ScienSage

Journal of Advanced Scientific Research

Available online through http://www.sciensage.info

ISSN
0976-9595
Research Article

PHARMACOKINETICS ACTIVITY AND INTERACTION OF VINBLASTIN AND VINCRISTINE COMPOUNDS OF *CATHARANTHUS ROSEUS* INVOLVED IN TIA BIOSYNTHEISIS

Renu[1], Mukesh Kumar Sharma*[1,2]

[1]*Department of Biotechnology, Maharaj Vinayak Global University, Jaipur, Rajasthan, India*

[2]*Department of Botany, Vishwa Bharti PG College, Sikar, Rajasthan, India*

**Corresponding author: mukeshsharma.dt@gmail.com*

ABSTRACT

Catharanthus roseus is a rich source of monoterpenoid indole alkaloids (MIA). These secondary metabolites are known for their actions against cancer, but the concentration of these when extracted is not very significant for medical use. Vinblastine and Vincristine are dimeric alkaloids screen from the Madagaskar periwinkle plant (*Catharantus roseus*), exhibit significant pharmacological activity and are used in the TIA biosynthesis. Lipinski's rule and ADMET toxicity profiling were carried out on the phytoconstituents of the *Catharantus roseus*, and the compounds were further promoted for network interaction study. It is observed that both the compounds passed the Lipinski rule of five with no violation and were selected for ADMET prediction. The STITCH method was used to analyse interaction between Vinblastine and vincristine and its interaction with tubulin protein, STITCH for analysing protein interaction the network between compounds and predicted functional nine proteins that interacted with Vinblastine and Vincristine compound through the STITCH database.

Keywords: STITCH, Biosynthesis, ADMET, Vinblastine, Vincristine.

1. INTRODUCTION

Online services and computational packages are heavily being used nowadays for the characterization of proteins. Various structural and physicochemical properties of proteins can be better exploited by using computational tools. For the purpose of protein structure prediction and identification, plenty of tools are available on World Wide Web which can either be used online or as standalone service. The basic primary sequence analysis of protein can yield information about sequence length, contribution of individual residues along with physicochemical properties of protein like atomic composition, molecular weight, extinction coefficient, theoretical isoelectric point (pI), estimated half-life, instability index and many more parameters. A molecule's functional, chemical and physical properties can solely be determined and characterized using amino acid sequence information. Although precise and accurate structure of proteins can be guaranteed by experimental methods yet they have the disadvantage of being expensive, time consuming and large amount of purified protein is required for this purpose. Computational methods are an excellent and cost-effective alternative, in this context. Despite of the fact that they are not as much reliable as experimental ones, still they can provide us nearly exact structure of proteins besides the deep understanding of structure-function relationship of protein at almost no cost.

Catharanthus roseus is a rich source of such monoterpenoid indole alkaloids (MIA). These secondary metabolites are known for their actions against cancer, but the concentration of these when extracted is not very significant for medical use. So, the knowledge about the biosynthesis of the alkaloids may be used for their artificial synthesis [1]. Vinblastine and vincristine are condensed from two MIA moieties, catharanthine and vindoline. Dimeric bis-indole alkaloids are formed by condensation of catharanthine and vindoline to form 3′,4′-anhydrovinblastine by the peroxidase enzyme α-3′,4′- anhydrovinblastine synthase (PRX1) [2] further leading to vinblastine and ultimately to vincristine [3]. The complicated structure of these metabolites makes the total chemical synthesis difficult and costly. Hence, in depth understanding of the biosynthesis of catharanthine and vindoline will be helpful for high yield commercial production of these crucial metabolites.

The vindoline biosynthesis pathway is a six-step pathway in which tabersonine is converted into the final product vindoline. The reaction sequence from tabersonine to vindoline is well established, the enzymes involved in the catalysis of the different steps have been identified and the respective amino acid sequences of all the enzymes are determined.

2. MATERIAL AND METHODS

2.1. Material

Vinblastine and Vincristine compound was retrieved from PubChem. PubChem [4, 5] (http://pubchem.ncbi.nlm.nih.gov) is a public repository of chemical structures and associated biological activities. It was launched as part of the Molecular Libraries Roadmap [6] from the National Institutes of Health (NIH), which aims to increase the discovery and use of chemical probes through high-throughput screening of small molecules [6, 7]. It is composed of three interconnected databases. The compound database contains unique chemical structures. The substance database contains batch/sample level descriptions of these chemical structures. The compounds used in the study of Vinblastine and Vincristine SMILE structure downloaded in this program with accession number CID: 13342 (vinblastine) and 5978 (Vincristine).

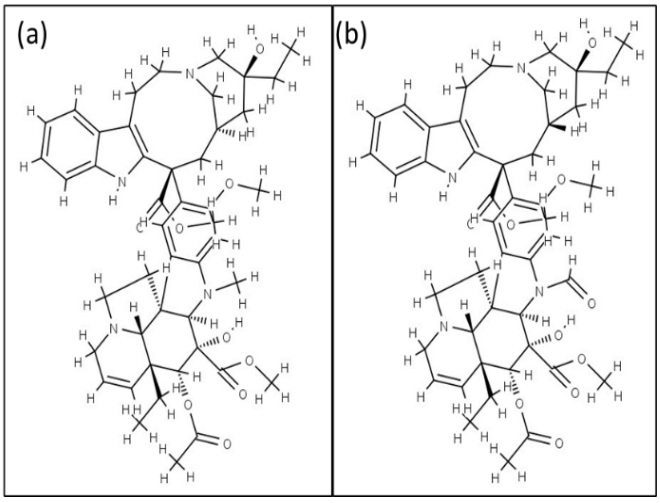

Fig. 1: 2D chemical structure of (a) Vinblastin (PubChem id: CID 13342) (b) Vincristin (PubChem id: CID 5978)

2.2. Protein compound interaction

STITCH was used to investigate the interaction of Vinblastine and Vincristine with proteins. The STITCH is a library of protein-compound interactions that combines observational and manually curated data with document information and interaction predictions from a variety of sources. The resulting interaction network, which may be found at http://stitch.embl.de, contains 390.000 compounds and 3.6 million enzymes from 1.133 species [8].

2.3. Drug-likeliness properties of the compounds

In the present examination and computer-aided methodologies in discovery to improve and estimate bioavailability of leading compounds and membrane penetrability 'the Lipinski lead of 5' is tested. It calculates the absorption of compound relying on their, log P (segment coefficient), molecular weight (MW), or the distribution of acceptor and donor hydrogen-bonds particles. These molecular properties were utilized in detailing "lead of five" [9]. Lipinski 's run expresses that particles with great membrane penetrability have MW ≤ 500, hydrogen bond donor's ≤ 5 and acceptors ≤ 10. Medication likeliness was investigated utilizing the molinspiration software online tool (http://www.molinspiration.com).

2.4. ADME profiling of the compounds

Vinblastine and vincristine constituent fulfilling the Lipinski's standard of five were further, chosen for expectation of the pharmacokinetics properties like absorption, distribution, metabolism, excretion and toxicology (ADMET) utilizing Pre Admet online server (http://preadmet.bmdrc.org). This point of view is to calculate different properties like Human Intestinal Absorption (% HIA), Caco-2 permeability, MDCK cell permeability, skin permeability, blood brain barrier penetration, carcinogenicity etc.

3. RESULTS AND DISCUSSION

Interact results from STICTH obtained show that Vinblastin and Vincristin can interact with nine different proteins, they are TUA5, TUB1, TUB3, TUB4, TUB5, TUB6, TUB7, TUB8, TUB9 are shown in table 1. Evidence for specific actions from tubelin protein and Vinblastin and Vincristin interaction are activation and expression which indicated by yellow and gray line. As for evidence for specific actions from TUB2 protein and Vinblastin and Vincristininteraction are activation which indicated by gray line while the other protein has evidence for specific actions as catalyst which indicated by purple line (Fig 2).

Table 1: Predicted Functional protein bind with Vinblastin and Vincristin

Node	Protein	Function	SCORE
	TUB2	tubulin beta chain 2; Tubulin is the major constituent of microtubules. It binds two moles of GTP, one at an exchangeable site on the beta chain and one at a non-exchangeable site on the alpha chain (450 aa)	0.733
	TUB4	tubulin beta chain 4; Tubulin is the major constituent of microtubules. It binds two moles of GTP, one at an exchangeable site on the beta chain and one at a non-exchangeable site on the alpha chain (444 aa)	0.733
	TUB8	tubulin beta 8; Tubulin is the major constituent of microtubules. It binds two moles of GTP, one at an exchangeable site on the beta chain and one at a non-exchangeable site on the alpha chain (449 aa)	0.733
	TUB6	beta-6 tubulin; Tubulin is the major constituent of microtubules. It binds two moles of GTP, one at an exchangeable site on the beta chain and one at a non-exchangeable site on the alpha chain (By similarity) (449 aa)	0.733
	TUB9	tubulin beta-9 chain; Tubulin is the major constituent of microtubules. It binds two moles of GTP, one at an exchangeable site on the beta chain and one at a non-exchangeable site on the alpha chain (By similarity) (444 aa)	0.733
	TUB7	tubulin beta; Tubulin is the major constituent of microtubules. It binds two moles of GTP, one at an exchangeable site on the beta chain and one at a non-exchangeable site on the alpha chain (449 aa)	0.733
	TUB1	tubulin beta; Tubulin is the major constituent of microtubules. It binds two moles of GTP, one at an exchangeable site on the beta chain and one at a non-exchangeable site on the alpha chain (447 aa)	0.733
	TUB5	tubulin beta-5 chain; Tubulin is the major constituent of microtubules. It binds two moles of GTP, one at an exchangeable site on the beta chain and one at a non-exchangeable site on the alpha chain (449 aa)	0.733
	TUB3	tubulin beta chain 3; Tubulin is the major constituent of microtubules. It binds two moles of GTP, one at an exchangeable site on the beta chain and one at a non-exchangeable site on the alpha chain (450 aa)	0.733

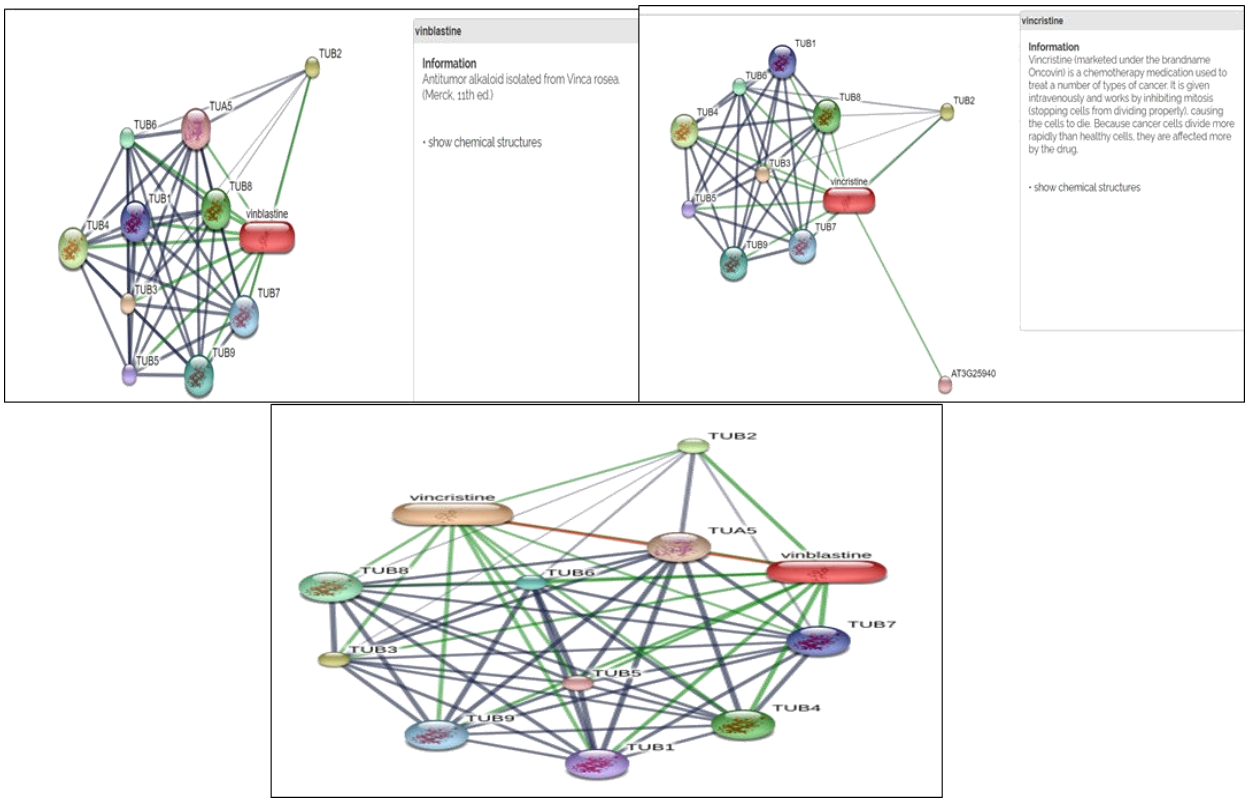

Fig. 2: Interactions of Vinblastin and Vincristin can interact with nine different proteins (TUA5, TUB1, TUB3, TUB4, TUB5, TUB6, TUB7, TUB8, TUB9)

3.1. Drug-likeliness prediction

The likening of the drug is to identify from biological compounds libraries is generally favored in the field of computer-aided drug design. The most prominent procedure of drug-likeliness channel is the Lipinski's standard of 5. In the violation that the selected is 1 or 0, it contains that compound proficiently binds to the receptor. If the number of violations exceeded than 2, the rejection of the selected compound are shown in Table 2. From the compounds, Vinblastine and vincristine passed the Lipinski rule of five with no violation and were selected for ADMET prediction [10].

3.2. ADMET prediction of compounds

Vinblastine and vincristine were additionally examined for their pharmacokinetics properties such as metabolism of the drug and potential toxic effect of the drug. For this, the nature of combinatorial chemistry of the drug and high throughput ADME screens were utilized. The prediction ADMET parameter of Vinblastine and vincristine was finished by online available tool PreADMET (preadmet.bmdrc.org). The Vinblastine and vincristine fulfilled the ADMET filters and were chosen for further analysis in future experiment (Table 4).

Table 2: *In silico* determination of physicochemical pharmacokinetics for Vinblastine and Vincristine by using online server Molinspiration

S. No.	Compound	miLogP	Molecular weight	Hydrogen bond donor	Hydrogen bond acceptors
1.	Vinblastine	5.56	810.99	3	13
2.	Vincristine	4.95	824.97	3	14

Table 3: Bioactivity of the Vinblastine and vincristine

Bioactivity parameter	Vinblastin	Vincristine
GPCR ligand	-1.76	-2.00
Ion channel modulator	-2.97	-3.13
Kinase inhibitor	-2.99	-3.17
Nuclear receptor ligand	-2.75	-2.94
Protease inhibitor	-1.53	-1.68
Enzyme inhibitor	-2.42	-2.55

Table 4: ADMET profiling of compounds of Vinblastine and vincristine

Compound	BBB	$CaCO_2$	HIA	PPB	MDCK	SP	TOXICITY		
							M	C	
								M	R
Vinblastine	1.49973	22.2815	100	-1	204.401	-1.86648	non-mutagen	-	+
Vincristine	13.47	23.63	100	100	57.06	-0.72	Non mutagen	-	+

4. CONCLUSION

Vinblastine and vincristine have the ability to interact with nine different proteins (TUA5, TUB1, TUB3, TUB4, TUB5, TUB6, TUB7, TUB8, TUB9). Vinblastine and Vincristine are essential for cell organisation and microtubule-based processes that bind to the tubelin protein. Vinblastine and vincristine interact, resulting in protein polymerization across the cytoplasmic membrane.

Conflict of interest

None declared

5. REFERENCES

1. Almagro L, Fernández-Pérez F, Pedreño MA. *Molecules*, 2015; **20(2)**:2973-3000.
2. Ahmad B, Banerjee A, Tiwari H, Jana S, Bose S, Chakrabarti S. *J. Mol. Model*, 2018; **24(3)**:1-4.
3. Pan Q, Mustafa NR, Tang K, Choi YH, Verpoorte R. *Phytochem. Rev*, 2016; **15(2)**:221-250.
4. Narayanaswamy R, Wai L K, Ismail IS. *J Chem Pharm Res*, 2017; **9**:39-44.
5. Ursu O, Rayan A, Goldblum A, Oprea TI. *Wiley Interdiscip. Rev. Comput. Mol. Sci*, 2011; **1(5)**:760-781.
6. Bolton EE, Wang Y, Thiessen PA, Bryant SH. *Annu. Rep. Comput. Chem*, 2008; **1(4)**:217-241.
7. Wang Y, Xiao J, Suzek TO, Zhang J, Wang J, Bryant SH. *Nucleic acids research*, 2009; **37(2):**W623-633.
8. Zerhouni E. The NIH roadmap.
9. Zerhouni EA. *J. Investig. Med*, 2006; **54(4)**:171-173.
10. Kuhn M, Szklarczyk D, Pletscher-Frankild S, Blicher TH, Von Mering C, Jensen LJ, Bork P. *Nucleic Acids Res*, 2014; **42(D1)**:D401-407.