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Novel Antiviral Activity of Anthocyanins: An *In Silico* Approach

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Abstract

HIV-1 protease [E.C.3.4.23.16] is an important enzyme involved in life cycle of HIV—a retrovirus causing AIDS. It cleaves the nascent polyprotein to generate the mature proteins of HIV virions, and its absence renders HIV uninfectious. Thus the HIV protease seems to be an interesting drug target for HIV. Utilising this property, this investigation aims to design a drug from the naturally available sources such as anthocyanins. Anthocyanins belong to flavonoid group of phytochemicals naturally present in tea, honey, wines, fruits, nuts, etc. . In this study, 10 anthocyanin compounds were designed and docked with HIV protease. In docking results, cyanidin, showing maximum dock score of 41.098, was found to be the best drug ligand.

Keywords: *HIV, HIV Protease, Anthocyanins, Flavonoid groups, Phytochemicals.*

Introduction

The term anthocyanin is derived from Greek word *anthos* (flower) and *kyanose* (blue) to describe the blue pigment of *Centaurea cyanus*[1-2] . Anthocyanins are plant pigments soluble in water and primarily present in fruits and vegetables having bright colours [3]. They belong to the phenolic compounds and around 500 structures have been reported by year 2000 [4]. Flavonoids are important C_{15} aromatic compounds of plant origin [5]. Chemically anthocyanins are glycoslyated, polyhydroxy or polymethoxy derivatives of 2-phenyl benzopyrlium containing two benzoyl rings, separated by a heterocyclic ring [2]. These plant components are known to exhibit several medically important biological activities such as antioxidative and radical scavenging activity [6-10], improving sight [11-12] and anti-diabetic properties [13-14]. Besides these, they can also enhance insulin secretion [15-16] and can act as chemoprotective agents [17-18]. They also show antiviral [19] and antimicrobial activity [20] and cure common cold [21]. In summary, anthocyanins, as an important group of phenolic compounds, have wide medical applications beneficial to humans [22]. The most common six known anthocyanins are the pelargonidin, cyanidin, delphinidin, peonidin, petunidin and Malvidin. The daily intake of dietary flavonoids is estimated to be about 20-25 mg/day, while, especially in US it is between 180-215 mg/day [23].

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The objective of the present experiment is to dock the anthocyanins with HIV protease (PDB ID: 1a8g)—a potential HIV drug target. This study focuses on the antiviral activity of the anthocyanins.

Methods

The objective of the experiment is accomplished by preparing the ligand and the protein for the docking studies. Following the Protein-Ligand docking method, interactions were conducted and results were analysed that gave the flexibility of docking based on the structure.

A. Ligand Preparation

Anthocyanins were used as ligands for the docking studies and their structures were drawn using Chemsketch (ACD LABS 12.0). The duplicates were removed and bonds were added. The CHARMm force field was applied to minimise the energy.

B. Protein Preparation

The structure of the protein (ID: 1a8g) was imported from the

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Protein Data Bank of high resolution to the Discovery Studio 2.5. The hetero-atoms and water molecules were removed from the structure. The chemistry of the missing hydrogens was corrected. By using alternate conformations and valence monitor options, crystallographic disorders and unfilled valence atoms were corrected.

C. Docking

The Protein–Ligand method was used for docking, which is based on molecular modelling. This method predicts the position and orientation of a small molecule called ligand when it binds to a receptor molecule, a protein or enzyme [24]. The docking was done on the Discovery Studio 2.5.

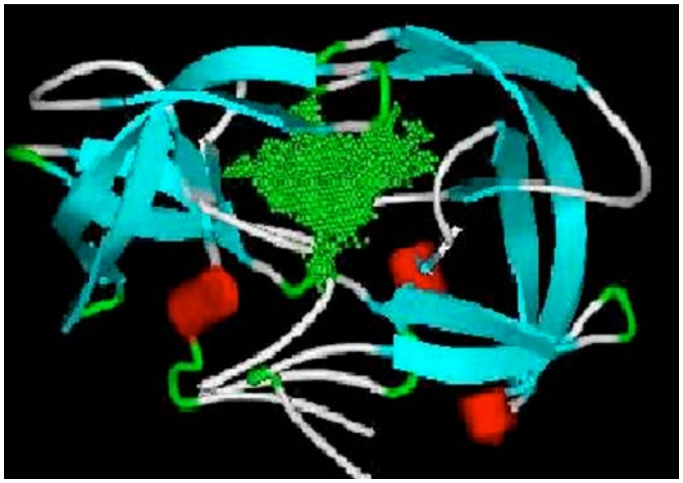


Figure 1: Active site pocket - Identification of Active site pocket by using Eraser algorithm in Discovery Studio.

Results and Discussion

Ligand Preparation

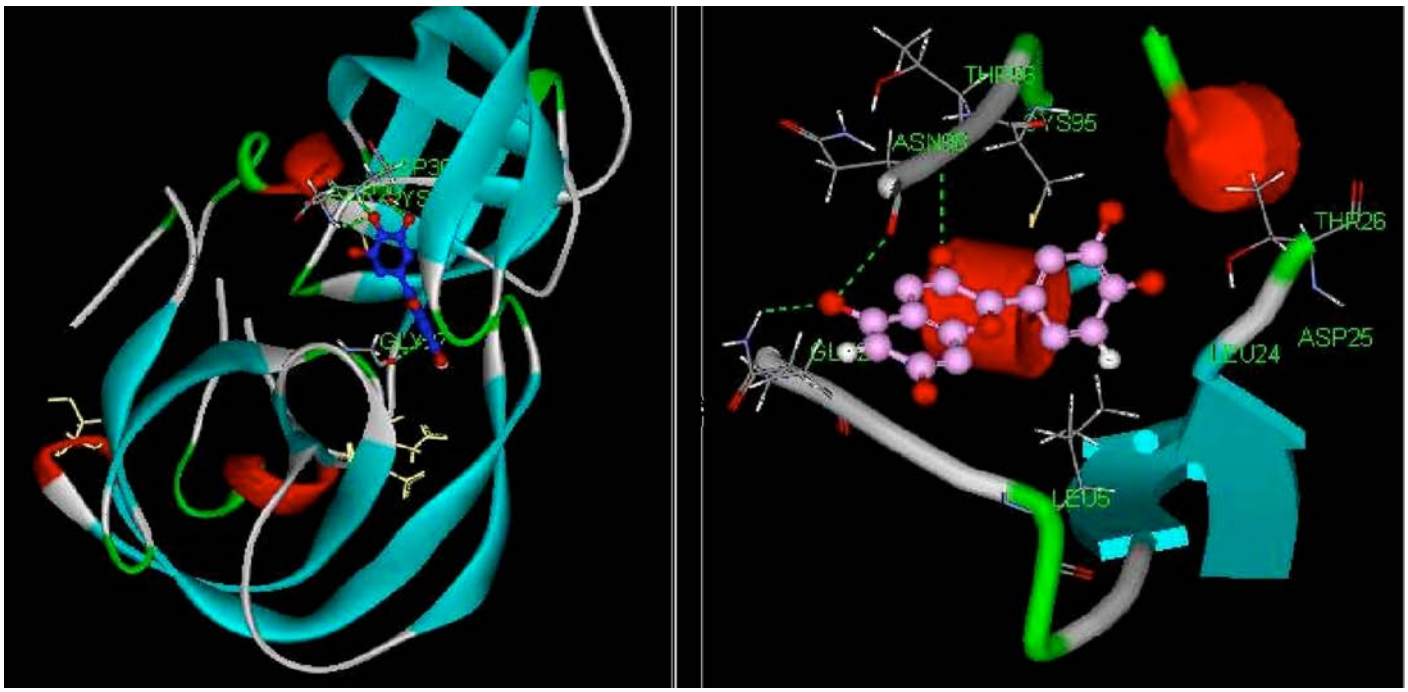
The ligands for the present study, anthocyanins were drawn in Chemsketch (ACD LABS 12.0). Ten ligands were drawn [25] and their 3D structures and sterioisomers were generated.

Protein Preparation

The protein (ID: 1a8g) was imported from the Protein Data Bank. The energy minimisation of the protein was done using the conjugate gradient method and steepest descent method till the convergence gradient was satisfied. The active site pockets were identified by using the Eraser Algorithm and a sphere was created around the active site.

Protein-Ligand Docking

The results of the protein ligand docking studies were analysed, which showed cyanidin and two of its sterioisomers to be the best compound exhibiting antiviral properties with the highest dock score of 41.098, 41.094 and 40.928, respectively.



Amino acids involved in the interactions
Gly27, Asp29, Cys95, Asp30

Amino acids involved in the interactions
Asn98, Thr96, Glu2

Figure 2: H- bond interactions of Cyanidin with active site pocket residue of HIV protease.

Table 1: Docking Results - Table showing the dock results of Protein-Ligand Interaction

	Name	Index	LigScore1_Dreiding	LigScore2_Dreiding	-PLP1	-PLP2	Jain	-PMF	DOCK_SCORE
1	cyanidin	11	1.72	4.6	72.62	53.26	-0.35	15.39	41.098
2	cyanidin	12	1.74	4.56	71.61	52.58	-0.21	14.4	41.094
3	cyanidin	13	1.74	4.56	71.61	52.58	-0.21	14.4	41.094
4	cyanidin	14	1.69	4.45	72.14	53.75	-0.17	13.33	40.928
5	cyanidin	15	1.59	4.58	64.96	54.62	-0.32	7.56	40.692
6	cyanidin	16	1.59	4.58	64.96	54.62	-0.32	7.56	40.692
7	aurantinidin	1	1.65	4.69	63.94	55.12	-0.39	9.55	40.608
8	aurantinidin	2	1.74	4.6	69.94	54.23	-0.45	12.57	40.583
9	cyanidin	17	1.45	4.62	62.54	49.49	-0.73	12.82	40.569
10	cyanidin	18	1.62	4.58	63.98	54.57	-0.26	9.6	40.562
11	cyanidin	19	1.6	4.63	60.61	52.56	-0.51	9.65	40.506
12	cyanidin	20	1.6	4.63	60.61	52.56	-0.51	9.65	40.506
13	luteolinidin	31	1.52	4.69	63.4	55.78	-0.08	10.33	40.48
14	luteolinidin	32	1.52	4.69	63.4	55.78	-0.08	10.33	40.48
15	aurantinidin	3	1.62	4.72	62.34	52.74	-0.52	9.89	40.447
16	aurantinidin	4	1.61	4.7	62.14	54.24	-0.42	8.74	40.411
17	aurantinidin	5	1.61	4.7	62.14	54.24	-0.42	8.74	40.411
18	aurantinidin	6	1.61	4.7	62.14	54.24	-0.42	8.74	40.411
19	aurantinidin	7	1.61	4.7	62.14	54.24	-0.42	8.74	40.411
20	luteolinidin	33	1.52	4.71	63.76	55.27	0	9.89	40.311
21	luteolinidin	34	1.52	4.71	63.76	55.27	0	9.89	40.311
22	luteolinidin	35	1.52	4.71	63.76	55.27	0	9.89	40.311
23	luteolinidin	36	1.52	4.71	63.76	55.27	0	9.89	40.311
24	luteolinidin	37	1.53	4.64	63.08	54.55	-0.02	11.27	40.258
25	aurantinidin	8	1.56	4.64	62.75	53.75	-0.66	11.01	40.218
26	aurantinidin	9	1.54	4.65	62.99	53.05	-0.73	10.9	40.151
27	aurantinidin	10	1.54	4.65	62.99	53.05	-0.73	10.9	40.151
28	luteolinidin	38	1.53	4.61	60.81	53.34	-0.01	10.14	40.064
29	luteolinidin	39	1.53	4.61	60.81	53.34	-0.01	10.14	40.064
30	luteolinidin	40	1.46	4.66	65.8	56.47	-0.21	10.1	40.049
31	pelargonidin	41	1.67	4.56	62.66	54.16	-0.28	8.54	39.934

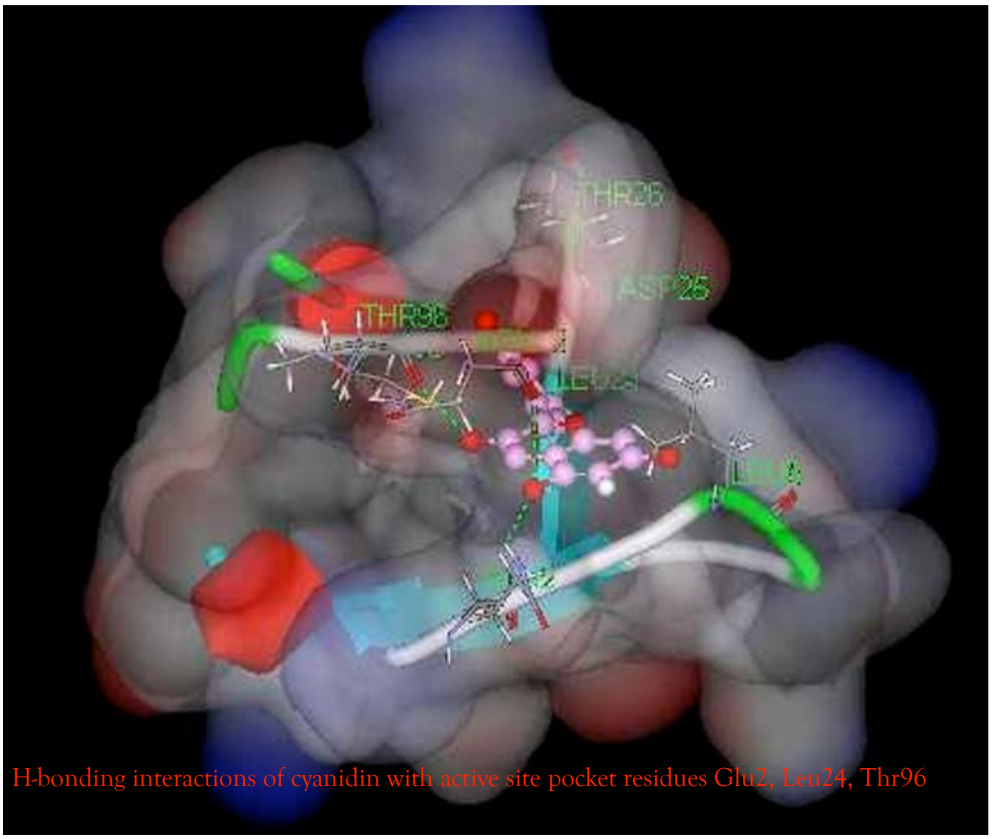


Figure :3 Showing the electrostatic surface area.

Conclusions

Anthocyanins the naturally available plant components are known to exhibit several medical properties. The present article successfully accomplishes the antiviral activity of the anthocyanins. Amongst the available anthocyanins, cyanidin proves to be the most lucrative drug against HIV.

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