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In-silico Molecular Docking Evaluation of Plumbagine Derivatives for Anticancer Activity

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Abstract

Plumbagin or 5-hydroxy-2-methyl-1,4-naphthoquinone is an organic compound with the chemical formula C_{11} H_8 O_3. It is regarded as a toxin and it is genotoxic and Anti mutagenic. Natural plimbagin and its derivatives have been extensively investigate as cardioprotective, potent antioxidant, anti-inflammatory, and anticancer agents. Starting from its potent chemotherapeutic activity against a wide variety of cancers, the plumbagin scaffold has been subject to synthetic manipulations with the aim of obtaining new analogues with improved anticancer activity and better bioavailability. Insilico approaches have been applied to search the drug likeness properties of the lead compounds, pharmacokinetic evaluation, toxicity evaluation and the potential interaction between the potential target and the molecule obtained from natural product or obtained by synthesis.

Keywords-Plumbagin derivatives, Anticancer, Insilico evaluation, Molecular docking

INTRODUCTION

Cancer prevention is currently one of the most widely researched areas. Because there are many mechanisms involved in the pathophysiology of cancer, different approaches are necessary. Decisive advances in cellular and molecular biology have led to the improvement of chemotherapeutic management of cancer. Plumbagin is a yellow dye, formally derived from naphthoquinone. It is named after the plant genus Plumbago, from which it was originally isolated. It is also commonly found in the carnivorous plant genera Drosera and Nepenthes. It is also a component of the black walnut drupe.

Chemically plumbagine is a naphthoquinone derivatives. Plumgagine have a hydroxyl group on the 5th position, which have the ability to triggers autophagy via inhibition of the Akt/mTOR pathway and which induces G2/M cell cycle arrest and apoptosis in A549 cells through JNK-dependent p53 Ser15 phosphorylation. When the m-TOR inhibition is occurs the cell division is arrested as which will leads to prevention of rapid cell growth inside the body [1].

In the docking studies the PARP macromolecule is used. Poly (ADP-ribose) polymerase (PARP) is a family of proteins involved in a number of cellular processes such as DNA repair, genomic stability, and programmed cell death. It composed of four domains of interest, a DNA-binding domain, a caspase-cleaved domain, an auto-modification domain, and a catalytic domain. The DNA-binding domain is composed of two zinc finger motifs. In the presence of damaged DNA, the DNA-binding domain will bind the DNA and induce a conformational shift. It has been shown that this binding occurs independent of the other domains. This is integral in a programmed cell death model based on caspase cleavage inhibition of PARP. The auto-modification domain is responsible for releasing the protein from the DNA after catalysis. Also, it plays an integral role in cleavage-induced inactivation. Protein objective were downloaded from database Protein Data Bank (PDB). 2LEO is the PDB id of the target protein. All water molecules were detached and hydrogen atoms were added to receptor molecule. Hence, the present study was at evaluating the anticancer activity of Plumbagine using insilico tools. [2, 3, 4].

MATERIALS AND METHODS

Docking studies of Plumbagin derivatives of selected macromolecules were performed using Autodock vina pyrx virtual screening tool, against the selected cancer macromolecules, where alteration of expression of each macromolecule corresponds to a different anticancer mechanism[4].

❖ Data source - Ligand

The 3D structure of ligand or drug like compound was retrieve from Pubchem. It contains the chemical structure of small organic molecules and information on their biological activities.

❖ Data source – Protein

Proteins are the large biomolecules or macromolecule consists of one or more long chain residues of amino acids. The 3D structure of the protein can be retrieved from the database named Protein Data Bank (PDB).

❖ Format conversion of ligand

Openbabel- 2.3.2/obgui.exe was used to convert SDF 3D structure of ligand in to PDB format.

Protein preparation and molecular visualization

PyMOL is open source software, which used for the target preparation as well as for the visualization of small molecules. PyMOL can produce high quality 3D image of small molecules and biological macromolecules such as proteins.

❖ Molecular docking

Virtual screening is a computational techniques used in drug discovery to search libraries of small molecules in order to identify those structures which are most likely to bind to drug target, typically a protein receptor or enzyme. Autodock vina Pyrx virtual screening tool was used to perform the molecular docking.

Table 1.1 Molecular descriptors

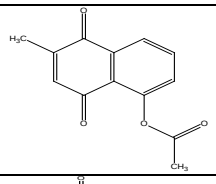
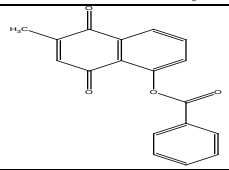
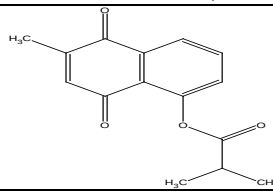
NAME	COMPOUND	MOLECULAR WEIGHT	LOG P	NUMBER OF HYDROGEN BOND ACCEPTORS	NUMBER OF HYDROGEN BOND DONORS
A		**250.22**	**1.55**	**4**	**16**
B		**292.29**	**3.86**	**4**	**13**
C		**258.27**	**2.56**	**4**	**16**

Table II Docking details

PARAMETERS	COMPOUND A	COMPOUND B	COMPOUND C
RESIDUAL NAME	ALANINE VALINE SERINE LUCINE ALANINE	TRIPTOPHAN SERINE LYSINE CYSTEIN ALANINE ASPARGINR LYSINE	VALINE LYSINE LYSINE LYSINE
RESIDUAL IDENTIFIER	A V S L A	W S L C A V L	V L L L
MEASUREMENT OF HYDROGEN BOND (highest)	24271.928 A *	1802 A* 1894 A*	1950 A*
GLIDE SCORE	13.4kcl/mol	12.8kcl/mol	9.5kcl/mol

RESULTS AND DISCUSSION

Four different substituted derivatives of plumbagin derivates are evaluated by using ADMET SAR software, their obeying tendency of towards the lipinsky rule was also evaluated. All compounds obey the lipinsky rule, they have the molecular weight less than 500 Dalton.The Log P value lies between -5 to 5, Number of hydrogen bond acceptor is less than 5 and Number of hydrogen bond donor is greater than 10. This details are summarized in table I

In the present study, Plumbagin derivatives were evaluated through molecular docking studies using insilico analysis. Initially, the structures of these molecules were generated. PARP inhibitors are strongly recommended for cancer treatment. PARP are necessary for the cell cycle. Docking studies against PARP revealed that all Plumbagin form H-bonds with PARP.

Three different derivatives of the plumbagin was used for the docking studies, they are named as compound A, compound B, compound C. Compound A have five hydrogen bond interaction with two Alanine, one Valine, one Srerine, one Lucine. Which also possess greatest hydrogen bond interaction around 24271.928 A *. Molecular docking details are summarized in table II, Docking images were shown in figure I, II, III.

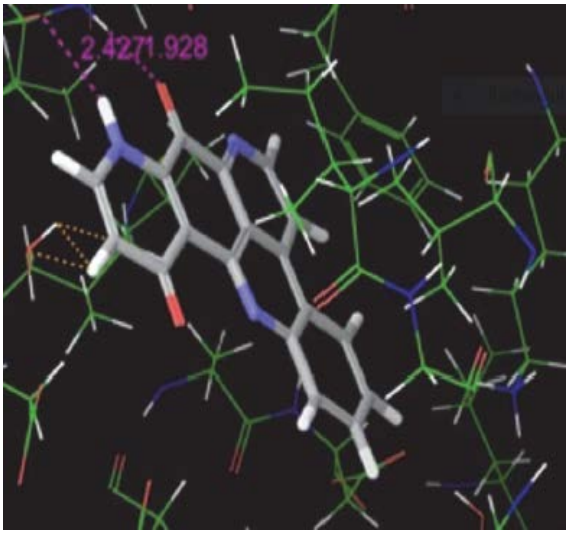


Figure I Doking of compound A

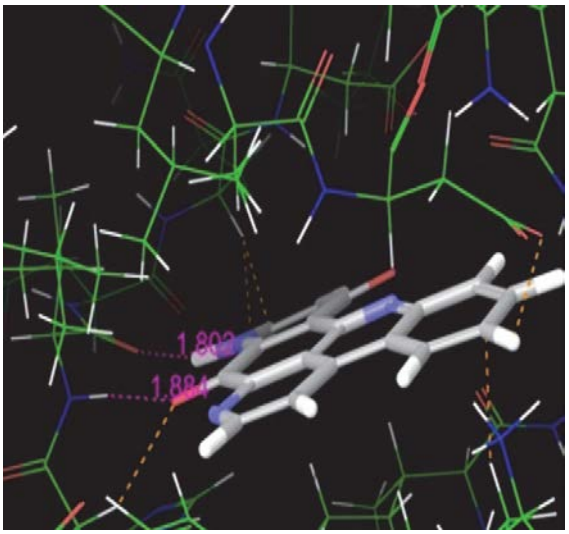


Figure II Docking of compound B

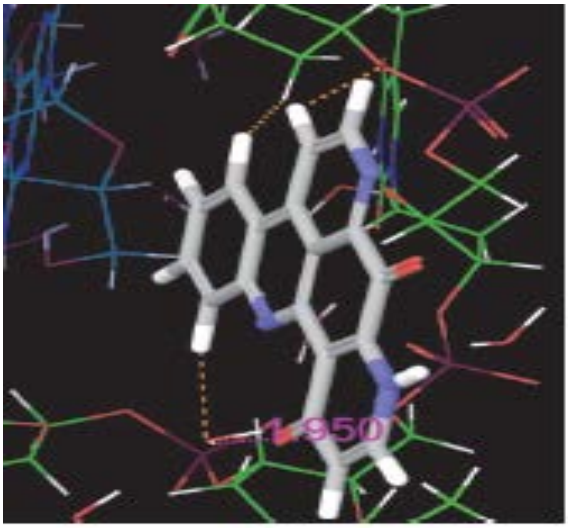


Figure III Docking of compound C

CONCLUSION

From the docking result the compound B have more hydrogen bond interaction with the target molecule, which is bind with triptophan, serine, lysine, cystein, alanine, asparginr, lysine also possess high strength towards the amino acid sequences.

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