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Computational Repositioning of Ethno Medicine Elucidated Anti-Harper Drug Target, E6 (1C4Z)

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Abstract

There are approximate more than 100 viruses comes under human Papillomavirus family and 40% of them are easily transmitted through sexual contact, from skin and mucous membrane of infected people. E6 protein of HPV mainly acts as an oncoprotein by stimulating the destruction of many host cell key regulatory proteins. The main aim of present study is to identify the potential natural inhibitors against E6 protein. Through literature search 28 inhibitors were selected and analyzed molecular descriptor properties, applied Lipinski's rule of 5 to select only drug-likeness ligands, thus 12 inhibitors remain. The docking was performed by Auto Dock and calculates lowest binding energy to select top hits. Curcumin and Dihydroisocoumarin bind more efficiently to target protein. Therefore, the outcomes of present study may provide new insights in understanding of selected twelve natural inhibitors which can be potential candidates against oncoprotein (E6).

Keywords: HPV; Inhibitor; Docking; Binding Energy; Molecular Descriptor

Introduction

Human papillomavirus(HPV) from the papillomavirus family, it is a DNA virus that is capable of infecting humans. There are more than 100 types of HPV but approximately 30 types can infect the genital area of both genders and approx. 15 of these are oncogenic like that HPV 16 and HPV 18 [1] cause cervical cancer, and other cancer of the genital area.

HPV 6 was southern blot hybridization in a tissue specimen of condyloma acuminate. The complete genome, later designated HPV 6b, was cloned in 1981 and fully sequenced and completely characterized two years later. This virus demonstrated that HPV-6 is polymorphic and consists of several genomic variants [2].

HPV type 6 and 11 have an infection with low risk can cause the development of low-grade precancerous lesions and genital warts. HPV 6 is responsible for approximately 10% of low grade precancerous lesions and 90% of all genital warts. HPV are causally involved in the etiology of benign and malignant neoplasia of cutaneous and mucosal epithelia [3]. HPV- 6 and HPV-11 (α 10) are the best studied of these, and responsible to produce external genital warts [4].

Thus natural/herbal compound could be treated as a drug for the types of protein. In this study, we have screened natural compounds with maximum effects on human being. Structure of the HPV was modelled, and finally natural compound were selected based on the binding energy.

Methodology

Protein selection

The E6 protein of Human papillomavirus was downloaded from RCSB protein databank PDB ID: 1C4Z (http://www.rcsb.org).

Ligands selection

The herbal based anti-cancerous agents were collected from review of literatures [5,6]; all compounds were retrieved from PubChem database (http://pubchem.ncbi.nlm.nih.gov). These compounds were downloaded in sdf format and converted into a PDB (Protein databank) format file using Openbable v2.0.2 [7].

Molecular descriptors calculation

Mol-inspiration online server [http://www.molinspiration.com] used to calculate twenty eight inhibitor (Supplementary Tables 1-4) which are Log P, polar surface area, Molecular weight, number of atom, number of N or O number of NH of OH, number of portable bond ,volume, drug likeness including GPCR ligand ,ion channel modulator, Kinase inhibitor and nuclear receptor ligand, and number of

violations to Lipinski's rule of five for all selected ligands (Figures 1-4).

Molecular docking

The 3D structure of E6 protein was used for molecular docking with the natural selected ligands using Auto Dock v 4.2 Protein structure was prepared by adding polar hydrogen atoms and calculates Gastegier charged by adding kollman charges as well AD4 atom types on newly added atoms in the structure. Grid map were generated around active region of protein with 60 × 60 × 60A. Docking parameters was set in default mode by applying genetic algorithm. Final output selection was based on top run which have lowest binding energy.

Results

The results are described in the tables and figures below.

Table 1 The binding free energy docking simulation result with HPV protein and number of amino acid residues involved in the interaction.

Ligand	Binding energy(Kcal/mol)	Interacted Residues	Distances A0
Curcumin	-7.7	GLY 795, VAL 794, SER 739	3.001 3.0
Diospyrin	-7.6	LEU 734, ASN 741, GLY 795, VAL 794, SER 739, ARG 740.	3.75 3.55
Daphnoretin	-7.5	ARG728, GLY 795, SER739, LEU734, VAL794.	3.05 2.72
6methoxygossypol	-7.5	VAL794, SER 739, ALA 792, GLY 795	3.04 3.24

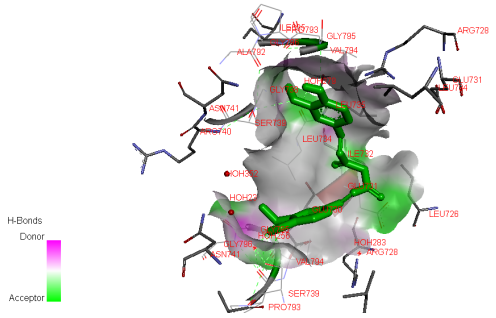

Figure 1 Curcuminss [CID- 969516]1C4Z protein showing interaction with these Amino acid GLY 795, VAL 794, SER 739.

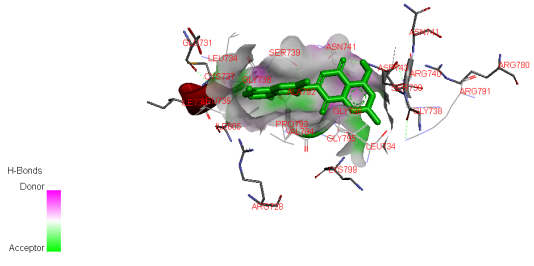

Figure 2 Diospyrin [CID- 308140]1C4Z protein showing interaction with these Amino acid LEI 734, ASN 741, GLY 795, VAL 794, SER 739, ARG 740.

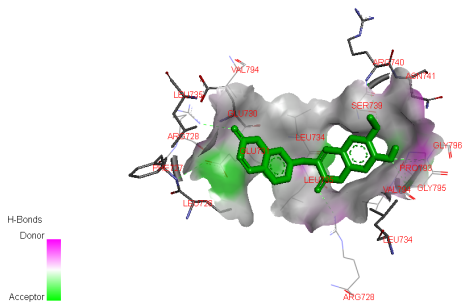

Figure 3 Daphnoretin [CID- 5281406]1C4Z protein showing interaction with these Amino acid ARG 728, GLY 795, SER 739, LEU 734, VAL 794.

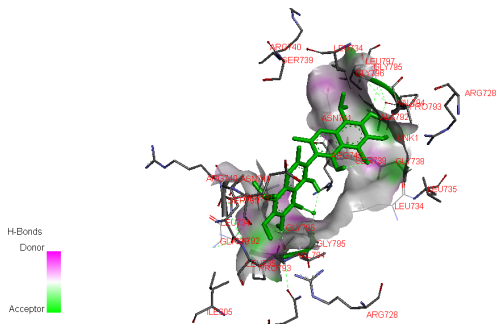

Figure 4 6-methoxygossypol [CID-3085061]1C4Z protein showing interaction with this Amino acid VAL 794, SER 739, ALA 792, GLY 795.

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Discussion

The E6 protein is a potential drug target for HPV6. The approach of finding new inhibitors using natural compound is crucial for new findings. We applied drug like property filter in 28 selected natural compounds as well molecular description from online server (table). Filter natural compounds (Table 1) were used for molecular docking against E6 protein. From the docking results based on lowest binding energy we selected following compounds as potent ligands viz, Curcumin (-7.7 kcal/mol), Diospyrin(-7.6 kcal/mol), Daphnoretin(-7.5 kcal/mol), Ellipticine(-7.4 kcal/mol) and Caulerpin(-7.4 kcal/mol).

The interaction analysis for binding site of natural compound with E6 protein has been done to find out the residues that play an important role in binding. The Curcumin shows highest affinity to bind with energy value -7.7 kcal/mol. On the basis of docking energies natural inhibitor Curcumin is the lead compound for prevention of various form of genital wart caused by HPV 6.

Curcumin is a phytopolyphenol pigment isolated from the plant curcuma longa, commonly known as turmeric, with a variety of pharmacologic properties.

Conclusion

The study has identified two molecular inhibitors one from phytopolylphenol[Curcumin/CID- 969516] and second from Naphthoquinone [Diospyrin/CID- 308140] that binds well to the active site of the target molecule chosen for the study (E6 oncoprotein of the HPV type 6). These molecules, predicted to dock well into the binding site of protein therefore should be seen as active inhibitors that need to be further examined in lab. In-silico study underscores the importance of computational approaches in drug discovery, supplementing classical methods, thus saving enormous amount of time and money.

Acknowledgement

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