International Journal of Science and Research Archive
eISSN: 2582-8185
Cross Ref DOI: 10.30574/ijsra
Journal homepage: https://ijsra.net/

(RESEARCH ARTICLE)

Check for updates

Mode of action of vinca alkaloids against cancer using Insilco analysis technique

Stuti Bhatnagar [1,*], Rashi Srivastava [1] and Rajesh Saxena [2]

[1] *School of Biotechnology, IFTM University, Delhi Road (NH 24), 244102 Moradabad, Uttar Pradesh, India*
[2] *Madhya Pradesh Council Science & Technology, 462003 Bhopal, Madhya Pradesh, India.*

International Journal of Science and Research Archive, 2022, 07(02), 181–188

Publication history: Received on 06 October 2022; revised on 13 November 2022; accepted on 16 November 2022

Article DOI: https://doi.org/10.30574/ijsra.2022.7.2.0257

Abstract

Plants have been known for their medicinal properties across the world for a long time. In the field of medicine, medicinal plants have played a critical role. *Catharanthus roseus* is one such plant with enormous medical significance and potential. C.roesus, often known as Madagascar periwinkle, is a major drug-producing plant. More than 200 alkaloids are found in all parts of the plant, including the leaf, root, shoot, and stem, and are used to treat a variety of diseases.

Vinca alkaloids are also effective cancer fighters. To see the mode of action of vinca alkaloids against cancer, 3D structure of Tubulin alpha-beta dimer was obtained from the database, The vinca alkaloids were obtained from Zinc database.

In recent years, protein-ligand docking has become a powerful tool for drug development. The final PDB file of Tubulin alpha-beta dimer (PDB Id: 1TUB) and alkaloids were directly fed into an online docking server, SwissDock (http://www.swissdock.ch/docking).

In this research we will find out that how Vinca alkaloids are commonly used in combination chemotherapy regimens for medicinal treatments. The vinca alkaloids have cytotoxic properties that can halt cell division and cause cell death.

Keywords: Vinca alkaloids; Cancer; 3D structures; Insilico analysis; Protein ligand docking

1. Introduction

Vinca alkaloids are a class of drugs derived from the Madagascar periwinkle plant. *Catharanthus roseus*, the pink periwinkle plant, is used to extract them naturally. *Catharanthus roseus* is a medicinally important plant that pharmaceutical companies use extensively in the production of anticancer drugs. Vinca alkaloids are used to treat diabetes, high blood pressure, and as disinfectants. Vinca alkaloids are also effective cancer fighters. Vinblastine (VBL), vinorelbine (VRL), vincristine (VCR), and vindesine.

(VDS) are the four main vinca alkaloids in clinical use. In the United States, VCR, VBL, and VRL have been approved for use (Kufe et al., 2003). Vinflunine is a new synthetic vinca alkaloid that has been approved in Europe for the treatment of second line transitional cell carcinoma of the urothelium and is being developed for the treatment of other cancers (Bennouna et al., 2008; Schutz et al., 2011).

* Corresponding author: Stuti Bhatnagar
School of Biotechnology, IFTM University, Delhi Road (NH 24), 244102 Moradabad, Uttar Pradesh, India

2. Material and methods

The 3D structure of Tubulin alpha- beta dimer ((PDB Id: 1TUB) was obtained from protein database (https://www.rcsb.org/). The vinca alkaloids were obtained from Zinc database (https://zinc.docking.org/). Screenshots of PDB and Zinc database were shown in figure 1& 2, respectively.

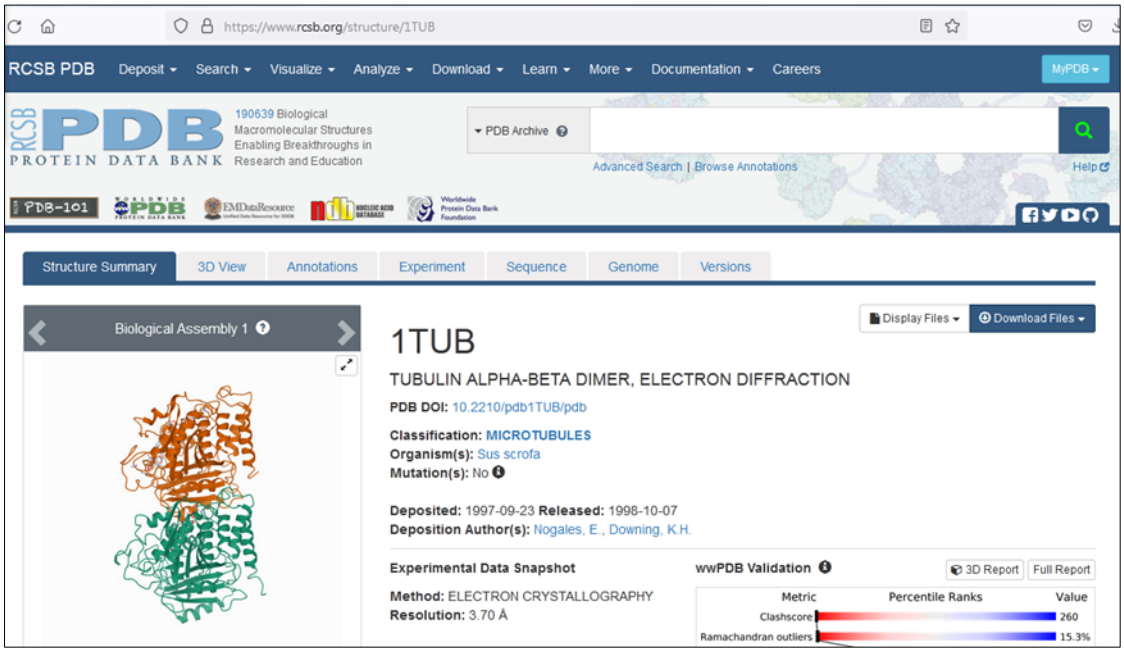

Figure 1 Screenshot of PDB database

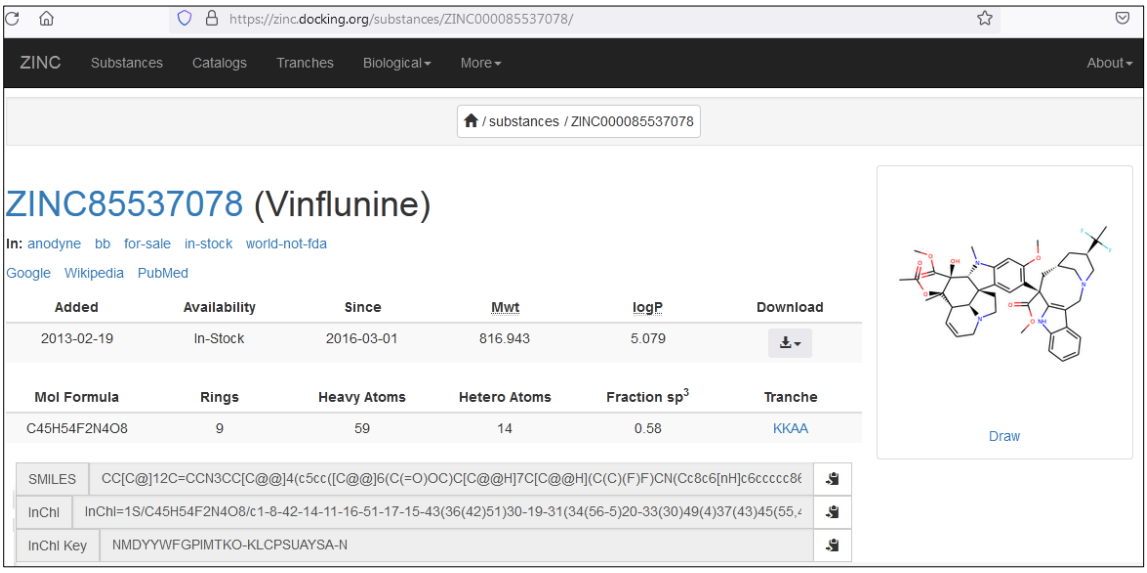

Figure 2 Screenshot of Swiss Dock server

Vinblastine (VLB) is an anticancer drug that was discovered in 1960 in the alkaloids of the Madagascar periwinkle (*Catharanthus roseus*) plant (Johnson et al., 1963). Because it binds to the tubulin heterodimer, it inhibits the polymerization of microtubules (MTs), preventing the formation of the mitotic spindle and, as a result, the cell proliferation process (Moudi et al., 2013; Li and Alisaraie, 2015). VLB is effective against many cancers, including renal cell carcinoma (Long et al., 2013), Hodgkin's lymphoma (Malik et al., 2016), and small cell cancers like lung, breast, and

colon cancer (Auyeung et al., 2014). The 2D structures of Vinblastine, Vinflunine, Vinorelbine, Vindesine, Vincristine and Catharanthine were shown in figure 3,4,5,6,7 & 8, respectively.

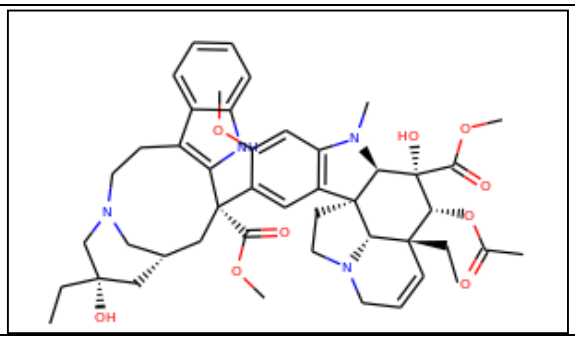

Figure 3 2D structure of Vinblastine (ZINC Id: 85432544)

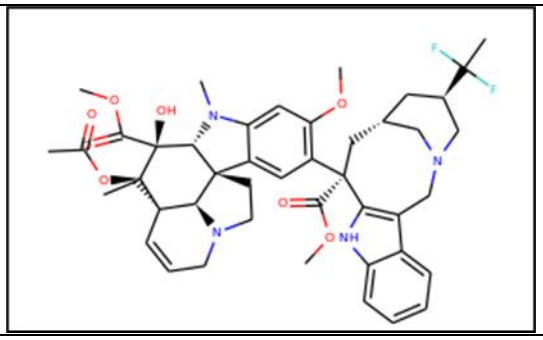

Figure 4 2D structure of Vinflunine (ZINC Id: 85537078)

Vinflunine (VFL) has been approved in Europe for second-line treatment of metastatic and advanced urothelial cancer after failure of platin-containing therapy (Gerullis et al., 2017).

It is considered a third-generation member of the vinca alkaloid family besides vincristine, vinblastine, vindesine and vinorelbine which all are antimitotic agents and are used in cancer therapy (Kruczynski et al. 1998). Vinorelbine (Navelbine) is a drug that is used to treat lung cancer (https://chemocare.com/chemotherapy/drug-info/vinorelbine.aspx).

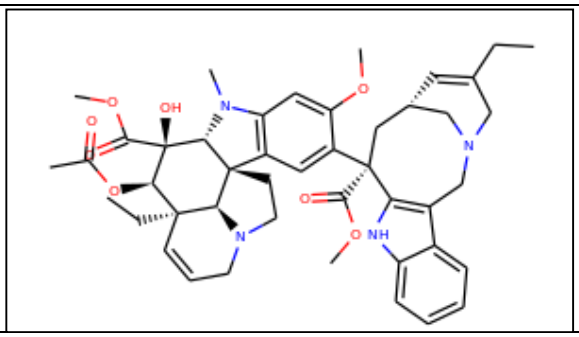

Figure 5 2D structure of Vinorelbine (ZINC Id:85536958)

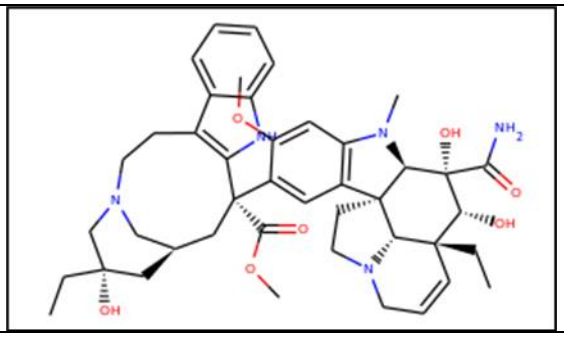

Figure 6 2D structure of Vindesine (ZINC Id:8214470)

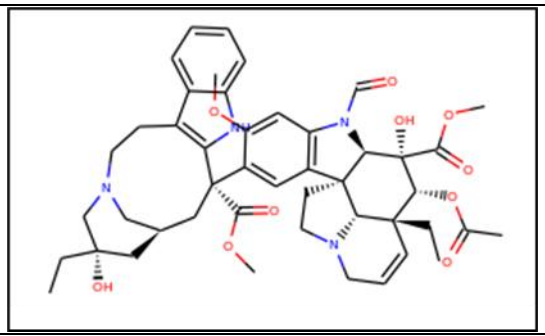

Figure 7 2D structure of Vincristine (ZINC Id: 85432549)

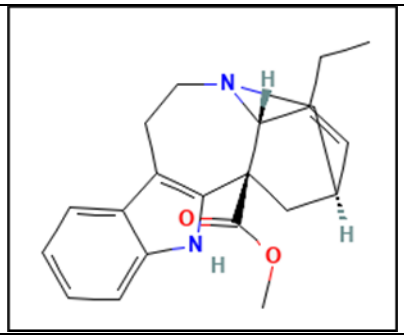

Figure 8 2D structure of Catharanthine (ZINC Id: 39336572)

Vindesine (Eldisine) is used to treat myelomas in leukaemia and diabetes (https://www.alleviareindia.com/buy-eldisine-vindesine/).

Vincristine is an oxidised form of vinblastine, which was first used as an anticancer drug in 1963. It is extremely rare in nature, but it can be synthesised in the laboratory from vinblastine to produce Leurocristine, which is marketed under the brand name ONCOVIN by Elli-Lilly & Company.

Catharanthine is an organic heteropentacyclic compound and monoterpenoid indole alkaloid produced by the medicinal plant *Catharanthus roseus* via strictosidine.

In recent years, protein-ligand docking has become a powerful tool for drug development. The final PDB file of Tubulin alpha-beta dimer (PDB Id: 1TUB) and alkaloids were directly fed into an online docking server, SwissDock (http://www.swissdock.ch/docking). SwissDock incorporates an automated in silico molecular docking procedure based on EADock DSS docking algorithm, which utilizes the CHARMM (Grosdidier et al., 2011). According to SwissDock, the minimum energy docked conformers are ranked in terms of their fullfitness score. The docked pose that has the least fullfitness score is used for further analysis. Input data screenshot of SwissDock server is shown in figure 9.

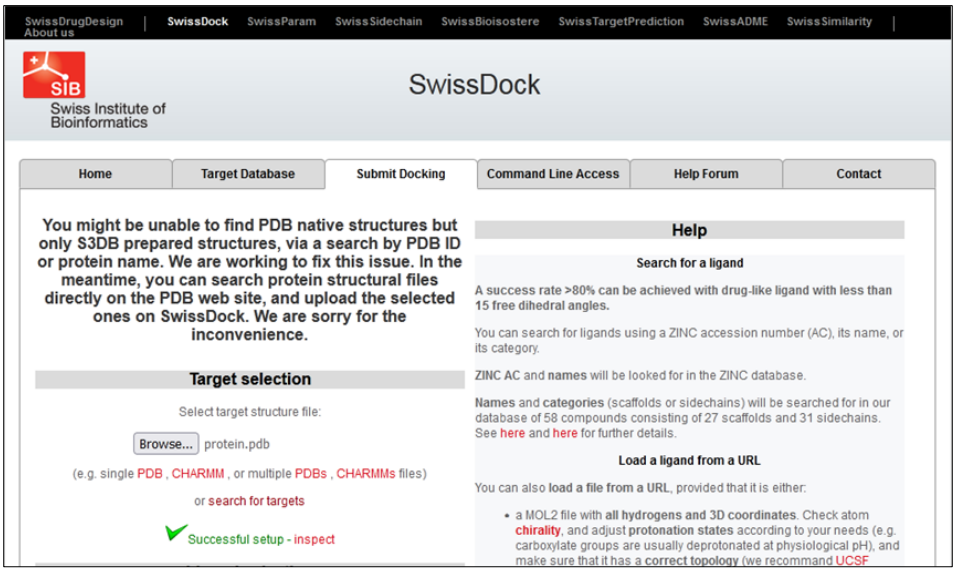

Figure 9 Input data screenshot of Swiss Dock server

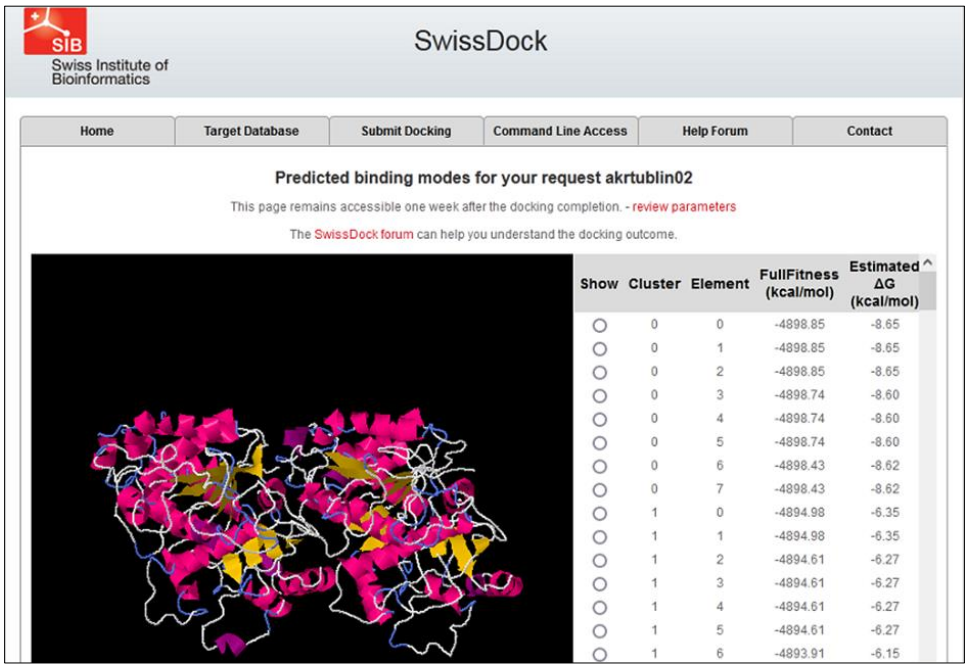

Figure 10 Output data screenshot of Swiss Dock server

3. Results and discussion

Vinca alkaloids were individually docked into the crystal structure of α/β-tubulin. Docked result in Swiss Dock server is shown in figure 10. The docking results were shown in table 1.

Docking results show that Vinblastine, Vinflunine and Vinorelbine have low estimated energy ΔG (-9.43, -9.44 & -9.29 kcal/mol respectively) compared to Vindesine, Vincristine and Catharanthine (-8.14, -7.45 &-7.11kcal/mol respectively). The docked complex of Vinblastine, Vinflunine, Vinorelbine, Vindesine, Vincristine and Catharanthine with alpha-beta tubulin were shown in figure 11,12,13,14,15,16 a & b, respectively.

Table 1 Interaction of Vinca alkaloids with α/β-tubulin dimer

Sl.No.	Compound Name	Full Fitness (kcal/mol)	Estimated ΔG (kcal/mol)
1	Vinblastine	-4816.45	-9.43
2	Vinflunine	-4877.15	-9.44
3	Vinorelbine	-4893.92	-9.29
4	Vindesine	-4832.04	-8.14
5	Vincristine	-4792.28	-7.45
6	Catharanthine	-4937.04	-7.11

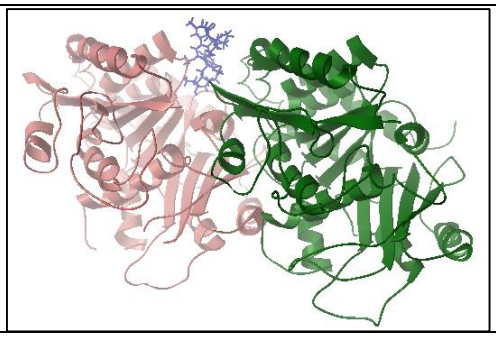

Figure 11a Docked complex of Vinblastine and α/β-tubulin dimer. Structure of alpha and beta-tubulin are coloured by green and maroon, respectively.

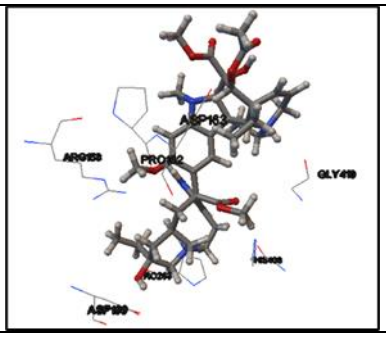

Figure 11b Binding interactions of Vinblastine docked into α/β-tubulin dimer. Interacting amino acids with alkaloid are represented by wireframe model. Vinblastine is shown in sticks with and balls model and colour by atom type.

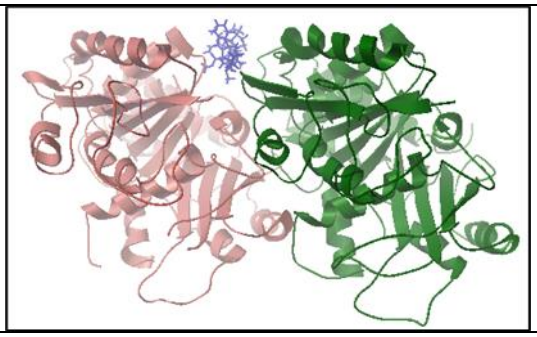

Figure 12a Docked complex of Vinflunine and α/β-tubulin dimer. Structure of alpha and beta-tubulin are coloured by green and maroon, respectively.

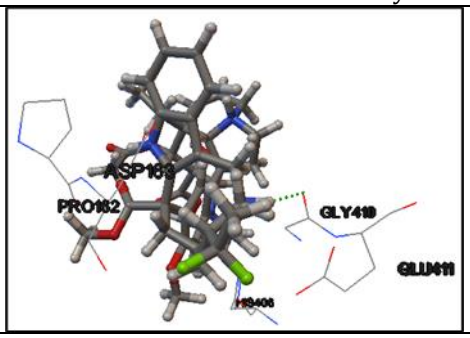

Figure 12b Binding interactions of Vinflunine docked into α/β-tubulin dimer. Vinflunine is shown in sticks and balls model and color by atom type. Interacting amino acids with alkaloid are represented by wireframe model. Vinflunine is display as dotted spheres line.

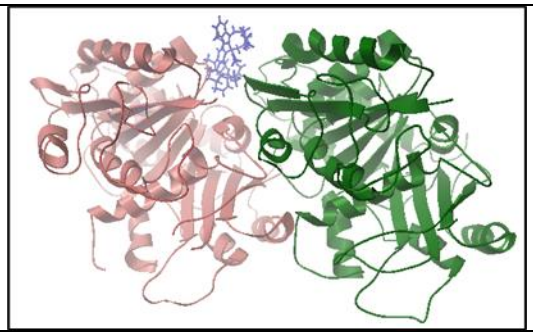

Figure 13a Docked complex of Vinorelbine and α/β-tubulin dimer. Structure of alpha and beta-tubulin are coloured by green and maroon, respectively.

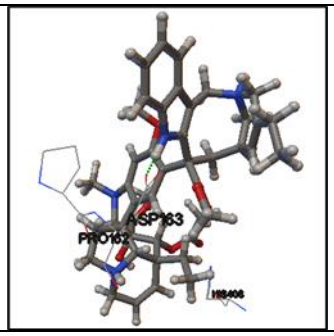

Figure 13b Binding interactions of Vinorelbine docked into α/β-tubulin dimer. Vindesine is shown in sticks and balls model and colour by atom type. Interacting amino acids with alkaloid are represented by wireframe model. Vinorelbine is display as dotted spheres line.

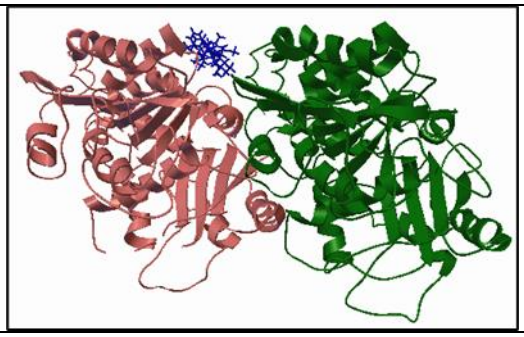

Figure 14a Docked complex of Vindesine and α/β-tubulin dimer. Structure of alpha and beta-tubulin are coloured by green and maroon, respectively.

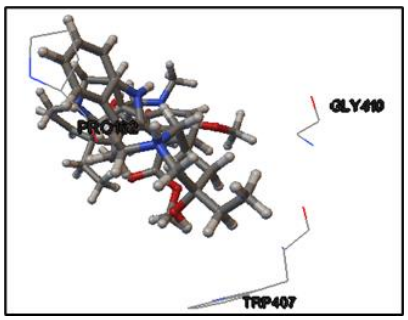

Figure 14b Binding interactions of Vindesine docked into α/β-tubulin dimer. Vindesine is shown in sticks and balls model and colour by atom type. Interacting amino acids with alkaloid are represented by wireframe model.

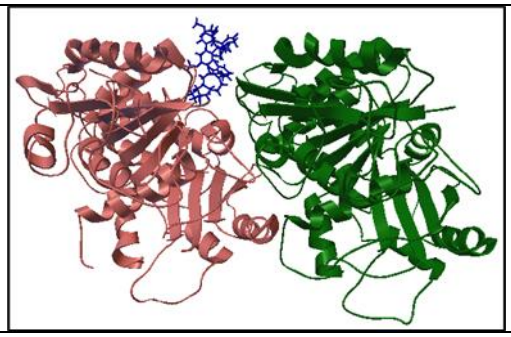

Figure 15a Docked complex of Vincristine and α/β-tubulin dimer. Structure of alpha and beta-tubulin are coloured by green and maroon, respectively.

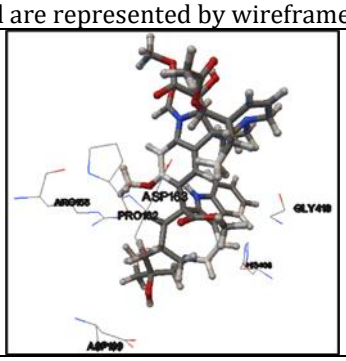

Figure 15b Binding interactions of Vincristine docked into α/β-tubulin dimer. Vincristine is shown in sticks and balls model and colour by atom type. Interacting amino acids with alkaloid are represented by wireframe model.

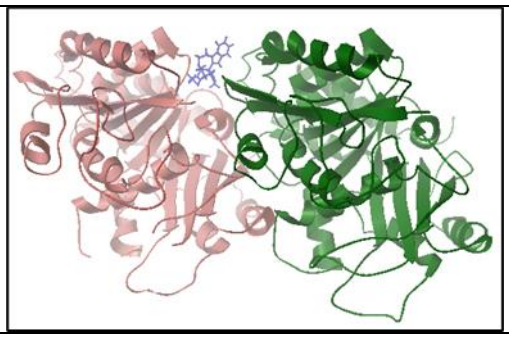

Figure 16a Docked complex of Catharanthine and α/β-tubulin dimer. Structure of alpha and beta-

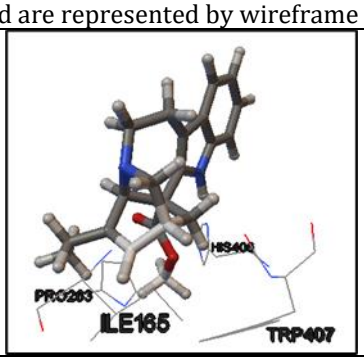

Figure 16b Binding interactions of Catharanthine docked into α/β-tubulin dimer. Catharanthine is shown in sticks and

tubulin are coloured by green and maroon, respectively.	balls model and colour by atom type. Interacting amino acids with alkaloid are represented by wireframe model.

The primary mechanisms of vinca alkaloids cytotoxicity are interactions with tubulin and disruption of microtubule function, particularly of microtubules comprising the mitotic spindle apparatus, resulting in metaphase arrest (Himes, 1991). They can, however, perform a variety of other biochemical activities that may or may not be related to their effects on microtubules. Many of the effects that do not involve microtubule disruption occur only after cells are treated with clinically insignificant doses of vinca alkaloids. Nonetheless, because microtubules are involved in many nonmitotic functions, vinca alkaloids and other antimicrotubular agents have an effect on both non-malignant and malignant cells in the nonmitotic cell cycle (Kufe et al., 2003).

4. Conclusion

Vinca alkaloids are commonly used in combination chemotherapy regimens for medicinal treatments. They do not interact with drugs that alkylate DNA and have a different mechanism of action. They have been used to treat diabetes, high blood pressure, as disinfectants, and as anti-cancer agents. The vinca alkaloids have cytotoxic properties that can halt cell division and cause cell death.

Compliance with ethical standards

Acknowledgments

We would like to thank the IFTM university first where all the experiments and research were conducted. I would like to thank Dr Rashi and Dr Rajesh for guiding me in every step of this research to achieve the desired result. Last but not the least I would like to thank every participant who were involved and supported me in this research.

Disclosure of conflict of interest

The authors declare no conflict of interest in this study.

References

[1] Johnson, I. S.; Armstrong, J. G.; Gorman, M.; Burnett, J. P., Jr. The Vinca Alkaloids: A New Class of Oncolytic Agents. Cancer Res. 1963,23, 1390−1427.

[2] Kufe DW, Pollock RE, Weichselbaum RR, Bast RC, Gansler TS, Holland JF, et al. Holland-Frei cancer medicine. 6th ed. Hamilton (ON): BC Decker Inc.; 2003.

[3] Bennouna J, Delord JP, Campone M, Nguyen L. Vinflunine: A new microtubule inhibitor agent. Clin Cancer Res 2008; 14:1625-32.

[4] Schutz FA, Bellmunt J, Rosenberg JE, Choueiri TK.Vinflunine: Drug safety evaluation of this novel synthetic vinca alkaloid. Expert Opin Drug Saf 2011; 10:645-53.

[5] Himes RH. Interactions of the Catharanthus (Vinca) alkaloids with tubulin and microtubules. Pharmacol Ther 1991; 51:257-67.

[6] Moudi, M.; Go, R.; Yien, C. Y.; Nazre, M. Vinca alkaloids. Int. J. Prev. Med. 2013, 4, 1231−1235.

[7] Li, Z.; Alisaraie, L. Microtubules dual chemo and thermo-responsive depolymerization. Proteins 2015, 83, 970−981.

[8] Long, Q.-Z.; Zhou, M.; Liu, X.-G.; Du, Y.-F.; Fan, J.-H.; Li, X.; He, D.-L. Interaction of CCN1 with αvβ3 integrin induces P-glycoprotein and confers vinblastine resistance in renal cell carcinoma cells. Anticancer Drugs 2013, 24, 810−817.

[9] Malik, M. Z.; Ahmad, M.; Muahammad, S.; Aamir, M. N. Pharmacokinetic evaluation of anticancer drugs in Hodgkin's lymphoma patients after their simultaneous administration. Pak. J. Pharm. Sci. 2016, 29, 2079−2082.

[10] Auyeung, K. K. W.; Law, P. C.; Ko, J. K. S. Combined therapeutic effects of vinblastine and Astragalus saponins in human colon cancer cells and tumor xenograft via inhibition of tumor growth and proangiogenic factors. Nutr. Cancer 2014, 66, 662−674.

[11] Grosdidier A, Zoete V, Michielin O (2007) EADock: docking of small molecules into protein active sites with a multiobjective evolutionary optimization. Proteins Struct Funct Bioinforma 67:1010–1025.

[12] Kruczynski, A., Barret, J., Etievant, C., Colpaert, F.,Fahy, J. and Hill, B. (1998) Antimitotic and tubulin-interacting properties of vinflunine, a novel fluorinated Vinca alkaloid. Biochem Pharmacol 55: 635–648.

[13] Gerullis H, Wawroschek F, Köhne CH, Ecke TH. Vinflunine in the treatment of advanced urothelial cancer: clinical evidence and experience. Ther Adv Urol. 2017;9(1):28-35