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Molecular docking of HBXIP with Chemical Analogues in comparison with Epicatechin

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Abstract

Background: HBXIP is an oncogenic viral protein binds to HBx leading to Hepatocellular carcinoma. The main aim of the present study is to target the HBXIP with commercial available antiviral and anticancer drugs comparing it with Epicatechin phytochemical. **Methodology:** HBXIP structure was retrieved from Protein Databank named 3MSH. The molecules were retrieved from ChemSpider, and generated using ISIS Draw. ADME and Toxicity of the chemical compounds were studied using Accelerys TopKat. Then the interaction of the compounds targeted to HBXIP was studied using Docking using Accelerys Discovery Studio. **Conclusion:** Final results were compared to the phytochemical Epicatechin interactions. This study is useful for development of Prodrug against HBXIP to inhibit the binding of HBXIP to HBx.

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HBXIP, Accelerys Discovery Studio, Epicatechin.

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INTRODUCTION

Hepatitis B virus (HBV) belongs to the Hepadnavirus family and is a significant cause of liver disease worldwide. Complications of HBV range from acute and chronic hepatitis to liver cirrhosis and hepatocellular carcinoma (HCC). HBV genome is a 3.2-kb circular, partially doublestranded DNA molecule with four overlapping open reading frames (ORFs) named C, S, P, and X coding for the viral core protein, e-antigen, surface antigen, reverse transcriptase, and X protein respectively. The X-ORF is located downstream of enhancer 1 (EnhI) and is partially overlapped by the P-ORF at its N terminus, and by the preC-ORF at its C terminus [1].

HBx is a multifunctional regulator that modulates host processes and transactivates various cellular transcriptional elements such as AP-1, AP-2, NF-kB, and cAMP response element site [2] [3]. HBx contains four regions important for transactivation, dimerization, p53 binding, and 14-3-3 protein binding motif [4].

Survivin is an anti-apoptotic protein that is over expressed in most human cancers. HBx up-regulates survivin expression in hepatoma tissues [5]. Survivin formed complexes with a cellular protein, HBXIP, originally recognized for its association with HBx. Survivin-HBXIP complexes bind pro-caspase-9 and thereby selectively suppress the initiation of apoptosis. HBx also interacts with such complexes and suppresses caspase activation in a survivin-dependent manner. Thus, HBXIP functions as a cofactor for survivin, and serves as a link between the cellular apoptosis machinery, and a viral pathogen involved in hepatocellular carcinogenesis [6].

Epicatechin is present highly in *Camellia sinensis*. The major bioflavonoids in *Camellia sinensis* are epicatechins. Epicatechins have apparent activity against human cancer promote apoptosis [7] [8], arrest metastasis by inhibiting metalloproteinases [9] [10], impair angiogenesis [11] [12] and reverse multidrug resistance [13] [14]. Although all epicatechins except EC can potentially suppress cell proliferation[15] [16].

Chemical analogues are selected in terms of two types such as anticancer and antiviral drugs. Antiviral drugs selected are Adefovir, Entecavir, Fumarate, Lamivudine, Mirplatin, Telbivudine, Tenofovir. Anticancer drugs selected are Sorafenib, Erlotinb. These drugs are commercially available and the present study focused the activity of these drugs against HBXIP which in then compared to that Epicatechin phytochemical present in most of the plants. This study focuses mainly on the interaction and also the binding energy of the compounds to HBXIP.

MATERIALS AND METHODS

Protein Databank

Protein Databank is a structural database contains information about experimentally determined structures of proteins, nucleic acids, and complex assemblies

ChemSpider

ChemSpider is a free chemical structure database providing fast text and structure search access to over 28 million structures from hundreds of data sources.

Isis Draw

Isis Draw is a chemical structure 2D drawing program supports chemical file formats. It is available free for academic and personal use. The mol files of the phytochemicals were generated using this tool.

Accelerys Discovery Studio

Accelerys Discovery Studio software provides comprehensive modeling and simulation capabilities for computational chemists, computational biologists, and other scientists engaged in small molecule and biotherapeutics based research.

Admet of phytochemicals

Open the phytochemical compound. Go to protocol ADMET. Select ADMET distributors click run. After job completed double click on it and view the results. Protocol ADMET. To predict Toxicity ADMET TOPKAT (Toxicity prediction Komputer Analysis Tool) is used. TopKat is performed by Protocol ADMET TOPKAT menu. Choose the models and Change the detailed report as true and then run. After job completed double click on it and view the results (pdf form).

Drug likeness activity of phytochemicals

The drug likeness activity of phytochemicals is studied through the compounds satisfying Lipinski's rule of five, partition co-efficient, ADMET properties. This process is analysed through the results of the ADMET from Accelerys Discovery studio.

Docking-Ligandfit

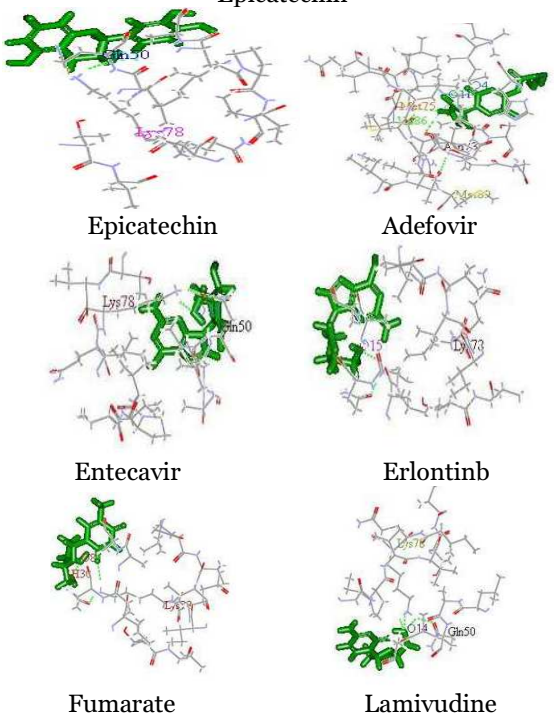
Open the compound. Open the minimized structure of protein and then select define selected molecule as

receptor and then find sites from receptor cavities. Then select the first site and click define sphere form selection. Then go to tools receptor ligand interaction and click Ligandfit. Run the molecule and view the results.

RESULTS

Our results observed that the phytochemical Epicatechin showed best results against the antiviral and anticancer compounds. ADMET results (Table 1) were observed that Epicatechin have good ADME and found to be non-toxic and the other commercial drugs were found to be toxic using TOPKAT analysis using Accelerys Discovery Studio. The interaction between the target HBXIP and the synthetic drugs along with the Epicatechin phytochemical was studied using Accelerys Discovery Studio through docking studies (Table 1). The docking study of the compounds (Fig 1), showed that Epicatechin binding energy were more than that of the other synthetic compounds. The binding energy and other parameters were found to be high when compared to that of the synthetic drugs.

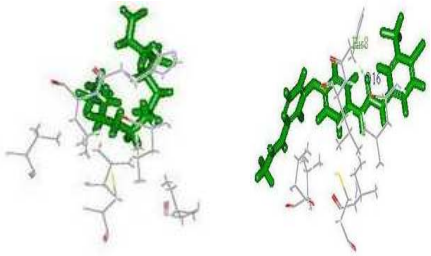
Fig 1: Docking results of the chemical analogues and Epicatechin



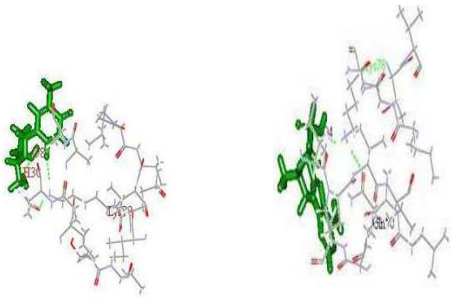
Epicatechin Adefovir

Entecavir Erlontinb

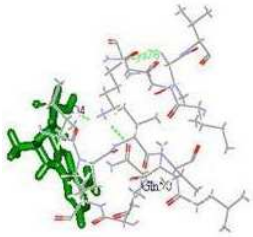
Fumarate Lamivudine



Mirplatin Sorafenib



Telbivudine Telbivudine



Tenofovir

Table 1: ADME of Chemical analogues with Epicatechin

Compound	BBB	Abs	Sol	Hep	CYP3D6	PPB
Epicatechin	4	2	4	0	0	0
Adefovir	4	1	4	1	0	0
Entecavir	4	1	4	0	0	0
Erlotinb	3	0	2	1	1	0
Fumarate	4	1	5	0	0	0
Lamivudine	3	0	4	0	0	0
Mirplatin	1	0	3	0	0	1
Sorafenib	3	0	3	0	0	2
Telbivudine	4	0	4	1	0	0
Tenofovir	4	1	3	0	0	0

*BBB-Blood Brain Barrier, Abs-Absorption, Sol-Solubility, Hep-Hepatotoxicity, PPB-Plasma Protein Binding

Table 2: Docking Results of Chemical Analogues with Epicatechin

Compound	Ligs 1	Ligs 2	-Plp1	-Plp2	Jain	-Pmf	Dockscore
Epicatechin	3.31	4.49	81.96	77.43	1.8	76.28	37.144
Adefovir	2.02	2.8	20.39	17.55	-3.07	26.98	24.784
Entecavir	1.29	3.09	22.45	18.4	-2.08	46.66	11.798
Erlotinb	0.25	2.65	25.16	22.53	-1.7	25.12	12.882
Fumarate	0.89	1.03	16.69	20.18	0.45	-1.37	27.72
Lamivudine	2.63	2.82	19.82	17.84	0.28	33.17	23.875
Mirplatin	0.64	3.02	37.71	33.41	-0.97	88.29	9.382
Sorafenib	0.16	2.25	31.03	34.13	-0.57	26.8	15.773
Telbivudine	1.76	2.67	26.34	24.53	0.25	30.52	15.619
Tenofovir	2	3.09	22.98	19.87	-2.32	44.41	8.472

DISCUSSION

The ADMET properties are given more importance in which Epicatechin phytochemical proved to have good ADMET then the synthetic drugs (Table 1). In Ligandfit docking, Piecewise Linear Potential is a fast, simple, docking function that has been shown to correlate well with protein-ligand binding affinities. PLP scores are measured in arbitrary units, with negative PLP scores reported in order to make them suitable for subsequent use in consensus score calculations. Higher PLP scores indicate stronger receptor-ligand binding. Epicatechin have the highest PLP score than that of the synthetic drugs(Table 2)(Fig 1).The binding energy of the compounds were found to be high than that of the synthetic drugs.

CONCLUSION

The chemical analogues for cancers have more side effects. The structures of the chemical compounds have poor binding capacity than that of the phytochemical Epicatechin. Epicatechin is available highly in most of the medicinal plants. Hence the study highly helps in the development of the prodrug against HBXIP.

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