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Molecular Docking Studies of Podophyllotoxin and Its Derivatives against Metabolic Enzymes Regarding Anticancer Therapeutic Strategies

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Molecular Docking Studies of Podophyllotoxin and Its Derivatives against Metabolic Enzymes Regarding Anticancer Therapeutic Strategies

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Abstract
The objective of this study was to analyze the molecular characteristics of the podophyllotoxins and its derivatives with the metabolic enzymes and regulate the designing of therapeutic mechanism against malignant cells. One such inhibitor is podophyllotoxin with anticancer activity because of the capability to stop the metabolic enzymes. In this study, we undertook the *in silico* analysis with respect to molecular docking podophyllotoxin and its derivatives using the Patchdock server. Moreover, drug likeness of podophyllotoxin, etoposide, and teniposide was investigated using Lipinski filter and SwissADME. According to the molecular docking score, podophyllotoxin indicated that both derivatives (especially teniposide) showed a good binding affinity toward selected protein receptors.

Keywords: Podophyllotoxin; Cyclins; Anticancer; Lipinski filter; Patchdock.

1. INTRODUCTION

It is well known that deadly or malignant cells show transformed metabolism that is considered a hallmark of cancer [1, 2]. Moreover, the transformed metabolism of malignant cells is commonly a regulatory process of enzymes catalyzing pathways like glycolysis and TCA or Kreb's cycle [3, 4]. Nowadays, the main approaches to inhibit the expression and activities of enzymes modulate and convey the transformed metabolic machinery of the newly derived cells [5, 6]. On the contrary, the tumor cells possess an excellent ability to drive such approaches through adaptive strategies that could be one of the important limitations of employing a single enzyme-specific inhibitor [7, 8]. Recent studies reveal that podophyllotoxin ($C_{22}H_{22}O_8$) is a major lignin because its derivatives were remembered as potential anticancer factors [9]. Podophyllotoxin was initially isolated by Podwyssotzki in North American plant podophyllumpeltatum and also called mayapple. Podophyllotoxin-derived anticancer promoters indulged etoposide and teniposide [10, 11]. These types of drugs have been fully utilized against various cancers such as breast, testicular, stomach, and ovarian cancers [12]. Both the derivatives serve as topoisomerase poisons and lead to DNA strand breaks by attaching to type II topoisomerase [13]. Etoposide serves as a part of multiple drug process to treatment for small cell lung cancer. Moreover, teniposide acts as a chemotherapy drug in childhood acute lymphoblastic leukemia [14-16].

2. METHOD(S)

The analysis of three-dimensional structures of target enzymes and ligands is retrieved from PubChem databases and Protein Data Bank, accordingly. Moreover, the drug likeness was investigated through ADME analysis and Lipinski filter.

2.1. Retrieval of Target Receptors

PubChem databases and Protein Data Bank were used for retrieving the structures of the respective receptors involved in glycolysis and TCA cycle. Moreover, the criteria for the structure were investigated by BLAST and Protein Data Bank analysis.

2.2. Homology Modeling for Topoisomerase II

The 3D structure was not available in Protein Data Bank, and the topoisomerase II protein sequence was retrieved from the NCBI databases for structure prediction. Moreover, templates were targeted using a homology search from PDB and NCBI databases. The homology of the selected template with topoisomerase was above 90% with respect to the percent identity [17, 18] (Table 1).

2.3. Ligands Preparation

The podophyllotoxin and its derivatives were recovered from PubChem databases (Figures 1-8). Moreover, these structures were employed for molecular docking calculation. Moreover, three-dimensional structures of selected ligands were retrieved from PubChem databases in SDF file format and converted to PDB format using PyMol.

2.4. Molecular Docking Analysis

For molecular docking analysis, the Patchdock server [19] was used for molecular docking analysis of podophyllotoxin and its derivatives (etoposide and teniposide) to the selected target receptors (Tables 2-4). The PDB format file of ligands and receptors was employed to the Patchdock server for the analysis using cluster RMSD at the default value of 4.0. Another tool was used for molecular docking, that is, YASARA for virtual screening [20, 21].

2.5. Drug-Likeness Analysis

The drug likeness was analyzed by the Lipinski filter (Table 5). To analyze the orally active drug, there are some criteria like molecular mass, cLogP, hydrogen bond donor and bond acceptor [22]. The properties of ligand were analyzed by admetSAR, which is known for drug discovery [9] (Tables 6, 7).

3. RESULTS AND DISCUSSION

3.1. Ligands

Figure 1: 3D structure of Podophyllotoxin

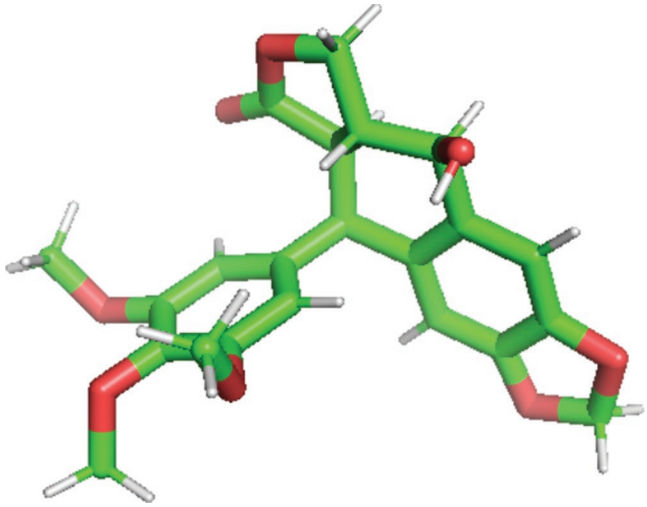


Figure 2: Etoposide.

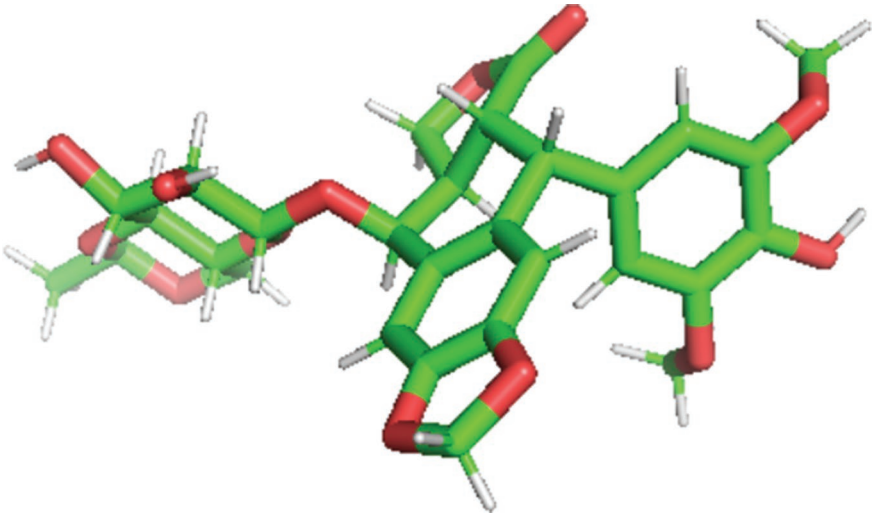


Figure 3: Teniposide.

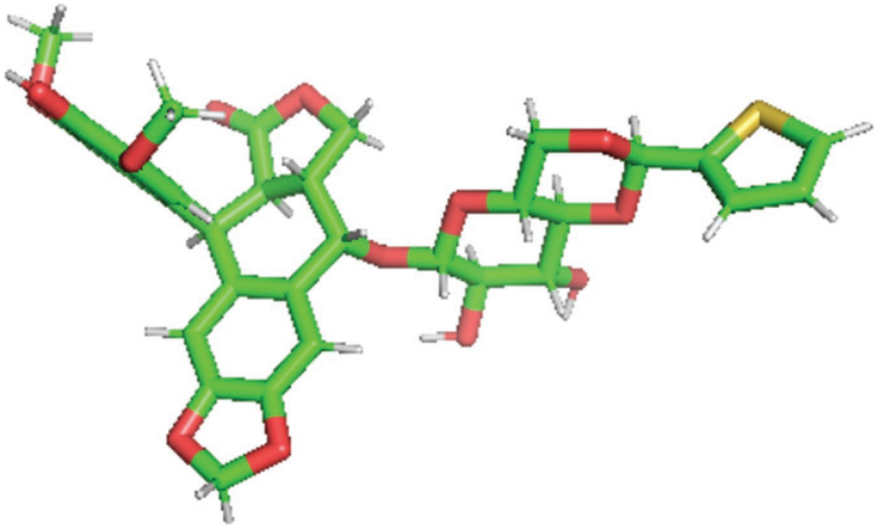


Table 1: Docking score of selected ligands with Topoisomerase II.

Ligands	Docking score	ACE (kcal/mol)
Podophyllotoxin	5528	–82.15
Etoposide	6532	–94.38
Teniposide	6728	–101.46

3.2. Drug-Likeness Analysis

Table 2: Docking score of selected ligands with Cyclin C Protein receptor.

Ligands	Docking score	ACE
Podophyllotoxin	5158	–94.88
Etoposide	6442	–119.12
Teniposide	6768	–128.34

Table 3: Docking score of selected ligands with Cyclin D Protein receptor.

Ligands	Docking score	Glide energy
Podophyllotoxin	4606	–114.34
Etoposide	5706	–54.69
Teniposide	5834	–174.41

3.3. Brain or Intestinal Estimated Permeation Method

3.4. Molecular Docking of Podophyllotoxin and Its Derivatives

The docking properties of podophyllotoxin with the selected enzyme and the ligand structure of podophyllotoxin recovered from the Pubchem database were investigated for docking purposes employing the Patchdock server (Figure 9) and iGemdock. Docking simulation of podophyllotoxin with the selected enzymes of the TCA and glycolysis cycle with respective parameters such as GSC score predicted binding energy.

Figure 4: Boiled egg.

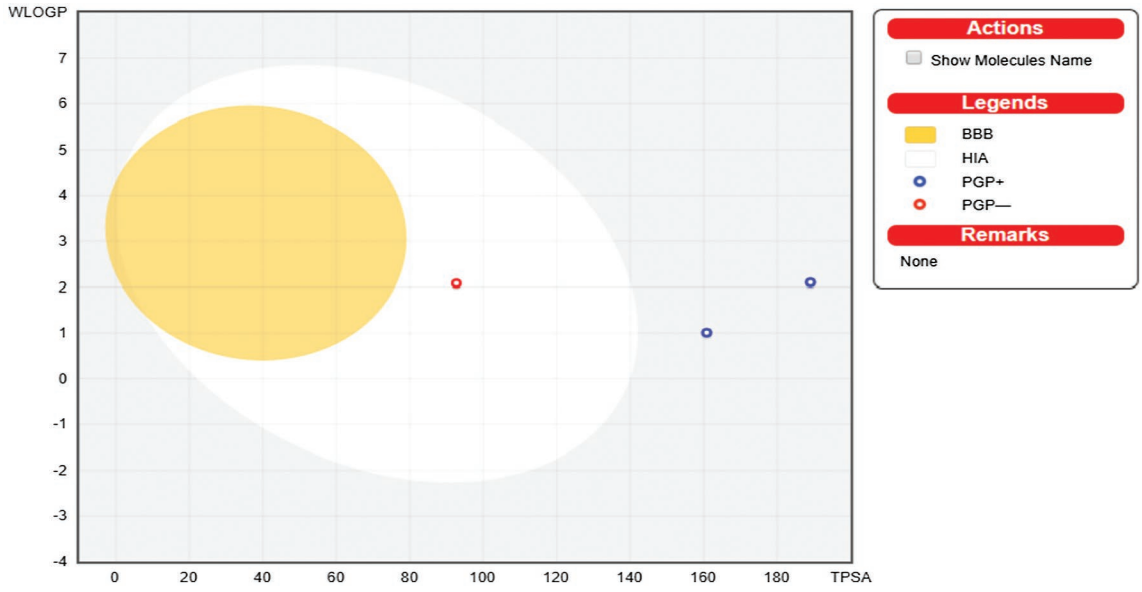


Figure 5: Molecular docking and virtual screening of podophyllotoxin and its derivatives with topoisomerase II.

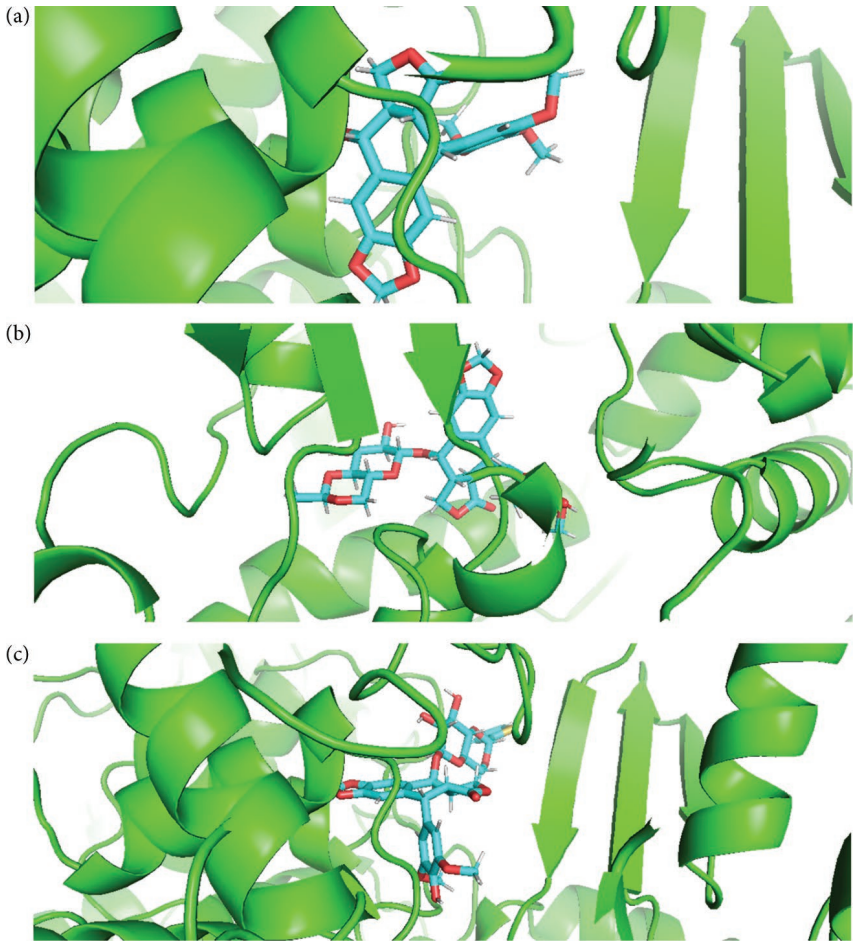


Table 4: Docking score of selected ligands with Cyclin E Protein receptor.

Ligands	Docking score	Glide energy
Podophyllotoxin	5204	–89.04
Etoposide	6046	–147.46
Teniposide	6646	–130.56

Figure 6: Molecular docking and virtual screening of selected ligands with cyclin C protein receptor.

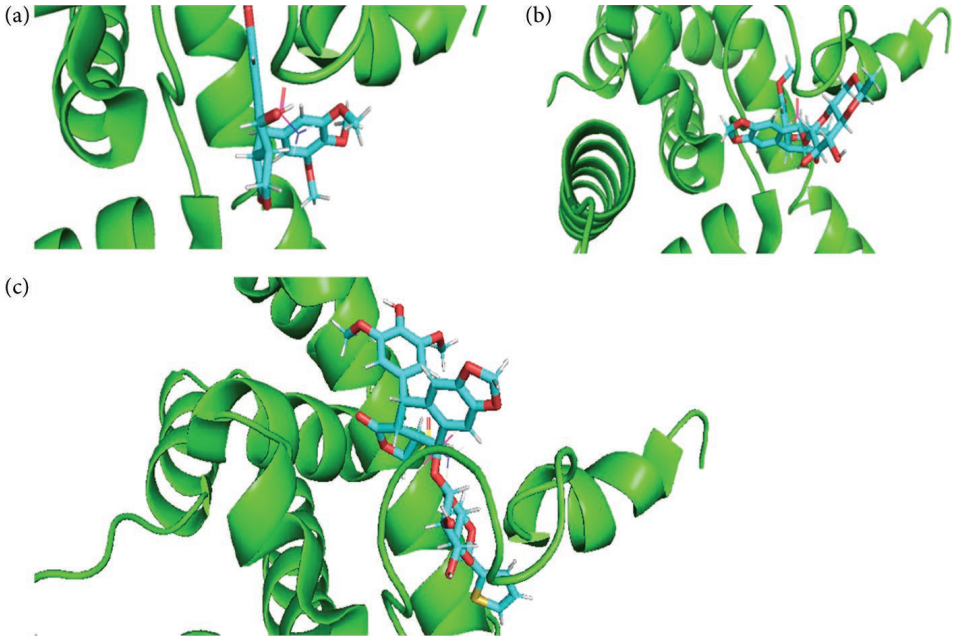


Figure 7: Molecular docking and virtual screening of selected ligands with cyclin D protein receptor.

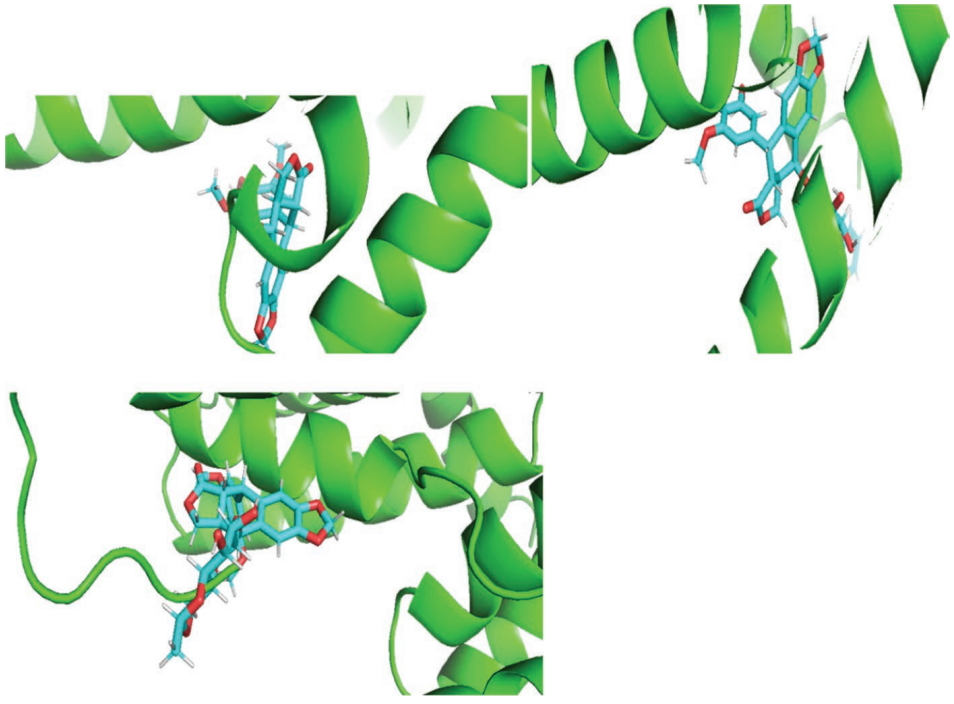


Table 5: Lipinski filter analysis.

Ligands	Molecular weight	Hydrogen bond donor	Hydrogen bond acceptor	cLogP	Molar refractivity
Podophyllotoxin	414.4 g/mol	1	8	2.33	103.85
Etoposide	588.6 g/mol	3	13	1.13	139.11
Teniposide	656.7 g/mol	3	14	1.77	156.66

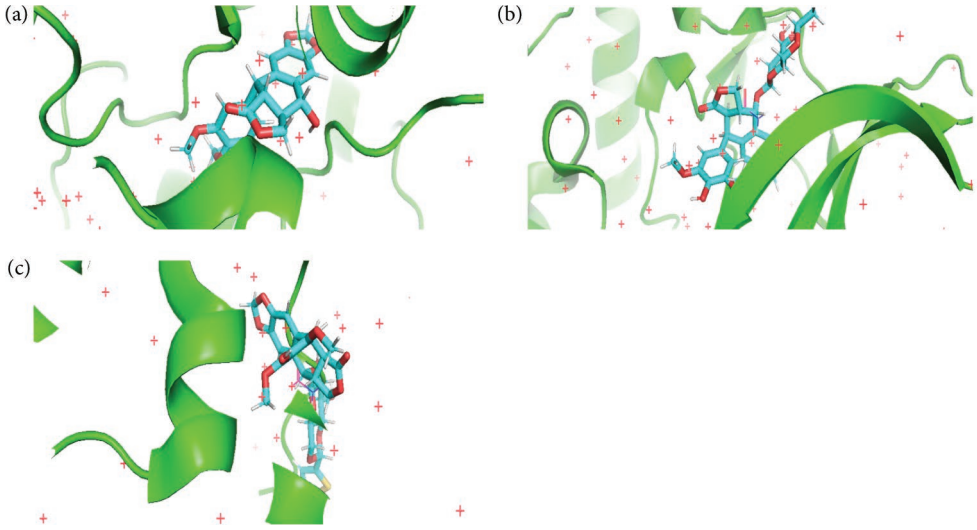
Table 6: Physiochemical properties of the ligands.

Ligands	Molecular formula	Molecular weight	Monoisotopic mass	Heavy atom count	Topological polar surface area
Podophyllotoxin	$C_{22}H_{22}O_8$	414.4 g/mol	414.131468 g/mol	30	92.7 Å²
Etoposide	$C_{29}H_{32}O_{13}$	588.6 g/mol	588.184291 g/mol	42	161 Å²
Teniposide	$C_{32}H_{32}O_{13}S$	656.7 g/mol	656.156362 g/mol	46	189 Å²

Table 7: AdmetSAR analysis.

Properties	Podophyllotoxin	Etoposide	Teniposide
Blood-brain barrier	No	No	No
GI absorption	High	Low	Low
p-gp substrate	No	Yes	Yes

Figure 8: Molecular docking and virtual screening of selected ligands with cyclin E protein receptor.

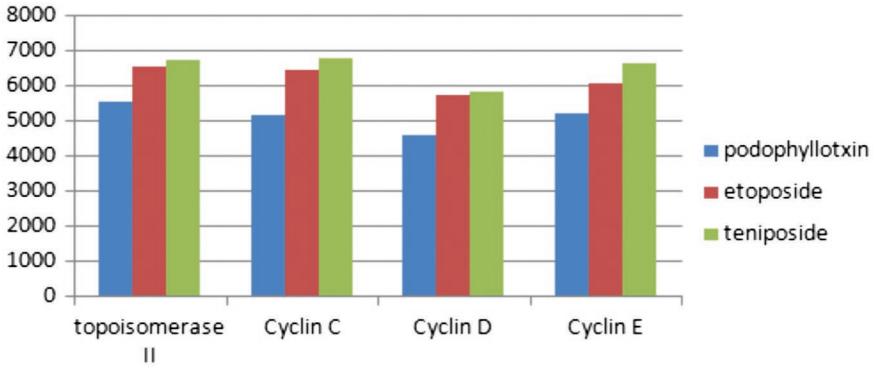


4. CONCLUSION

This study analyzed the potential between podophyllotoxin and its derivatives (etoposide and teniposide) to metabolic enzymes, thereby showing the enormous interaction like hydrophobic interaction and hydrogen bonds depending on the biochemical properties of the docking simulation and selected enzymes. According to molecular docking, the podophyllotoxin and its derivatives in glycolysis and TCA cycle show excellent efficiency to the malignant cells.

According to the docking score, the scores revealed that teniposide was superior to podophyllotoxin and etoposide. These derivatives are also predicted to drug-likeness analysis in terms of *in vitro* and *in vivo* investigations on the tumor-bearing host to operate the therapeutic efficacy.

Figure 9: Molecular docking analysis of podophyllotoxin and its derivatives using the Patchdock server against selected target protein receptors.



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Authors' Contribution
Both authors contributed equally to this work.

Conflict of Interest
None.

References

1. Hanahan D, Weinberg RA. Hallmarks of cancer: The next generation. Cell. 2011; 144:646-74.
2. Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: The metabolic requirements of cell proliferation. Science. 2009; 324:1029–33.
3. DeBerardinis RJ, Lum JJ, Hatzivassiliou G, Thompson CB. The biology of cancer: Metabolic reprogramming fuels cell growth and proliferation. Cell Metab. 2008; 7:11–20.
4. Pelicano H, Martin DS, Xu R-H, Huang P. Glycolysis inhibition for anticancer treatment. Oncogene. 2006; 25:4633–46.
5. Dang CV, Hamaker M, Sun P, Le A, Gao P. Therapeutic targeting of cancer cell metabolism. J Mol Med. 2011; 89: 205-12.
6. Vander Heiden MG. Targeting cancer metabolism: A therapeutic window opens. Nat Rev Drug Discov. 2011; 10:671-84.
7. Petrelli A, Giordano S. From single- to multi-target drugs in cancer therapy: When aspecificity becomes an advantage. Curr Med Chem. 2008; 15:422-32.
8. Suda K, Mitsudomi T. Successes and limitations of targeted cancer therapy in lung cancer. Prog Tumor Res. 2014; 41:62-77.
9. Cheng F, Li W, Zhou Y, Shen J, Wu Z, *et al*. admetSAR: A comprehensive source and free tool for assessment of chemical ADMET properties. J Chem Inf Model. 2012; 52:3099–105.
10. Gordaliza M, García PA, del Corral JM, Castro MA, Gómez-Zurita MA. Podophyllotoxin: Distribution, sources, applications and new cytotoxic derivatives. Toxicon. 2004; 44(4):441–59.
11. Damayanthi Y, Lown JW. Podophyllotoxins: Current status and recent developments. Curr Med Chem. 1998; 5(3):205-52.
12. Attia AM, Bakrey OA, Fakhrey Abd El-Motaleb SM. The use of podophyllotoxin for treatment of genital warts. Menoufia Med J 2015; 28:367-71.
13. Ross W, Rowe T, Glisson B, Yalowich J, Liu L. Role of topoisomerase II in mediating epipodophyllotoxin-induced DNA cleavage. Cancer Res. 1984; 44:5857-60.
14. Nelson EM, Tewey KM, Liu LF. Mechanism of antitumor drug action: Poisoning of mammalian DNA topoisomerase II on DNA by 4′-(9-acridinylamino)-methanesulfon-*m*-anisidide. Proc Natl Acad Sci U S A. 1984; 81:1361-65.
15. Ketron AC, Denny WA, Graves DE, Osheroff N. Amsacrine as a topoisomerase II poison: importance of drug-DNA interactions. Biochemistry. 2012; 51:1730–39.
16. Jehn U, Heinemann V. New drugs in the treatment of acute and chronic leukemia with some emphasis on *m*-AMSA. Anticancer Res. 1991; 11:705-11.
17. Madhusudhan MS, Marti-Renom MA, Eswar N, John B, Pieper U, *et al*. Comparative protein structure modeling. In "The Proteomics Protocols Handbook." Editor - Walker JM (ed). Springer Protocols Handbooks. Humana Press (2005). https://doi.org/10.1385/1-59259-890-0:831

18. Kuntal BK, Aparoy P, Reddanna P. EasyModeller: A graphical interface to MODELLER. BMC Res Notes. 2010; 3:226-27.
19. Schneidman-Duhovny D, Inbar Y, Nussinov R, Wolfson HJ. PatchDock and SymmDock: Servers for rigid and symmetric docking. Nucleic Acids Res. 2005; 33:W363-67.
20. Krieger E, Vriend G. YASARA View—Molecular graphics for all devices—From smart phones to workstations. Bioinformatics. 2014; 30: 2981-82.
21. Trott O, Olson AJ. AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. J Comput Chem. 2010; 31:455-61.
22. Lipinski CA. Lead- and drug-like compounds: The rule-of-five revolution. Drug Discov Today Technol. 2004; 1:337-41.