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Research Article

INSILICO STUDIES OF ANTIGEN-E (HEPATITS-B) AGAINST PRINCIPAL COMPONENTS OF 9 MEDICINAL PLANTS

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ABSTRACT

Hepatitis-B is an infectious disease of the liver and it is a serious health problem with more than two billion sufferers worldwide, around 350 million of which are chronic carriers of the disease. Associated risks include cirrhosis of the liver and liver cancer from which more than one million people die annually. The standard treatment for Hepatitis-B is alpha-2b-interferon which is expensive, has serious adverse effects and does not always prevent recurrence of the disease. Historically herbal medicines have been used to treat liver disease, including chronic Hepatitis-B.
The natural compounds of various plant extracts have potential effects in the treatment of Hepatitis-B. The pharmacological effects of these extracts have been demonstrated in inhibiting the levels of Antigen E in patients affected by Hepatitis B. To understand the binding mechanism of the 57 phytocompounds from nine different plant sources molecular docking studies has been performed with Antigen-E of Heptitis-B virus using GOLD (Genetic Optimization of Ligand Docking) software. These compounds show favorable interactions with the amino acid residues thereby substantiating their proven efficacy as anti-viral compounds. Complete utilization of the medicinal values of herbal plants with the use of similar bioinformatics approaches can take the science of pharmacology to higher level. The use of similar approaches to identify the most active compound from the plant extracts will help in treating the diseases with the best compound.

Keywords: Hepatitis B, Antigen E, GOLD, Medicinal Plants.

INTRODUCTION

Two billion people worldwide have been infected with HBV, and more than 350 million people are estimated to be chronic carriers of HBV (Safioleas M et al., 2007) Hepatitis B virus (HBV) infection is a severe health problem in the world; however, there is still no satisfactory therapeutic strategy for the HBV infection. As current therapies are not able to eradicate the virus completely, prolonged treatment is necessary, giving rise to resistance mutations (Arbuthnot P et al., 2007) In search for new anti-HBV agents with higher efficiency and less side effects numerous phytocompounds from medicinal plants has been reported, but the relative molecular mechanism of these compounds in yet to be explored. Hence the present work employs an insilico approach to study the mechanism of natural compounds from plants using Molecular Docking studies. We have here considered 57 compounds from nine different medicinal plants of Asian origin namely, *Schisandria wilsonia, Potentialla ansernia, Rheum plamatum, Rubia cordifolia, Phyllanthus sp., Swertia mileenis, Geranium caroliniaum, Jasminum officinale* and *Selaginella moellendorffii*. The 57 compounds were screened against the Antigen E of Hepatitis B virus (PDB ID: 1QGT) using GOLD (Genetic Optimization of Ligand Docking).

MATERIALS AND METHODS

CRYSTAL STRUCTURE OF ANTIGEN E FROM HEPATITIS B VIRUS

The X-Ray crystallographic structure of Antigen E from Hepatitis B virus was obtained from the Protein Data Bank (PDB) (Wynne SA *et al*, 1999). The PDB ID 1QGT corresponds to the crystal structure of the receptor. The structure of Antigen E is composed of four polypeptides chains with 142 amino acids. We have employed the GOLD software to screen the activity of the 57 compounds against the receptor 1QGT. The consensus scoring and ranking was used to determine the results of Molecular screening.

ACTIVE SITE

The active site of the receptor 1QGT was determined using the Q-Site Finder (www.modelling.leeds.ac.uk). The active site of the protein includes Glu64, Trp62, Leu65, Leu68, Leu31, Gly63, Thr67, Leu68, Gly63, Met66, Trp71, Val27, Arg28, Thr70, Asn90, Ala69, Val89, Val86, Ala69, Asn74, Asn87, Gly73 and Arg82.

NATURAL COMPOUNDS FROM VARIOUS MEDICINAL PLANTS

The structures of the chemical compounds were searched in various literatures. The compounds from the plants belong to lignans, terpenoids, saponins, quinines, flavonoids, lactones, glycosides and flavones. The 2D structures of the resulting 57 compounds from the nine plants were drawn using ACD Chemsketch (www.acdlabs.com/). The structures were then converted to 3D, their geometries were optimized and saved in "MDL mol file" format.

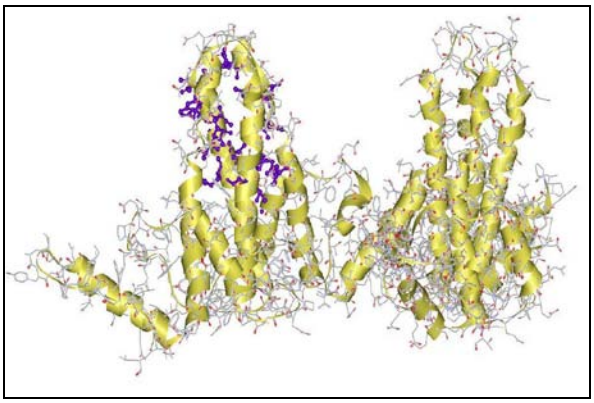

Fig 1: Active site of Antigen E. Secondary structures are shown in Yellow and Active site shown in blue

GOLD DOCKING SIMULATIONS

All molecules of plant extracts (1–57) under study were docked in to the binding site of the receptor (PDB ID: 1QGT) using GOLD (Genetic Optimization of Ligand Docking) software provided by CCDC,U.K. (Jones et al., 1997). The GOLD program uses a genetic algorithm (GA) to explore the full range of ligand conformational flexibility and the rotational flexibility of selected receptor hydrogens. Grid was prepared for the protein with the center and the size of the bounding box set on 10 Å. The coordinates of the enclosing box (x = 121 Å; y = 87 Å; z = 45 Å) were defined starting from the set of active site residues.

RESULTS AND DISCUSSION

Docking of all the 57 compounds with the receptor, Antigen E form Hepatitis B virus using the GOLD software resulted in identifying the best compound that interact with the receptor. The software generated 10 different conformations of each compound used for the study. The results were evaluated based on the binding compatibility i.e. Docked energy in kcal/mol.

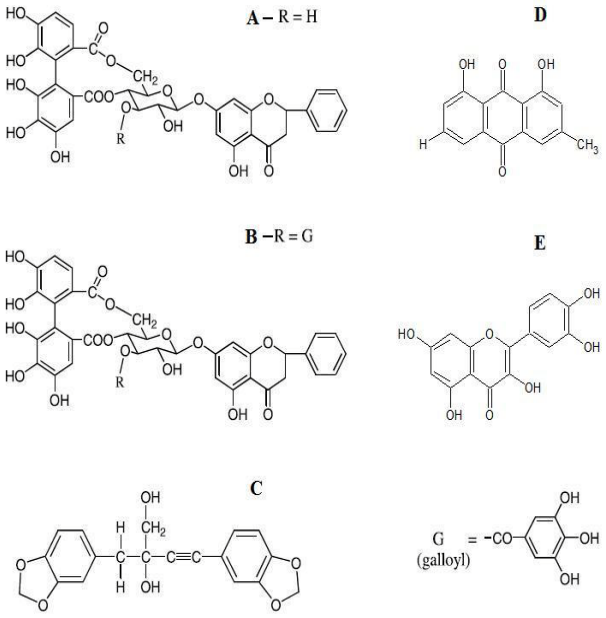

Fig 2: Active compounds from plant sources. Pinocembrin-7-O-(4″,6″-(S)-HHDP)-β-d-glucose (A), pinocembrin-7-O-(3″-O-galloyl-4″,6″-(S)-HHDP)-β-d-glucose (B), Virgatyne (C), Chrysophanol(D) and Quercitin (E).

BINDING MODES AND INTERACTIONS

The 23 amino acid active site pocket provides a cavity for the active plant compounds to interact with the receptor. The active compound Chrysophanol from *Rheum palmatum* binds with the receptor with the highest GOLD Score of 47.87, comparatively the active compounds Pinocembrin-7-O-(4″,6″-(S)-HHDP)-β-d-glucose, pinocembrin-7-O-(3″-O-galloyl-4″,6″-(S)-HHDP)-β-d-glucose and Virgatyne binds with the receptor with the GOLD scores of 47.16, 45.88 and 45.76 respectively. Quercitin, the active compound from *Germanium carolinianum* also shows a significant binding affinity with a GOLD score of 38.34.

From the analysis of the H-bond formations between the active compounds from plant sources and the receptor, pinocembrin-7-O-(3″-O-galloyl-4″,6″-(S)-HHDP)-β-d-glucose from *Phyllanthus amarus* form five H-bonds, Pinocembrin-7-O-(4″,6″-(S)-HHDP)-β-d-glucose and Virgatyne forms four H-bonds. Though Chrysophanol from Rheum palmatum has the highest GOLD score, it forms only 2 H-bonds with the receptor whereas Quercitin forms four H-bonds. The figure shows the binding of the active compounds with Antigen E.

From the analysis it is evident that Chrysophanol exhibits a better anti hepatitic compound when compared to the other active plant compounds. Alternatively the three active compounds Pinocembrin-7-O-(4″,6″-(S)-HHDP)-β-d-glucose, pinocembrin-7-O-(3″-O-galloyl-4″,6″-(S)-HHDP)-β-d-glucose and Virgatyne although having a lesser GOLD score an better anti-hepatic compounds since they form a good H-bond formation with Antigen E.

Table1: Docking results of 57 natural compounds from nine plant sources.

S.No	Plant Name	Compound	GOLD Score	Reference
1	*Potentilla anserina*	brevifolin	31.14	Zhaoa. Y.L et al, 2008.
2	*Germanium carolinianum*	Quercitrin	44.7	Jiyang LI et al, 2008
3		Hyperin	32.09	
4		Hirustrin	34.88	
5		Quercitin	38.34	
6		Kampherol	37.44	
7	*Selaginella moellendorffii*	Carboxymethyl	37.06	Yuan Cao et al, 2010
8		Carboxymethylester	39.09	
9		Carboxybutylester	38.6	
10	*Rheum palmatum*	Chrysophanol	47.87	Zhi Li et al, 2007
11	*Swertia millenus*	Swerilactone A	43.25	Chang-An Geng et al, 2010
12		Swerilactone B	29.08	
13		Swerilactone E	42.35	
14		Swerilactone F	38.84	
15		Swerilactone G	37.94	
16	*Rubia cordifolia*	Mollugin	32.08	Leng Chee Chang et al,2000
17		Furomollugin	33	
18		Rubioncolin B	25.09	
19	*Phyllanthus amarus*	Napthoquinone	33.38	Ray-Ling Huang et al,2003
20		niranthin	34.3	
21		hypophyllanthin	34.98	
22		nintetralin	28.58	
23		phyltetralin	33.25	
24		hinokinin	38.58	
25		butyrolactone	36.04	
26		virgatusin	36.35	
27		virgatyne	45.76	
28		sodium galangin 8 sulphonate	37.49	
29		sodium galangin 3 o glucoside 8 sulphonate	33.63	
30		sodium kaempferol 8 sulphonate	35.68	
31		indole 3 carboxyaldehyde	27.48	

32		indole 3 carboxylic acid	29.87	
33		brevifolin	31.9	
34		methyl brevifolin carboxylate	32.38	
35		potassium brevifolin carboxylate	34.21	
36		corilagin	44.95	
37		geraniin	31.58	
38		roseoside	20.47	
39		ellagic acid	29.97	
40		1,6-O-galloyl D glucose	31.9	
41		1346 tetra o galloyl beta D glucose	32.76	
42		byzantionoside	30.91	
43		picocembrim	47.16	
44		Picocenmbrim Galloyl	45.88	
45		schisanwilsonin	29.33	Wen-Hui Ma et al, 2009
46		schisanwilsoninB	-87.44	
47	*Schisandria Wilsonia*	schisanwilsoninC	-18.99	
48		schisanwilsoninD	-18.41	
49		schisanwilsoninE	38.91	
50		schisanwilsoninF	40.97	
51		schisanwilsoninG	29.39	
52		SchisantherinA	5.17	
53		DeoxySchisanderinA	26.83	
54		gomisink3	20.37	
55		gomisinH	4.6	
56		Schisantherin C	27.29	
57	*Jasminum officinale*	oleuropein	10.29	Guiqin Zhao et al, 2009

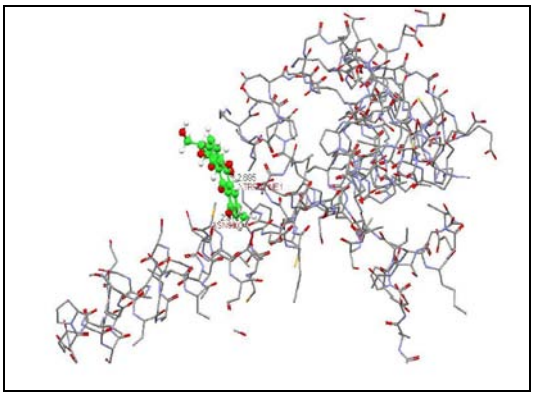

Fig3: Interactions between 1QGT and Chrysophanol.

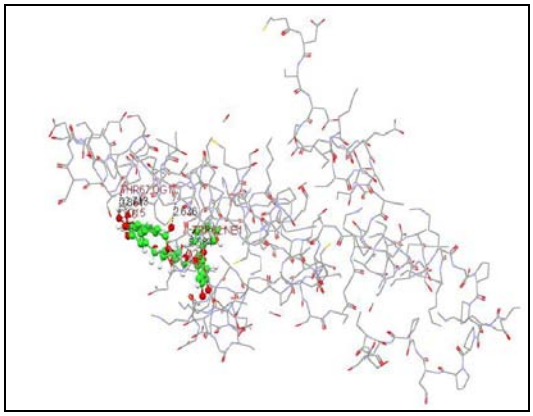

Fig 4: Interactions between 1QGT and Pinocembrin-7-O-(4″, 6″-(S)-HHDP)-β-d-glucose.

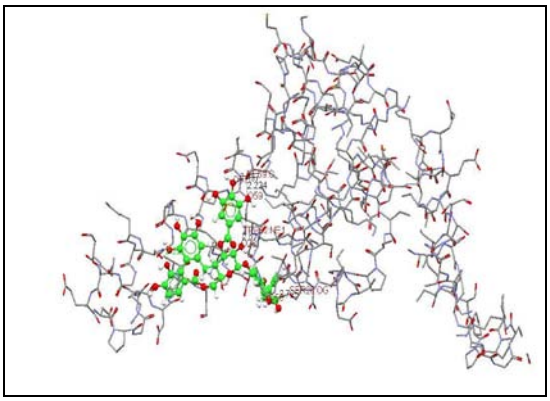

Fig 5: Interactions between 1QGT and pinocembrin-7-O-(3″-O-galloyl-4″, 6″-(S)-HHDP)-β-d-glucose.

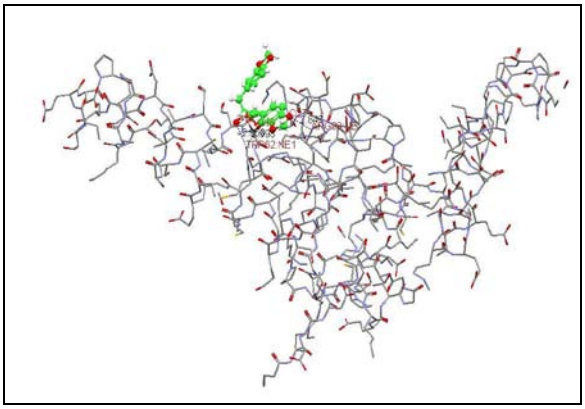

Fig 6: Interactions between 1QGT and Virgatyne.

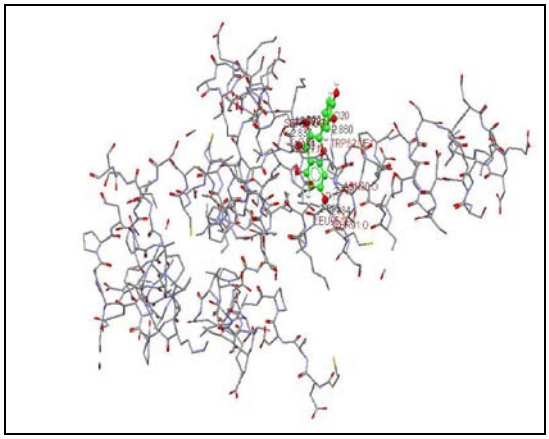

Fig 7: Interactions between 1QGT Quercitin.

CONCLUSION

The molecular docking methods are widely used to reduce the cost and time involved in the process of drug discovery. The method used in the current study has already been proved to be efficient in identifying novel anti-hepatic inhibitors from the wide library of compounds. The active compound Chrysophanol showed high binding affinity with Antigen E. The docked conformation of Chrysophanol exactly fits the active site of the receptor Antigen E (1QGT). The compounds Pinocembrin-7-O-(4″,6″-(S)-HHDP)-β-d-glucose,pinocembrin-7-O-(3″-O-galloyl-4″,6″-(S)-HHDP)-β-d-glucose and Virgatyne though with low GOLD score has better affinity. Hence this study has its importance in identifying plant compounds as safer drugs without causing any side effects. Hence the approach can be used as a good insight to learn about the pharmacophoric patterns of the compounds that has a better biological activity for treating Hepatitis B.

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