgen receptor negative breast cancer cells, suppresses osteoclastogenesis induced in breast cancer and disrupts EZH2-EED interaction and thus it is a potential drug candidate for the treatment of breast cancers and PRC2-dependent cancers [129-134]. Daurinol displayed antitumor activity and was found superior than etoposide (with respect to body weight and the haematological parameters) in xenografted tumor models [137-139]. Daurinol exhibited a wide spectrum of anticancer activities and *in vivo* radio-sensitizing activity [139]. Fisetin is important agent to use along with cisplatin in cancer chemotherapy as it exerts renoprotective effects, ameliorates cisplatin-induced renal impairments, protects kidneys from cisplatin-induced nephrotoxicity, and increases cytotoxic potential of cisplatin on tumor cells [141-144]. SQDG is another promising anti-leukemic agent as it exerts anti-leukemic activity *in vivo* and synergies with etoposide and doxorubicin [153]. Echinoside A might serve as a potential anticancer agent since it exerts antitumor activity against hepatocellular carcinoma *in vivo* [123].

CONCLUSION

Topoisomerase inhibitors are effective anticancer agents [19, 98]. However, they affect rapidly growing normal cells by damaging cellular DNA (e.g. etoposide and doxorubicin) and also become inactive at physiological pH (e.g. camptothecins) and thus their clinical use is limited. The novel naturally occurring topoisomerase inhibitors discussed in this review demonstrate the chemical and structural diversities of topoisomerase inhibitors with distinct mechanisms of inhibition. Structures of these inhibitors offer novel skeletons for development of more effective and targeted chemotherapeutic agents. Among these inhibitors some possesses excellent anticancer activities. However, merely identifying anticancer activities does not make them therapeutically useful anticancer drugs and more sophisticated studies on the effects of these molecules are necessary for their use in the cancer chemotherapy. Using genomics and proteomics approaches study of global cellular changes in the gene and protein expressions in response to these agents will certainly reveal their mechanisms and effects on cells and will help to better understand their chemotherapeutic potentials [177, 178]. In addition, novel drug delivery strategies have been developed in recent years, which may be utilized to enhance the anticancer efficacies of chemotherapeutic drugs and to deliver them at targeted sites with reduced side effects and increased drug availability at desired sites [179-183].

LIST OF ABBREVIATIONS

ALL	=	Acute lymphoid leukemia
ATM	=	Ataxia telangiectasia mutated
ATR	=	Ataxia telangiectasia and Rad3-related
BDDE	=	bis (2,3-dibromo-4, 5-dihydroxybenzyl) ether
BRCA1	=	Breast cancer 1
CDC25A	=	Cell division cycle 25 homolog A
CHK	=	Checkpoint-like protein kinase
CDK	=	Cyclin-dependent kinase
COX-2	=	Cyclooxygenase-2
EZH2	=	Enhancer of Zeste Homolog 2
GADD	=	Growth arrest and DNA damage, DNA double-stranded braks, DSBs
HMG	=	High mobility group

IKK	=	Inhibitor of kappa B kinase
iNOS	=	Inducible nitric oxide synthase
LPS	=	Lipopolysaccharide
MMR	=	Mismatch repair
mtDNA	=	Mitochondrial DNA
TOP1MT*	=	Mitochondrial TOP1
MDR	=	Multidrug resistant
NO	=	Nitric oxide
PARP	=	Poly (ADP-ribose) polymerase
top*	=	Prokaryotic DNA topoisomerase
PTMs	=	Post-translational modifications
ROS	=	Reactive oxygen species
top1*	=	*Shizosaccharomyces pombe* DNA topoisomerase I
SMC	=	Structural maintenance of chromosomes
SQDG	=	Sulfonoquinovosyl diacylglyceride
TOP*	=	Topoisomerase
TNF-α	=	Tumor necrosis factor-alpha

*The official symbol of the National Center for Biotechnology Information for the human (Homo sapiens) DNA topoisomerase I is TOP1 for protein, and TOP1 for the gene. Similarly, TOP2A is for the human DNA topoisomerase II alpha, and human TOP2B is for DNA topoisomerase II beta. The same designations were used for Saccharomyces cerevisiae, while *Shizosaccharomyces pombe* enzymes are designated as top1 (top2 and top3). Prokaryotic DNA topoisomerases are designated as topA (topB and topC). Mitochondrial DNA topoisomerase from Homo sapiens is designated as TOP1MT.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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