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## Review Article

### PODOPHYLLOTOXIN AND THEIR GLYCOSIDIC DERIVATIVES

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#### ABSTRACT

Podophyllotoxin is a naturally occurring lignin from the rhizomes of *Podophyllum hexandrum* Royle (*Berberidaceae*), have important antineoplastic and antiviral properties. Podophyllotoxin and their glycosidic derivatives (Etoposide and Teniposide) have different mode of action. Podophyllotoxin inhibit the microtubules but its glycosidic derivatives like Etoposide and Teniposide inhibit DNA topoisomerase II by stabilising the covalent topo II- DNA cleavable complex. So glycosidic derivatives of podophyllotoxin reduce the side effect. Podophyllotoxin have been widely used in traditional herbal medicine of many diverse cultures as remedies for purgative, snakebites, periodontitis, skin disorders, coughs, various intestinal worm disease, venereal wart condyloma acuminatum, lymphadenopathy and certain tumours, but its glycosidic derivatives are mainly used in the treatment of cancer disease.

**Keywords:** Podophyllotoxin, Etoposide, Teniposide, Topoisomerase II, Etopophos.

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#### INTRODUCTION

Podophyllotoxin is a non-alkaloid toxin lignan extracted from the roots and rhizomes of *Podophyllum* species with important antineoplastic and antiviral properties and supported by detailed understanding of their mechanism of action, and facilitated by chemical manipulations that have amplified their bioactivity, the podophyllotoxin analogues have advanced to the forefront of several areas of therapeutic and developmental chemotherapy. Podophyllotoxin- $\beta$ -D-glucopyranoside as the

main component and its 4'-demethyl derivative from the Indian *podophyllum* species, the research efforts were then focussed on a program to chemically modify both the glucosides and aglucones of a wide range of podophyllotoxin derivatives, which eventually lead to discovery of the clinically important anticancer drugs Etoposide and Teniposide,<sup>1</sup> interestingly, it was not until 20 years later that the interaction of this drug with DNA began to be understood and was recognised that the effects were mediated by topoisomerase II. At that time, it began to become clear that etoposide induced

doublestranded breaks by stabilising a complex formed between topoisomerase II and DNA that is referred to as the cleavable complex. Ross *et al.* demonstrated this by showing that topoisomerase II was the most likely cellular target in the double stranded breaking activity of epipodophyllotoxin like Etoposide and Teniposide.<sup>2</sup> In parallel, Long and coworkers studied a range of related derivatives to establish a correlation between DNA cleaving or cytostatic activities of various molecules and the extent to which they inhibited topoisomerase II activity. In this way, he demonstrated that the cytotoxicity of analogues of Etoposide was associated with inhibiting DNA topoisomerase II by stabilising the covalent topo II- DNA cleavable complex.<sup>3</sup> Although Etoposide is active in the treatment of many cancers and is widely used in the therapy, it presents several limitations, such as moderate potency, poor water solubility, development of drug resistance, metabolic inactivation, and toxic effects.<sup>4</sup> Therefore in order to obtain better therapeutic agents and extensive synthetic efforts have been devoted to overcome these problems cited above. As highlights, a water-soluble phosphate ester prodrug of Etoposide, Etopophos, was launched in 1996 by Bristol-Myers Squibb. This prodrug was readily converted *in vivo* by endogenous phosphatase to the active drug and exhibited similar pharmacological and pharmacokinetic properties as Etoposide. The *in vivo* bioavailability was increased from 0.04% to over 50% through this prodrug approach and thus constituted an improved formulation of Etoposide.<sup>5</sup> With increasing the information about its structure- activity relationships wide investigations have generated exciting chemotherapeutic candidates and successful applications of drug development from Podophyllotoxin-related lead, such as NK611, GL-331, Azatoxin, TOP53, Tafluposide. 2"-dimethylamino analogue of Etoposide, NK611, was conducted first at the Institute of Microbial Chemistry and then was identified at Nippon-

Kayaku, it was proved that NK611 improve bioavailability as a result of the molecule-altered physicochemical properties and more potent than in topo II inhibition and cytotoxicity assays against a variety of human cancer lines<sup>6</sup>. Studies by Lee *et al.* led to the synthesis of a *p*-nitroanilino group at position 4b analogue GL-331, which showed topo II inhibition and caused DNA double strand breakage and G2 phase arrest, it could induce cell death by stimulating protein tyrosine phosphatase activity and apoptotic DNA formation. GL-331 was also shown to be active in many multidrug-resistant cancer cell lines, due to good stability and biocompatibility, and its favourable pharmacokinetic profiles similar to those of etoposide.

### Structure of Podophyllotoxin

The structure of podophyllotoxin was first elucidated in the 1930s.<sup>7</sup> Podophyllotoxin bears four consecutive chiral centers, labelled C-1 through C-4.

The molecule also contains four almost planar fused rings. Four ends of podophyllotoxin have oxygen atoms at the functional groups dioxoles, methoxys, lactone, and secondary alcohol.<sup>8</sup>

### Glycosides Derivatives of Podophyllotoxin

Modifications at the C-4 position in ring C are mostly acceptable and bulky groups at this position enhance both anticancer and topoisomerase activities. So glycosides is attach on C-4 position in ring C.

### Etoposide

Etoposide is one of the most commonly prescribed anticancer drugs in clinical use. This agent exerts its chemotherapeutic effects by increasing levels of covalent topoisomerase II-cleaved DNA complexes.<sup>9</sup> Although these complexes are normal intermediates in the DNA strand passage<sup>10</sup> reaction catalyzed by topoisomerase II,<sup>11</sup> when present in high concentrations, they trigger mutagenic and cell death pathways.<sup>12</sup> Thus, etoposide and other

chemotherapeutic agents that stimulate topoisomerase II-mediated DNA cleavage are referred to as topoisomerase II “poisons” because they convert this essential enzyme to a potent cellular toxin. While the success of topoisomerase II poisons in the treatment of human malignancies has been significant, the response of different patients and or cell types varies considerably.<sup>13</sup> Unfortunately, the basis for altered cellular sensitivity to topoisomerase II-targeted drugs is not well understood. It is often assumed that resistance of catalytically active type II enzymes toward anticancer agents results from a decreased drug binding affinity. While this mechanism has been shown for a quinolone resistant DNA gyrase from *Escherichia coli*<sup>14</sup> altered drug binding has never been demonstrated for any drug-resistant type II topoisomerase from a eukaryotic species. Thus, the “decreased drug binding” hypothesis for the resistance of topoisomerase II to anticancer drugs.

#### *Teniposide*

It is a semisynthetic glucosidic cyclic acetals of podophyllotoxin. They are currently used in the chemotherapy for various types of cancer, including small cell lung cancer, testicular carcinoma, lymphoma, and Kaposi's sarcoma. To improve their clinical efficacy and overcome the problems of drug resistance, myelosuppression and poor oral availability,<sup>15</sup> we have been engaged for years in the synthesis and testing of epipodophyllotoxin derivatives.<sup>16</sup> Interestingly, although podophyllotoxin is known as an antimicrotubule agent, the epipodophyllotoxins, its 4 $\alpha$ - congeners, are potent inhibitors of DNA Topoisomerase II. The proposed mechanism of epipodophyllotoxin's antitopoisomerase II activity is to inhibit the catalytic activity of the target enzyme by stabilizing the covalent topoisomerase II-DNA cleavable complex.<sup>17</sup> An early structure-activity relationship (SAR) study suggested that the structural features essential for the

antitopoisomerase activity include 4-demethylation, 4-epimerization, and 4-substitution. On the basis of this assumption, most of our research efforts have been focused on exploring different 4-substituted 4-O demethylepipodophyllotoxin (DMEP) derivatives. Some of these derivatives have displayed better pharmacological profiles than those of etoposide. GL-331 has been successfully pushed into phase II clinical trials against gastric carcinoma, colon cancer, nonsmall cell carcinoma, and etoposide-resistant malignancies. To construct an informative SAR model and improve further design of potentially bioactive compounds, a previous molecular modelling study from these groups.

#### *Other derivatives*

In order to discuss the glycosidic derivatives of podophyllotoxin, such as NK611, Etoposide, Tafluposide. Here firstly podophyllotoxin have been widely used in traditional herbal medicine of many diverse cultures from remote times to modern times as remedies for purgative, snakebites, periodontitis, skin disorders, coughs, various intestinal worm disease, venereal wart condyloma acuminatum, lymphadenopathy and certain tumours.<sup>18</sup> Today, podophyllotoxin is still an effective, and comparatively safe drug choice in the treatment of venereal wart condyloma acuminatum. Actually, there are different biological activities in podophyllotoxin analogues that make them interesting in wide lines of research, such as reverse transcriptase inhibition and anti-HIV activity, immunomodulatory activity, effects on cardiovascular system, anti-leishmaniasis properties, 5-lipoxygenase inhibition, antirheumatic, antipsoriasis, insecticidal activity, phyto-growth inhibitory activity and ichthyotoxic activity and antimalarial and antiasmatic properties.<sup>19</sup>

These are the most widely used derivatives for the treatment of lymphomas, acute leukaemia, testicular cancer, small cell lung cancer, ovarian,

bladder, brain cancers, etc.<sup>20</sup> antitumour activity and metabolism study showed that the transfused g-lactone D ring in podophyllotoxin and its analogues is the strict structural requirement for their antitumour activity, since the transfused g-lactone D ring in podophyllotoxin and its analogues is susceptible to isomerise to the biologically inactive picropodophyllotoxin when exposed to mild base. The biological activity of picropodophyllotoxin as well as that of the other *cis* analogues is either much lower activity than that of transfused isomers or is lacking altogether. Also, the metabolism of etoposide results in inactivation by epimerisation of the *trans*-lactone ring and the *cis*-hydroxy acid which results from the opening of the lactone ring with subsequent epimerisation. From the chemotherapeutic point of view, these epimerisation metabolisms are undesirable, since limiting the physiological lifetime of these compounds would set an upper limit to their biological effectiveness. In order to avoid or minimise the C-2 epimerisation and / or the problem of metabolic inactivation, several different approaches have been proposed. Gensler *et al.* have reported a series of delactonised derivatives, including D-ring cyclopentane, cyclopentanone, ether, sulfide, sulfone and sulfoxide analogues, these delactonised derivatives were found to be less active than their parent compounds in mitotic inhibition and cytotoxic assay.<sup>21</sup> Furthermore, a series of 2-substituted podophyllotoxin derivatives, including 2-methyl-, 2-chloro-, 2-hydroxy-, and 2-bromo-podophyllotoxin, were prepared by Glinski and coworkers and tested for *in vivo* activity against P388 and L-1210 tumour cells. Among these compounds, only the chloro-derivatives showed significant activity in the P-388 and L1210 assays, giving a T/C of 156 against P-388 leukemia at 40mg/kg dosing.<sup>22</sup> More recently, Kuo-Hsiung Lee *et al.* synthesised 2-fluoropodophyllotoxin and several 4 $\beta$ - anilino-2-fluoro-4'-O-demethyl podophyllo-

toxin analogues and evaluated in both antineoplastic and antiviral assays.

### Mode of Action

King and Sullivan have shown that the mechanism of cytostatic action at the cellular level of podophyllin was the same as that of colchicine, i.e. an inhibition of the formation of the mitotic spindle, resulting in an arrest of the cell division process in metaphase and a clumping of the chromosomes(c-mitosis). Later it was shown that, at the subcellular level, this is due to binding of podophyllotoxin to tubulin, preventing these macromolecules to form a microtubules, which constitute the fibers of the mitotic spindle<sup>23</sup>. Podophyllotoxin acts as an inhibitor of assembly of microtubules and arrests the cell cycle in metaphase. These PDT lignans block the catalytic activity of DNA topoisomerase II by stabilizing a cleavage enzyme-DNA complex in which the DNA is cleaved and covalently linked to the enzyme. It binds at the colchicine site of the tubulin. From podophyllotoxin to etoposide/teniposide, some chemical modifications were made that also led to a change in the mechanism of action, from the inhibitor of microtubule formation by the parent compound PDT to DNA topoisomerase II inhibitor by etoposide and congeners.

Podophyllotoxin is an Antimicrotubule agent while Etoposide/Teniposide are DNA topoisomerase II inhibitor.<sup>24</sup>

### Chemistry and Cytotoxicity

In 1964, Schreier made use of Boron trichloride in the selective cleavage of the methylene-dioxy A-ring of podophyllotoxin analogues to produce the 6,7-dihydroxy derivative, methylation on the 6,7-dihydroxy group with diazomethane to further give the 6,7-dimethoxy derivatives.<sup>25</sup> Later on, Lee and co-workers applied the slightly modified Schreier methods and introduced the C-4 $\beta$ -substituted-arylamino group into the compound and PDT, their biological results showed that all of the A-ring opened compounds

were less active than the corresponding A-ring intact 4'-O-demethyl-4 $\beta$ -arylamino-4- desoxy-podophyllotoxin in KB, DNA topoisomerase II and protein- DNA complex formation assays, which indicated that the maintenance of an intact methylenedioxy-type ring A system, in general, appeared to be more important than a ring-A-opened system in contributing to the enhanced ability in inhibiting human DNA topoisomerase II and causing the protein-linked DNA breakage.<sup>26</sup> In general, modifications at the C and D rings of camptothecin led to complete loss of cytotoxicity. If we see these rings, the only positions available for modifications are C-5, C-14 and C-17. Several derivatives have been reported either with less activity or with loss of activity. It might be because the CPT molecule loses its planarity on these modifications to some extent, which is presumed essential for enzyme-DNA-CPT ternary complex stabilization. This was further supported by di-aza derivatives, which showed significant cytotoxicity due to their shape and planarity being quite close to camptothecin.<sup>27</sup> Reduction of 17-carbonyl leads to inactive molecules as the pyridine carbonyl is essential for receptor binding.

### **Structure-Activity Relationship (SAR) of Podophyllotoxin and Their Analogues**

Podophyllotoxin contains a five-ring system (i.e., A, B, C, D and E rings). Only the A and E rings are essential for its activity. Earlier it was reported that all the rings are essential for its activity, but now the statement is modified. D-ring in lactone form is preferred for better activity. Modifications at the C-4 position in ring C are mostly acceptable and bulky groups at this

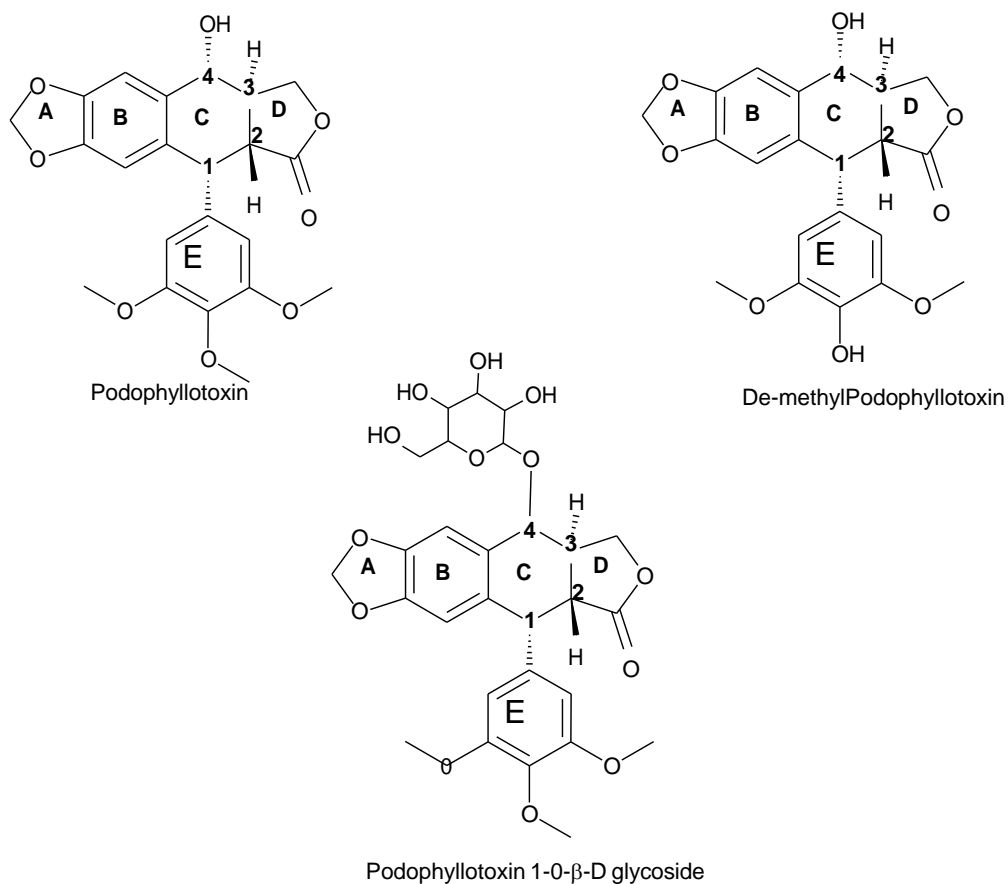
position enhance both anticancer and topoisomerase activities.<sup>28</sup> Modification of the A-ring gave compounds having significant activity but less than that of etoposide, whereas modification of the B-ring resulted in the loss of activity. One of the modifications in the D-ring produced GP-11 which is almost equipotent with etoposide. E-ring oxygenation did not affect the DNA cleavage which led to the postulation of the third mechanism of action. It has also been observed that free rotation of E-ring is necessary for the antitumor activity. The C4-substituted aglycones have a significant place in these recent developments.

### **CONCLUSION**

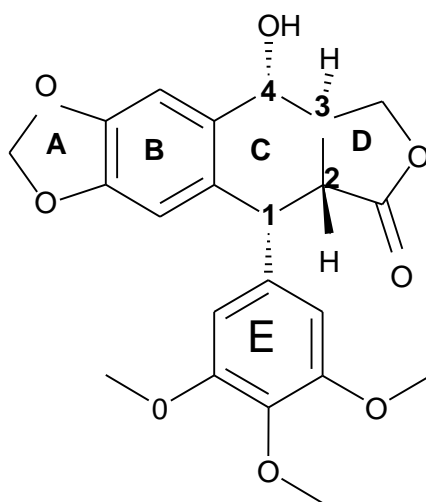
Podophyllotoxin have anticancer activity but have more side effect, So modification in podophyllotoxin at various site. Podophyllotoxin contains a five-ring system (mention in structure of PDT). Modification of the A-ring gave compounds having significant activity but less than that of Etoposide, whereas modification of the B-ring resulted in the loss of activity. E-rings is essential for its anticancer activity and D-ring in lactone form is preferred for better activity. So only modification site of Podophyllotoxin is ring C preferred. Modifications at the C-4 position in ring C are mostly acceptable and bulky groups at this position enhance anticancer activity.

### **ACKNOWLEDGEMENTS**

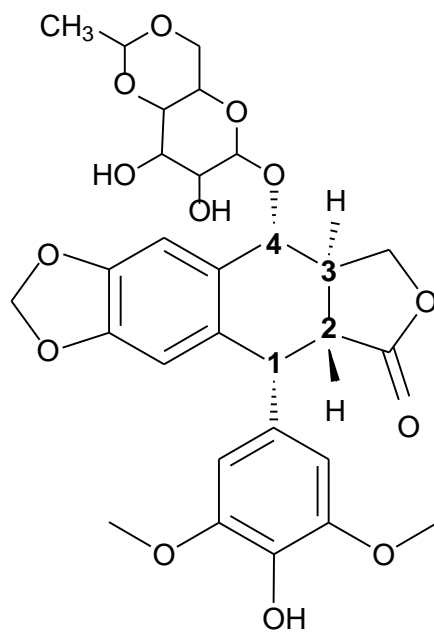
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**Figure1:** Various compounds of Podophyllotoxin and their Glycosidic derivatives

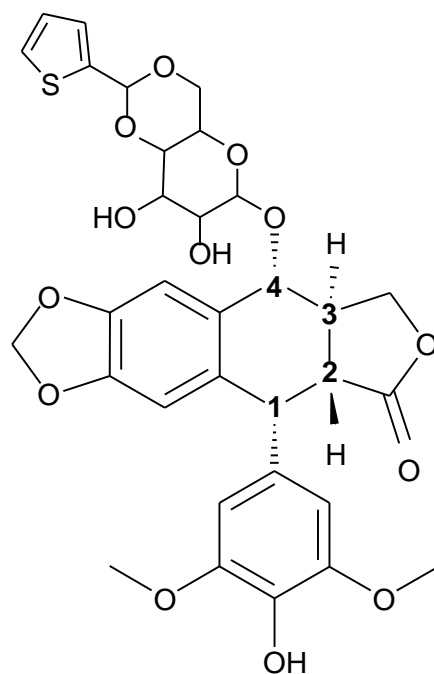


**Figure 2:** Structure of Podophyllotoxin

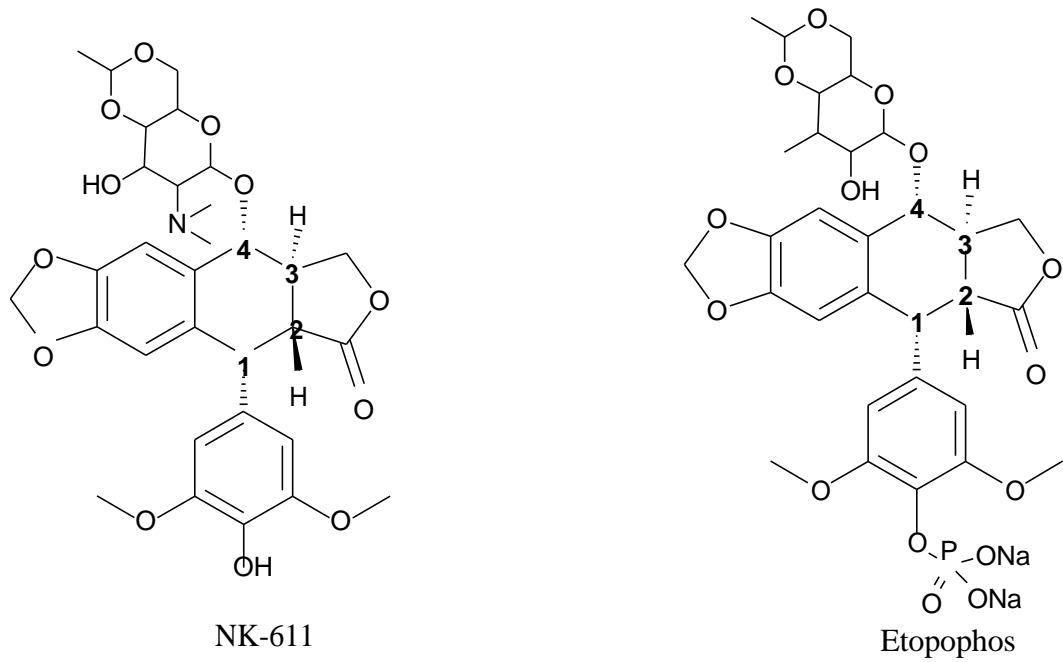


Etoposide

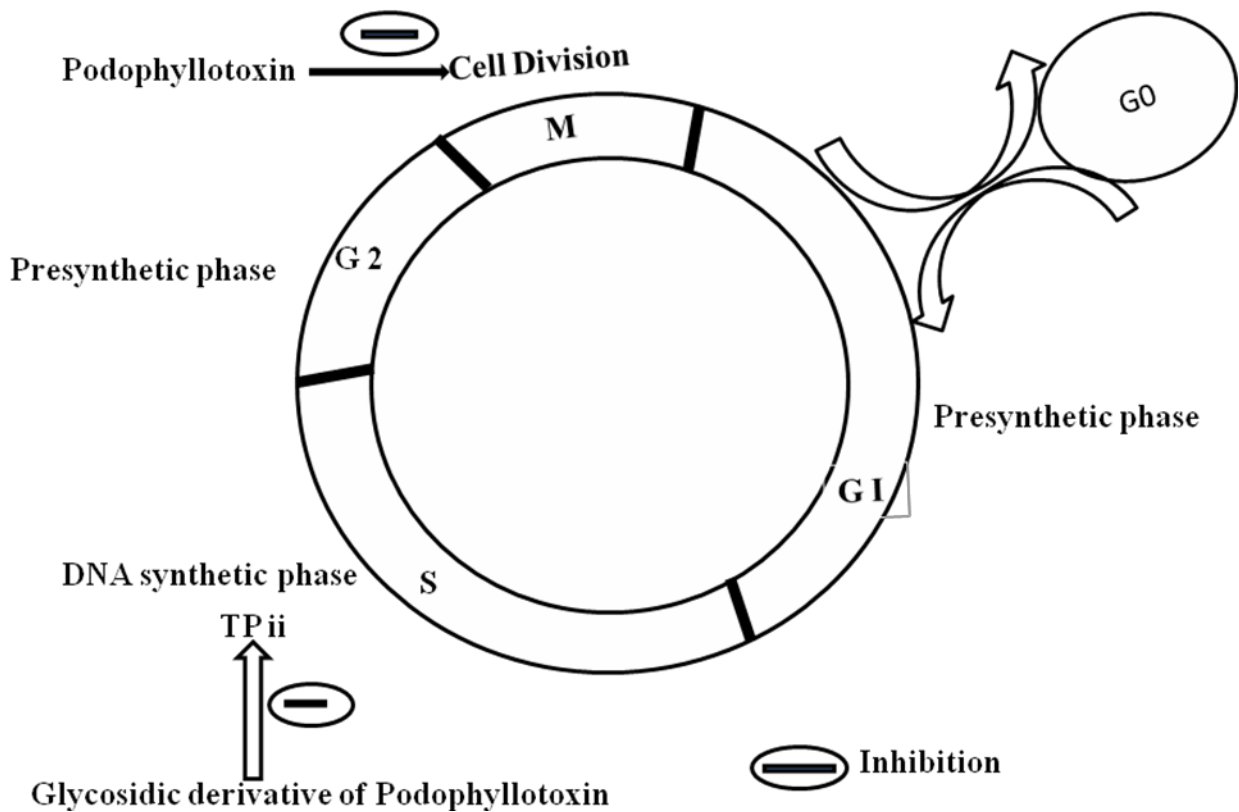
**Figure 3:** Structure of Etoposide



**Figure 4:** Structure of Teniposide

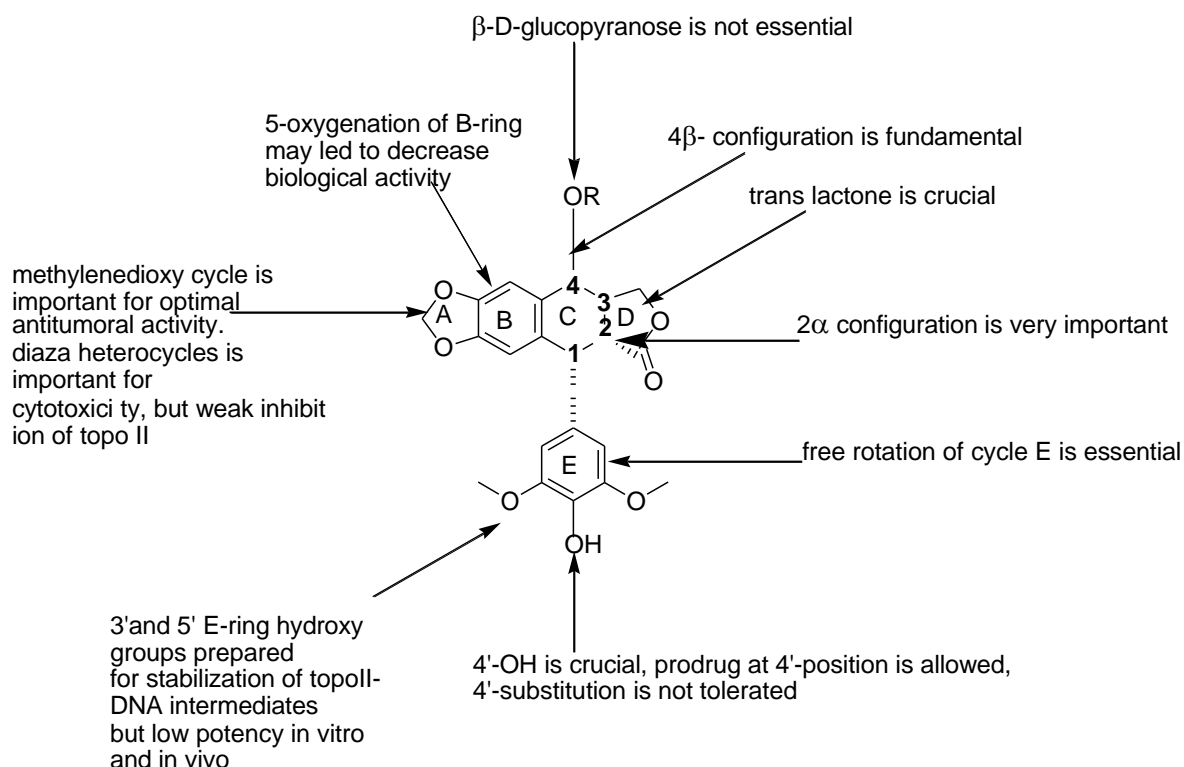


**Figure 5:** Structure of NK-611 and Etopophos



**Figure 6:** Mode of action, Podophyllotoxin & their Glycosidic derivative





**Figure 7:** SAR of Podophyllotoxin analogs

## REFERENCES

1. (a) Stoll, A; Renz, J and Wartburg, AV (1954), "The isolation of podophyllotoxin Glucoside", *J. Am. Chem. Soc.*, Vol.76, 3103-3104. (b) Emmenggger, H; Staehelin, H; Rutschmann, J and Wartburg, A (1961), "Chemistry and Pharmacology of podophyllum glucosides and derivatives", *I. Arzneimittel Forsch*, Vol.11, 327-333. (c) Kuhn, M and Wartburg, A (1968), "Synthesis of epipodophyllotoxin D-glucopyranoside", *Helv. Chim. Acta*, Vol.51, 1631-1641. (d) Kuhn, M and Wartburg, A (1969), "Mitosis-inhibiting substances.glycosidation process.II. Glycosides of 4'-demethylepipodophyllotoxin", *Helv. Chim. Acta*, Vol.52, 948-955. (e) Keller-Juslen, C; Kuhn, M; Wartburg, A and Staehelin, H (1971), "Synthesis and antimetabolic activity of glycosidic lignan derivatives related to podophyllotoxin", *J. Med. Chem.*, Vol.14, 936-940.
2. Ross, W; Rowe, T; Glisson, B; Yalowich, J and Liu, L (1984), "Role of topoisomerase II in mediating epipodophyllotoxin-induced DNA cleavage", *Cancer Res.*, Vol.44, 5857-5860.
3. (a) Long, BH and Minocha, A (1983), "Inhibition of topoisomerase II by VP-16 (etoposide), VM-26 (teniposide) and structure congeners as explanation for *in vivo* DNA breakage and cytotoxicity", *Proc. Am. Ass. Cancer Res.*, Vol. 24, 1271. (b) Long, BH; Musial, ST and Brattain, MG (1984), "Comparison of cytotoxicity and DNA breakage activity of congeners of podophyllotoxin including VP16-213 and VM26: a quantitative structure-activity relationship" *Biochemistry*, Vol. 23, 1183-1188.
4. Zhu, XK; Guan, J; Tachibana, Y and Bastow, KF *et al.* (1999), "Synthesis and Biological Evaluations of 4-Mono-, -Di-, and -Tri substituted Aniline-4'-O-demethyl-podophyllotoxin and Related Compounds with Improved Pharmacological Profiles", *J. Med. Chem.*, Vol. 42, 2441-2446.
5. Greco, FA and Hainsworth, JD (1996), "Clinical Studies of Etoposide phosphate", *Semin. Oncol.*, Vol.

- 23 (suppl), 45-50.
6. Saito, H; Yoshikawa, H; Nishimura, Y and Kondo, S *et al.* (1986), "Studies on Lignan Lactone Antitumor Agents.II. Synthesis of N-Alkylamino and 2, 6-Dideoxy-2 Aminoglycosidic Lignan Variants Related to Podophyllotoxin", *Chem. Pharm. Bull.*, Vol. 34, 3741-3746.
  7. Jackson, DE and Dewick, PM (1984), "Aryltetralin lignans from *Podophyllum hexandrum* and *Podophyllum peltatum*", *Phytochemistry*, Vol. 23, 1147– 1152.
  8. Tian, X; Gao, R and Zhang, X (2000), "Insecticidal activity of deoxypodophyllotoxin" *Acta Universitatis Agriculturae Boreali-occidentalis*, Vol.28, 19–24.
  9. (a) Smith, MA; Rubinstein, L; Cazenave, L and Ungerleider, RS *et al.* (1993), "Binding of Etoposide to Topoisomerase II in the Absence of DNA", *J. Natl. Cancer Inst.*, Vol.85, 554-558. (b) Smith, M A; Rubinstein, L and Ungerleider, RS (1994), "Treatment of acute leukemias", *Med. Pediatr. Oncol.*, Vol. 23, 86-98.
  10. (a) Chen, AY and Liu, L F (1994), "DNA topoisomerase, Essential Enzyme and Lethal Targets", *Annu. Rev. Pharmacol. Toxicol.*, Vol.34, 191-218. (b) Corbett, A H and Osheroff, N (1993), "DNA topoisomerase protocols", *Chem. Res. Toxicol.*, Vol.6, 585-597. (c) Froelich-Ammon, SJ and Osheroff, N (1995), "Assessing Sensitivity to Antibacterial Topoisomerase II Inhibitors", *J. Biol. Chem.*, Vol.270, 21429-21432.
  11. (a) Osheroff, N; Zechiedrich, EL and Gale, KC (1991), "HMGB1 interacts with human topoisomerase II $\alpha$  and stimulates its catalytic activity", *BioEssays*, Vol.13, 269-273. (b) Watt, PM and Hickson, ID (1994), "In vitro inhibitory effects of DNA topoisomerase II by fernane-type triterpenoids isolated from a *Euphorbia* genus", *Biochem. J.*, Vol. 303, 681- 695.
  12. (a) Hickman, JA (1992), "Apoptosis induced by anticancer drugs. Cancer Metastasis", *Rev.*, Vol.11, 121-139. (b) Anderson, RD, and Berger, NA (1994), "Mutagenicity and carcinogenicity of topoisomerase interactive agents", *Mutat. Res.*, Vol.309, 109-142. (c) Ferguson, LR and Baguley, BC (1994), "Inhibition of Human Topoisomerase II *in vitro* by Bioactive Benzene Metabolites", *Environ. Mol. Mutagen.*, Vol.24, 245-261.
  13. (a) Larsen, AK and Skladanowski, A (1998), "The Antitumor Triazoloacridone C-1305 is a Topoisomerase II Poison", *Biochim. Biophys. Acta*, Vol.1400, 257-274. (b) Dingemans, AMC; Pinedo, HM and Giaccone, G (1998), "Clinical resistance to topoisomerase-targeted drugs", *Biochim. Biophys. Acta*, Vol.1400, 275-288.
  14. Willmott, CJ and Maxwell, A (1993), "Antimicrobial agents", *Chemother.* Vol.37, 126-127.
  15. (a) Maanen, JMS; Retel, JD; Vries, J and Pinedo, HM (1988), "Etoposide is an important antineoplastic", *J. Natl. Cancer Inst.*, Vol.80, 1526-1533. (b) Hainsworth, JD; Williams, SD; Einhorn, LH and Birch, R (1985), "The interaction of cisplatin plus etoposide", *J. Clin. Oncol.* Vol.3, 666-671.
  16. (a) Lee, KH; Imakura, Y; Haruna, M and Beers, SA *et al.* (1989) "Antitumor Agents", *J. Nat. Prod.*, Vol.52, 606-613. (b) Wang, ZQ; Kuo, YH; Schnur, D and Bowen, JP *et al.* (1990), "Plant Phenolic Compounds as Cytotoxic Antitumor Agents", *J. Med. Chem.*, Vol.33, 2660-2666. (c) Lee, KH; Beers, SA; Mori, M and Wang, ZQ *et al.* (1990) "Antitumor Agents. Derivatives of 4-Demethylepipodophyllotoxin as Potent Inhibitors of Human DNA Topoisomerase II", *J. Med. Chem.*, Vol.33, 1364-1368. (d) Zhou, XM; Wang, ZQ; Chang, JY and Chen, HX *et al.* (1991), "Antitumor Agents New 4-Substituted Benzylamine and Benzyl Ether Derivatives of 4-O-Demethylepipodophyllotoxin as Potent Inhibitors of Human DNA Topoisomerase II" *J. Med. Chem.*, Vol.34, 3346-3350. (e) Hu, H; Wang, ZQ; Liu, SY and Cheng, YC *et al.* (1992) "Antitumor Agents, 4 $\alpha$ -Substituted Aniline Derivatives of 6,7-O,O-Demethylpodophyllotoxin and Related

- Compounds as Potent inhibitors of Human DNA Topoisomerase II”, *J. Med.Chem.*, Vol.35, 871-877.
17. (a) Osheroff, N; Zechiedrich, EL and Gale, KC(1991), “Catalytic Function of DNA Topoisomerase II”, *BioEssays*, Vol.13, 269-275. (b)Alton, PA and Harris (1993), “Synthesis and Characterization of New Diketone Analogues of Podophyllotoxin”*A.L. Annotation. Br. J. Haematol.*, Vol.85, 241-245.
  18. Liu, CJ and Hou, SS (1997), “Current Research Status of Podophyllotoxin. Lignans” *Nat. Prod. Res. Develop.*, Vol.9, 81-89.
  19. Gordaliza, M; García, PA; Miguel DC, JM and Castro, MA *et al.*( 2004), “Podophyllotoxin: sources, extraction, and preparation of cytotoxic analog compounds”,*Toxicon*, Vol.44, 441-459.
  20. Schacter, L (1996), “Etoposide phosphate”, *Semin. Oncol.*, Vol.6 (Suppl 13), 1-7.
  21. Walter, J; Gensler, CD and Murthy, MHT (1977), “Nonenolizable Podophyllotoxin Derivatives”, *J. Med. Chem.*, Vol.20, 635-644.
  22. Glinski, MB; Freed, JC and Durst, T (1987), “Preparation of 2-Substituted Podophyllotoxin Derivatives”, *J. Org. Chem.*, Vol. 52, 2749-2753.
  23. (a) Haar, E; Rosenkranz, HS; Hamel, E and Day, BW (1996), “Synthesis of combretastatin analogues with their potent anticancer analogues”, *Bioorg. Med. Chem.*, Vol. 4: 1659-1671. (b)Desbene, S and Giorgi-Renault, S (2001), “The 1, 4-dihydroquinoline-lactones 2 present very interesting antitumor properties”.*Curr. Med. Chem.*, Vol.1, 71-90. (c)Islam, MN and Iskander, MN (2004), “Microtubulin binding sites as target for developing anticancer agents” *Mini-Rev. Med. Chem.*, Vol. 4, 1077-1104.
  24. Berger, JM; Gambin, SJ; Harrison SC and Wang, JC (1996), “Structure and mechanism of DNA topoisomerase II”, *Nature*, Vol.379, 225-232.
  25. Von Schreier, E (1964), “Partial syntheseseder 6, 7-Dimethoxy-Analogen”, *Helv. Chim.Acta*, Vol.47, 1529-1554.
  26. Wang, ZQ; Hu, H; Chen, HX and Cheng, YC *et al.* (1992), “ Substituents on Etoposide That Interact with Human Topoisomerase II $\alpha$  in the Binary Enzyme–Drug Complex: Contributions to Etoposide Binding and Activity”, *J. Med. Chem.*, Vol.35, 871- 877.
  27. Nicolas, AW; Wani, MW; Manikumar, G and Wall, ME *et al.* (1990), “A new family of camptothecin antitumor agents” *J. Med. Chem.*, Vol.33, 972.
  28. Tian, X; Gao, R and Zhang, X (2000), “Insecticidal activity of deoxypodophyllotoxin”, *ActaUniver-sitatis Agriculturae Boreali-occidentalis*, Vol.28, 19-24.