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Research Article

In silico Evaluation of Solanine Compound as New Potential Inhibitors of Cancer Causing Enzymes

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Abstract

Explore the interaction mode and binding orientation of lead compound with target proteins by molecular docking studies and understand the structural insights and functional properties of potent target protein by autodock tools. Aim of this study to analyze the interaction of Solanine with cancer causing enzymes. Cyclin-dependent kinase 6, Cytochrome P450, Topoisomerase I, Topo IIa ATPase, anti-apoptotic protein Bcl-2 and Vegfr2 are critical molecules that control cell cycle progression from one phase to the other. However, mutational changes in these molecules lead to the purturbed cell cycle leading to uncontrolled cellular proliferation or cell death. Docking pose is almost close to the substrates for most of the receptors. Remarkably 1t8i - Topoisomerase I and 1zxm - TopoIIa ATPase docking was completely blocking the binding of the substrate with high affinity by the action of Solanine. The molecular docking was applied to explore the binding mechanism and to correlate its docking score with the activity of plant derived compounds.

Keywords: Solanine; Auotdock; Topoisomerase; Molecular Docking; Cell Cycle

Abbreviations

CDK2: Cyclin-Dependent Kinase 2; ADT: AutoDockTools.

Introduction

Solanine is a glycoalkaloid found in species of the nightshade family (Solanaceae) such as the potato as well in tomato. It can occur naturally in any part of the plant, including the leaves, fruit and tubers. [1] reported the glycoalkaloid content in potato tubers and α solanine and α-chaconine content varied between differen types of potatoes which glycoalkaloid content data was also characterized by a wide range of values. Solanine has fungicidal and pesticidal properties, and it is one of the plant's natural defenses.

Molecular docking is a key tool in structural molecular biology and computer assisted drug design. Computer-aided docking is an important tool for gaining understanding of the binding interactions between a ligand (small molecule) and its target receptor (enzyme) (Schneider, 2010). Various growth factors that regulate angiogenesis are vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), fibroblast growth factor (FGF) and interferon. Among, VEGF is the most prominent inducer of angiogenesis. Which play key roles in migration, proliferation of endothelia cells and leads to formation of capillary structure. They have binding effect to its receptors on the endothelial cells, activate the downstream signaling pathway finally leading to tumor vascularization [10,11].

Materials and Methods

Sequence retrieval

Many bioinformatics processes require a sequence as input. Retrieval of sequence is an important step in any bioinformatics analysis. Each and every sequence has its own unique accession number in any database. Sequence can be retrieved either by querying with keywords or by the accession number.

Ligand preparation

Structure of alpha solanine has been downloaded from Pubchem database with IDS (CID 262500). The 2D structure obtained had been converted to 3D structure using Molconvert module from ChemAxon with low energy conformer. Ligand had been further prepared for docking study using Prepare_ligand4.py module from AutoDockTools(ADT) to add gasteiger charges and repairs bonds and add hydrogens. The prepared Ligand had been written in PDBQT format to use in Docking.

Receptor preparation

Three dimensional structure of following proteins listed below,

- Cyclin-Dependent Kinase 2 (CDK2)
- Cytochrome P450
- Topoisomerase I
- Cyclin-dependent kinase 6
- Topo IIa ATPase
- Anti-apoptotic protein Bcl-2
- Vegfr2.

With corresponding PDB IDS (1di8, 1dt6, 1t8i, 1xo2, 1zxm, 2o2f, 2oh4) had been downloaded from Protein data bank database. These receptors had been cleaned by removing the non standard amino acids, water molecules and hetero atoms including any co-crystalized small molecules. Receptors had been further prepared for docking study using Prepare_receptor4.py module from AutoDockTools(ADT) to add gasteiger charges, add hydrogens and the output is stored in PDBQT format.

Tools used for *in silico* analysis

AutoDock vina

AutoDock Vina is an open-source program for doing molecular docking. It was designed and implemented by Dr. Oleg Trott in the Molecular Graphics Lab at The Scripps Research Institute. AutoDock Vina significantly improves the average accuracy of the binding mode predictions compared to AutoDock 4. AutoDock Vina is released under a very permissive Apache license, with few restrictions on commercial or non-commercial use, or on the derivative works.

AutoDock tools

AutoDock Tools is graphical front-end for setting up and running AutoDockVina- an automated docking software designed to predict how small molecules, such as substrates or drug candidates, bind to a receptor of known 3D structure.

MolConverter

MolConverter is a command line program in Marvin Beans and JChem that converts between various file types which also converts 2D confirmations to 3D with high accuracy.

Chimera

UCSF Chimera is a highly extensible program for interactive visualization and analysis of molecular structures and related data, including density maps, supramolecular assemblies, sequence alignments, docking results, trajectories, and conformational ensembles. High-quality images and animations can be generated.

GRID BOX generation

Grid Box has been generated using AutoDockTools(ADT) for each receptor, Grid points and Box size parameters had been optimized to cover the complete protein for a blind docking.

AutoDock vina docking

Generated grid parameters had been given as input along with prepared receptor and ligand files for docking process. Number of pose has been set to 9 as default for all receptors and docking was performed against each receptor with alpha solanine.

Interaction of ligand and protein

A plant derived compounds of solanine posse's potential anticancer properties. The selected compound were subjected to docking simulations using Autodock 3.0.5. The docking was performed using different enzymes (receptors) such as Cyclin-Dependent Kinase 2 (CDK2), Cytochrome P450, Topoisomerase I, Cyclin-dependent kinase 6, Topo IIa ATPase, anti-apoptotic protein Bcl-2, Vegfr2. The docking energy were calculated which is a preliminary tool for screening of inhibitors.

Results and Discussion

To study the interaction of solanine with the role of cancer proteins in apoptotic pathways by using *in silico* tools (Autodock vino)

in figure 1 and table 1. Here, cyclin dependent kinases are critical molecules that control cell cycle progression from one phase to other. However, mutational changes in these molecules lead to change in the cell cycle which leads to uncontrolled cellular proliferation or cell death. Docking pose is almost close to the substrates for most of the receptors. Remarkably 1t8i - Topoisomerase I and 1zxm - TopoIIa ATPase docking was completely blocking the binding of the substrate with high affinity by the action of Solanine. [6] investigated the docking allows virtually screening a database compounds and predicting the strongest binders based on their scoring functions. It explores ways in which two molecules, such as drugs and an enzyme human cyclin dependent kinase 2 receptor fit together and dock each other well. The molecules binding to a receptor, inhibit its function. Yan Qiu meng., *et al*. 2005 reported the Natural products have promising new leads in pharmaceutical development. New anticancer drugs derived from research on plant triterpenes and its derivatives are effective for human leukemia HL-60 cell culture inhibited DNA synthesis in HL-60 cells.

S. No	Receptors	Affinity (kcal/mol)	Interacting Residues
1	1di8 - CDK2	-8.5	GLU-12, VAL-18, PHE-80, GLN-131, LEU-134, ALA-144, THR-165
2	1dt6 - CYTOCHROME P450	-8.3	GLU-395, ASP-394, SER-390, ASN-375, GLU-81, HIS-78, GLY-79, PRO-63
3	1t8i - Topoisomerase I	-8.4	LYS-374, PHE-361, GLY-363, GLN-421, ASP-533, THR-498, THR-501, LYS-493, GLY-490, ALA-489, ASN-491, ARG-488
4	1xo2 - CDK6	-7.6	ARG-78, LEU-79, PHE-80, ASP-81, VAL-82, TRP-145, LYS-144
5	1zxm - Topo IIa ATPase	-9.1	GLU-41, LEU-44, LEU45, ARG46, ASP-153, ASP-154, GLY-199
6	2o2f - anti-apoptotic Bcl-2	-7.6	THR-93, GLN-96, ALA-97, ASP-100, PHE-101, ARG-104, TYR-105, TYR-199, GLY-142, ARG-143
7	2oh4 - Vegfr2	-8.2	ALA-879, GLU-883, ARG-1025, ASP-1026, PRO-1066, GLY-1046, ALA-1048, ILE-1051

Table 1: Binding affinity of ligand and proteins

Remarkably 1t8i - Topoisomerase I and 1zxm - Topo IIa ATPase docking was completely blocking the binding of substrate with high affinity.

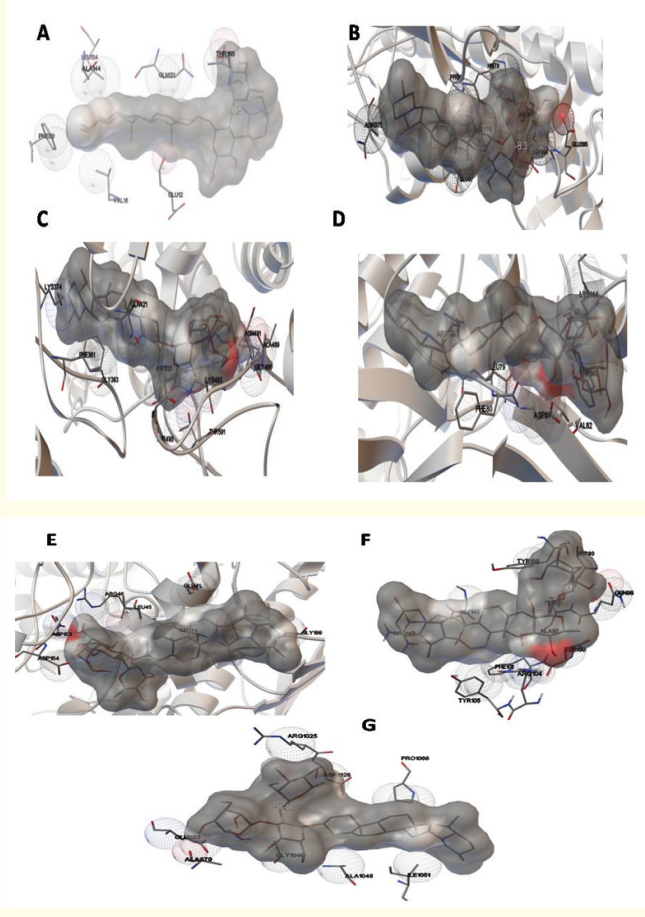

Figure 1: Solanine binding affinities to different proteins

A. 1di8-CDK2 interacting with solanine. B. Idt6-cytochromeP450 interacting with solanine. C. 1t8i-Topoisomerase I interacting with solanine D. 1xo2-CDK6 interacting with solanine. E. 1zxm-Topo IIa ATPase interacting with solanine. F. 2o2f-anti-apoptotic Bc1-2 interacting with solanine G. 2oh4-Vegfr2 interacting with solanine.

Molecular docking explain about the best-fit orientation of a ligand that binds to a particular protein of interest and is used to predict the structure of the intermolecular complex formed between two or more molecules. Protein ligand interaction was the most interesting and its application was seen in particularly in medicines. Ligand was a small molecule, which interacts with protein binding sites. There are several possible mutual conformations in which binding may occur. These are commonly called binding modes [4].

As protein tyrosine kinases play a key role in signal transduction pathways that regulate numerous cellular functions including proliferation, differentiation, migration, and angiogenesis, the key targets was to fight against cancer and EGFR, VEGFR2 inhibitors have been considered as a promising agents to treat cancer [5-9].

Cyclin dependent kinase 2 enzyme was responsible for nearly 50% of cancers. Preliminary in-silico screening were performed of natural polytriterpene phytochemical that are thought to have potential to inhibit mutated 1GII. Out of the two triterpenes boswellic acid and ursolic acid, boswellic acid shows inhibition activity against CDK2 protein [2].

Conclusion

Molecular docking study is a well-established technique to determine the interaction of two molecules and find the best orientation of ligand would form a complex with overall minimum energy. The protein and ligand interaction plays a significant role in structural based designing. Our findings we have take the Molecular docking studies were conducted in order to validate the receptor of human cyclin dependent kinase 2 and identified a solanine bioactive phytochemical obtained pharmacological data and to provide understandable evidence for the observed anticancer potential of the solanine compound with different enzymes.

Acknowledgements

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Conflict of Interest

There is no conflict of interest.

Bibliography

1. Nilsson and Fredrik. Glycoalkaloid content in potato tubers with different levels of resistance to phytophthora infestans, Thirteenth Euroblight workshop St. Petersbug (Russia) (2011): 9-12 .
2. Heena V Sanghani., *et al*. "Molecular Docking Studies of Potent Anticancer Agen". *Journal of Computer Science and Systems Biology* 5.1 (2012): 012-015.
3. Sharma. *Indian Journal of Medical and Paediatric Oncology* 30.1 (2009): 1-8.
4. Sharma., *et al*. *Journal of Advanced Scientific Research* 1 (2010): 67-72.
5. Liao JJ. *Journal of Medicinal Chemistry* 50.3 (2007): 409-424.
6. Srivastave V., *et al*. "Molecular docking studies on DMDP derivatives as human DHFR inhibitors". *Bioinformation* 3 (2008): 180-188.
7. Lemmon M and Schlessinger J. *Cell* 141.7 (2010): 1117-1134.
8. Visentin M., *et al*. *Pharmacology Therapy* 128.1 (2010): 82-90.
9. Pallis AG and Syrigos KS. *Lung Cancer* 80.2 (2013): 120-130.
10. Polverini PJ. *Critical Reviews in Oral Biology and Medicine* 6.3 (1996): 230-247.
11. Balaji KS., *et al*. *Medicinal Chemistry* 6 (2016): 515-520.
12. Yan Qiu Meng., *et al*. "Synthesis of Boswellic acid derivatives and primary research on their activities". *Chinese Chemical Letters* 16 (2005): 867-870.

Volume 5 Issue 11 November 2021