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In Silico Targeting of influenza virus haemagglutinin receptor protein using Diosmetin, Tangeritin, and Anthocyanidins as potential drugs

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ABSTRACT

Influenza viruses cause acute respiratory illnesses in birds, humans, and other mammals, and are a major public health concern around the world. Pandemic flu could be caused by an unforeseen human adaptation of an influenza subtype or strain rather than currently circulating influenza viruses. The need for plant metabolites-based new anti-influenza drugs appears to be urgent. Blocking Haemeagglutinin (HA) protein is one of the most appealing drug targets to halt the growth of the virus. The influenza virus can acquire resistance to currently existing therapies, therefore necessitating the development of new medications. The plant's bioactive metabolites, flavanoids are having potential medicinal efficacy. The current study aimed to identify certain flavonoids (Diosmetin, Tangeritin, and Anthocyanidins) that might interact with the HA protein of the influenza virus and help in inhibiting its growth. We used PyRx v0.8 for virtual screening and docking studies. The highest binding affinity docked structures were analyzed using PyMOL and Discovery Studio Visualizer. The present study revealed that these naturally occurring compounds interacted with HA protein, resulting in the minimization of energy in the range

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of -5.2 to -7.0 kcal/mol. Diosmetin showed the best binding affinity of -7.0Kcal/mol. The molecular binding studies revealed that Diosmetin, Tangeritin, and Anthocyanidins are potential compounds to test against HA protein and can be used to develop effective anti-influenza agents.

1 Introduction

Influenza A (H1N1) virus causes acute respiratory illnesses in birds, humans, and other mammals, and is a serious public health issue globally (Kapoor and Dhama 2014; Bonilla-Aldana et al. 2020; Philippon et al. 2020; Kessler et al. 2021)**.** The influenza A virus (IAV) is known to spread by wild birds. Strain avians can adapt to their human host through acquired mutations and attain human-to-human transfer (Das 2012; Dhama et al. 2013; Yeo and Gan 2021). Rather than currently circulating influenza viruses, a pandemic flu could be triggered by an unanticipated human adaptation of an influenza subtype or strain. It is seasonal and kills between 2,50,000 and 5,00,000 people (Wu et al. 2017). The Spanish flu (1918 H1N1), Asian flu (1957 H2N2), Hong Kong flu (1968 H3N2), and swine flu (2009 H1N1) pandemics demonstrate the devastating socioeconomic and public health consequences of pandemic flu and keep us alert for the next one (Dhama et al. 2012; Joseph et al. 2017; Kessler et al. 2021;)**.** Approximately 50,000 people die each year from seasonal flu. Because of its high mortality (about 60%) and contagious nature, the H5N1 type IAV, infected 18 patients in Hong Kong and in 1997 six patients were killed, posing a major threat to human health in the coming time (Yang et al. 2013). The life cycle of the influenza virus has so far been thoroughly studied and various treatment targets have been validated. Thus, the need for new anti-influenza drugs appears to be pressing. Blocking Haemeagglutinin (HA) protein is one of the most appealing among them. HA is a homotrimer protein whose inactive monomer is HA0 which contains 566 amino acids, plus signal peptide is broken down into two subunits i.e. HA1 subunit contains 325 amino acids and HA2 contains 222 amino acids in the extracellular medium. Sialic acids on the surface of infected cells are recognized by the antigenic sites of the global head of the HA1 subunit. Because of the fusion peptide, the HA2 subunit is organized as a helix stem and is heavily involved in the membrane fusion process. There are now 18 subtypes of HA, which can be further split into 5 clades and 2 groupings. The flexible nature of HA makes rational medication creation extremely difficult. Both antigenic drift and shift may also help to increase the diversity of HA (Wilson et al. 1981; Stevens et al. 2006)**.** The current study discussed how HA protein can be a potential target in the influenza virus by using various flavonoids.

When virus influenza enters the endosome, the endosome's acidic pH i.e. about 5 causes a conformational modification in which the HA1 subunits separate from each other and the HA2 subunit goes through the spring-loaded process and converts into a linear helix, hence membrane fusion begins when fusion peptide enters the endosome membrane, allowing the influenza genome to be integrated into the host's cell. The previous study discovered invariant residues and SLs group in this loop zone, indicating that this location could be a promising target for avoiding therapeutic evasion (Lao and Vanet 2017). Nine residues make up this possible binding site. The residues E392, E397, E401, F393, N394, N405, and N402 are in variants, while SLs residues are K395 and K398. The influenza virus can acquire resistance to currently existing therapies, necessitating the development of new medications such as Zanamivir and Lanamivir (Chavan et al. 2014). Researchers showed that leaf extracts of *Jatropha curcas* contain many flavanoids, tannins and saponins that inhibit the hemagglutinin protein of the H1N1 virus (Patil et al. 2013). Liu et al. (2018) also conduct a study on other surface receptors such as Neuraminidase, of the influenza virus and concluded that herbal extracts of some medicinal plants have inhibitory action against the receptor and inhibit the growth of the influenza virus. The authors also revealed that *Allium sativum* and *Plumbago indica* inhibit the synthesis of viral nucleoprotein and polymerase activity which inhibits (H1N1) pdm09 virus (Chavan et al. 2016). He et al (2011) demonstrated the role of dandelion, a traditional Chinese medicine (TCM) against, human A/PR/8/34, influenza virus type A, and WSN (H1N1) and showed a negative effect against virus growth (He et al. 2011). Chavan et al (2014) used an *in-silico* approach against Neuraminidase, Hemagglutinin, and M2 protein channel of the H1N1/A/2009 virus by using Allicin and Plumbagin as a potential multidrug target. Therefore, the current study was designed to identify the potential utility of phytochemicals to interact with viral protein receptors i.e. haemagglutinin.

2 Materials and Methodology

2.1 Retrieval of three-dimensional receptor structure

3-D crystal structure of influenza haemagglutin in with PDB ID: 1HTM with the resolution of 2.50 Å was retrieved from the online database RCSB-PDB (Research Collaboratory Structural Bioinformatics-Protein Data Bank) (Figure 1) (Bullough et al. 1994). For docking studies, water molecules and heteroatoms were removed from the 3-D structure of the target protein.

2.2 Preparation of ligand's preparation and analysis of ADME properties

Three phytochemicals were selected as ligands for virtual screening and their 3-D structures were downloaded in sdf format

from PubChem. The Open Babel was run to convert df format of ligand structures into pdb format (Figure 1). The unfavorable absorption, distribution, metabolism, and elimination (ADME), the online tool was used to determine the profiling of studied ligands (pH 7) (Jayaram et al. 2012). Lipinski's rule of five, i.e. physiochemical properties of ligand viz. LogP (<5), H-bond acceptor (<10), molar refractivity, H-bond donor (5), molecular weight (<500 Da), and drug likeliness were considered (Lipinski 2004) (Table 1).

2.3 Molecular docking of phytochemicals with Influenza Haemagglutinin

PyRx v0.8 was used for virtual screening and docking studies. For energy minimization of ligands Universal force field (UFF) was applied and then ligands structures were converted into pdbqt by OpenBabel (O'Boyle et al. 2011). The highest binding affinity docked structures were visualized using Discovery Studio Visualizer and PyMOL.

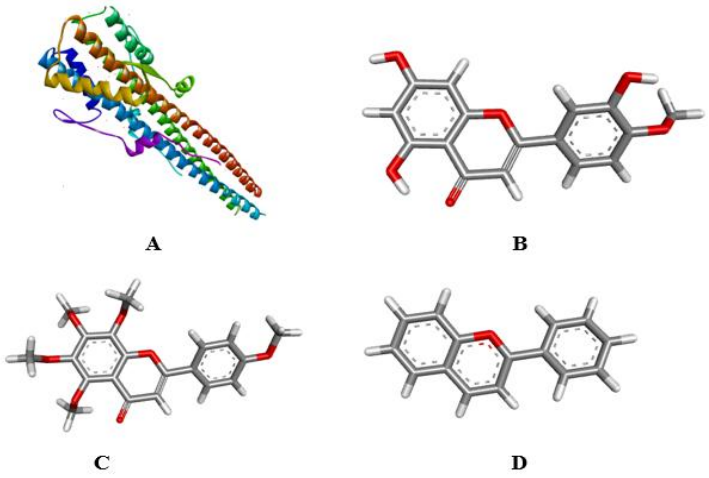

Figure 1 3D view of the receptor (A) Chemical structures of Diosmetin (B), Tangeritin (C), Anthocyanidins (D)

Table 1 Physio-chemical or ADME Properties of ligands

S. No.	Ligands (Pub Chem CID)	ADME Properties (Lipinski's Rule of Five)		Drug Likeliness
		Properties	Values	
1	Diosmetin (5281612)	Molecular weight (<500 Da)	300	Yes
		LogP (<5)	2.4	
		H-bond donor (5)	3	
		H-bond acceptor (<10)	6	
		Molar Refractivity	77.3	
2	Tangeritin (68077)	Molecular weight (<500 Da)	372	Yes
		LogP (<5)	3.3	
		H-bond donor (5)	0	
		H-bond acceptor (<10)	7	
		Molar Refractivity	98.5	
3	Anthocyanidins (145858)	Molecular weight (<500 Da)	20	Yes
		LogP (<5)	4.1	
		H-bond donor (5)	0	
		H-bond acceptor (<10)	1	
		Molar Refractivity	65.3	

Table 2 Binding affinity and RMSD value of Diosmetin with Influenza Haemagglutinin

Ligand	Binding Affinity (Kcal/mol)	rmsd/ub	rmsd/lb
Diosmetin_uff_E=178.56	-7.0	0	0
Diosmetin_uff_E=178.57	-6.9	6.096	1.183
Diosmetin_uff_E=178.58	-6.7	6.052	0.846
Diosmetin_uff_E=178.59	-6.4	5.988	1.019
Diosmetin_uff_E=178.60	-6.3	14.311	12.878
Diosmetin_uff_E=178.61	-6.3	14.277	12.886
Diosmetin_uff_E=178.62	-6.1	3.212	1.99
Diosmetin_uff_E=178.63	6.0	2.235	1.892
Diosmetin_uff_E=178.64	-6.0	2.408	1.517

Table 3 Binding affinity and RMSD value of Anthocyanidins with Influenza Haemagglutinin

Ligand	Binding Affinity (Kcal/mol)	rmsd/ub	rmsd/lb
Anthocyanidins_uff_E=324.34	-6.7	0	0
Anthocyanidins_uff_E=324.35	-6.4	7.495	1.799
Anthocyanidins_uff_E=324.36	-5.8	8.769	3.186
Anthocyanidins_uff_E=324.37	-5.7	8.218	2.242
Anthocyanidins_uff_E=324.38	-5.5	15.664	14.21
Anthocyanidins_uff_E=324.39	-5.4	15.886	14.356
Anthocyanidins_uff_E=324.40	-5.3	16.488	15.01
Anthocyanidins_uff_E=324.41	-5.3	18.023	15.401
Anthocyanidins_uff_E=324.42	-5.1	18.24	15.615

Table 4 Binding affinity and RMSD value of Tangeritin with Influenza Haemagglutinin

Ligand	Binding Affinity (Kcal/mol)	rmsd/ub	rmsd/lb
Tangeritin_uff_E=556.89	-5.7	0	0
Tangeritin_uff_E=556.90	-5.4	9.108	3.393
Tangeritin_uff_E=556.91	5.3	7.884	2.187
Tangeritin_uff_E=556.92	-4.9	33.138	29.191
Tangeritin_uff_E=556.93	-4.9	7.958	2.521
Tangeritin_uff_E=556.94	-4.9	33.723	29.442
Tangeritin_uff_E=556.95	-4.8	34.562	32.078
Tangeritin_uff_E=556.96	-4.8	16.347	14.342
Tangeritin_uff_E=556.97	-4.8	15.063	13.877

3 Results and Discussion

Nowadays *in silico* molecular docking is considered as an important method to find potential drug candidature. Computational screening offers the advantage of rapid, convenient, and cost-effective testing. Virtual screening suggested a mechanism of binding receptor proteins to molecules (Skariyachan et al. 2020). In virtual docking, the binding affinity score is calculated. Docked structures with the least binding energy and highest binding affinity were considered as the most stable structures. Current study results revealed that Diosmetin, Tangeritin, and Anthocyanidins showed binding affinity in the range of -5.2 to -7.0 kcal/mol with the target molecule (Tables 2, 3, and 4). Molecular docking studies revealed that among studied ligands diosmetin exhibited the highest binding affinity of -7.0 kcal/mol. Diosmetin interacts with Arg123, Phe138, Ser93, Ala96,

and Leu126 residues of influenza haemagglutinin. While anthocyanidin interacts via Leu126, Ala96, Val100, and Phe119.136 residues of target protein whereas tangeritin formed interactions with Ileu140, Val100, Arg123, and Leu126 of haemagglutinin. The docked pose of ligand and haemagglutinin (PDB ID: 1HTM) receptor has been shown in Figures 2, 3, and 4. Du et al. (2021) investigated the anti-influenza activity of an imidazopyridine based compound to inhibit the activity of group 2 IAVs and suggested it as a promising drug candidate. They also conducted *in silico* molecular docking interactions of their novel compound against hemagglutinins protein receptors (Du et al. 2021). In addition, Makau et al. (2017) explored the utility of 4-hydroxyquinolinone compound to inhibit the replication of the influenza virus and docked the said molecule against NP monomer (PDB ID: 2IQH) receptor protein (Makau et al. 2017). Results of the current study are also in agreement with an earlier study by Liu et al. (2015) who reported that quercetin, chlorogenic acid, oleanolic acid, and baicalein were potential inhibitors for neuraminidase of H7N9. Further, Behera et al. (2012) reported that B-Sialic acid and O-Sialic acid potentially inhibited both Hemagglutinin and Neuraminidase receptors from Influenza. Paramivir, Aramivire, Munimivire, and Anamivire were also reported as inhibitors for neuraminidase of H7N9 (Khan et al. 2017). Moreover, Sadati et al. (2019) reported that some

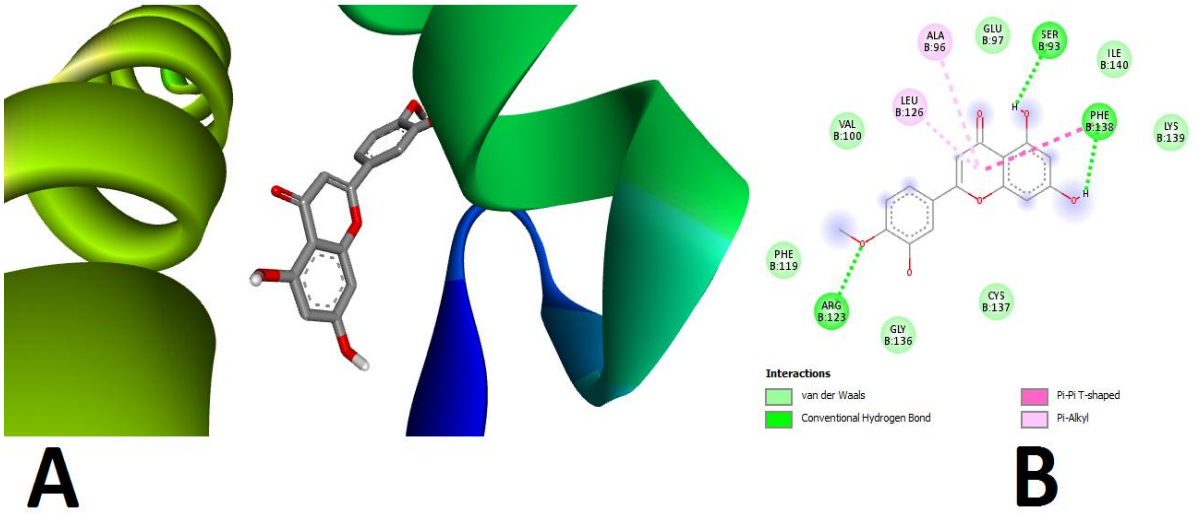

Figure 2 The molecular docking of Influenza Haemagglutinin and Diosmetin (A) Best binding mode in the pocket of protein; (B) The interacting amino acid of the target with ligand

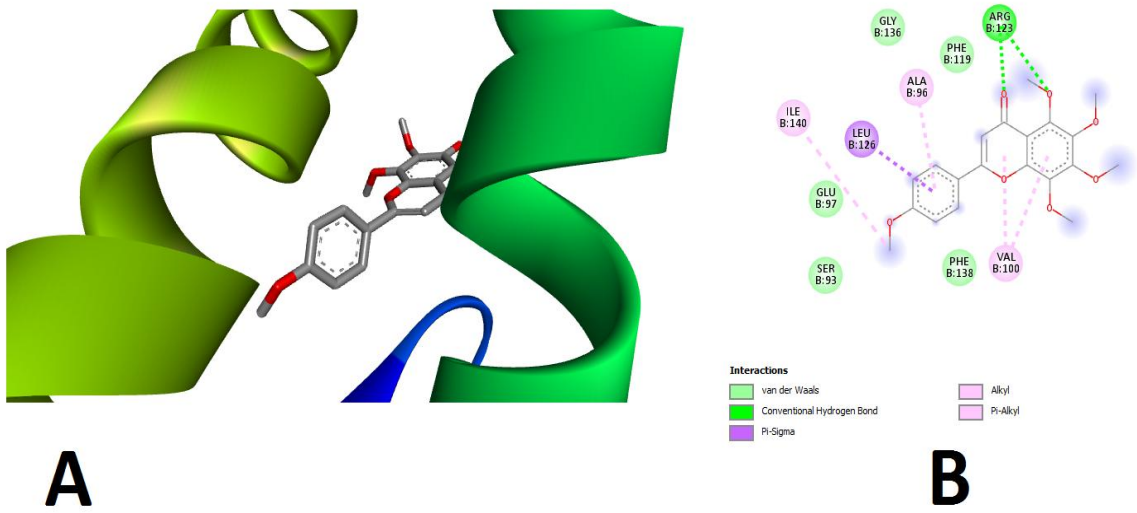

Figure 3 The molecular docking of Influenza Haemagglutinin and Tangeritin (A) Best binding mode in the pocket of protein; (B) The interacting amino acid of the target with ligand

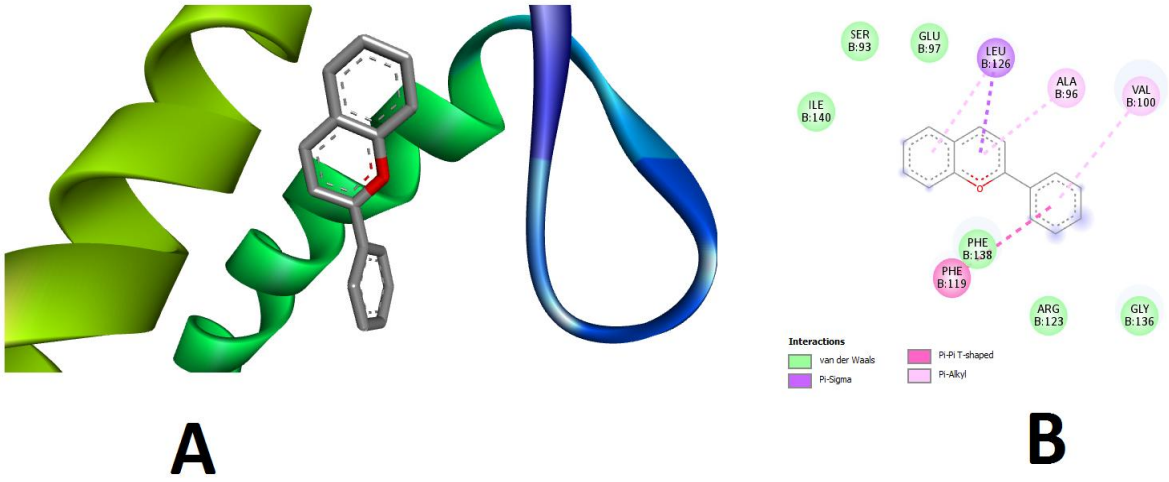

Figure 4 The molecular docking of Influenza Haemagglutinin and Anthocyanidins (A) Best binding mode in the pocket of protein; (B) The interacting amino acid of the target with the ligand

Table 5 Best binding affinity and interacting residues of studied ligands with Influenza Haemagglutinin

S. N.	Ligands	Binding Affinity (kcal/mol)	Interacting residues
1	Diosmetin	-7.0	Ser93, Phe138, Ala96, Leu126, Arg123
2	Tangeritin	-5.7	Arg123, Ala96, Leu126, Ile148, Val100
3	Anthocyanidins	-6.7	Leu126, Ala96, Val100, Phe138

flavonoids i.e. kaempferol, quercetin, luteolin, catechin, luteolin, hispidulin, chrysin, and vitexinmay act as anti-influenza agents. Recently Bui et al. (2022) reported natural alkaloids i.e. Berberine, lycorine, hemanthamine, aloperin, and dendrobine act as anti-influenza agents. Similarly, in silico docking studies of compounds as anti-influenza agents were reported in the literature (Hariyono et al., 2021; Mtambo and Kumalo 2022; Abdullahi et al., 2022a, b). Table 5 represented an overview of the current study and highlights top binding affinities and majorly interacting amino acid residues.

Conclusion

Influenza is considered to be an emerging viral infection in birds, humans, and various other mammals. Recent mutations in the structure of the virus further result in the development of drug resistance. Therefore, such drug resistance-based incidents are always to known initiate novel therapeutic agents with promising health benefits. The results of the present study explored molecular docking interactions between ligands (Diosmetin, Tangeritin, and Anthocyanidins) and the HA protein of IAV. In the present study, molecular interactions between HA protein and chosen phytochemicals were found in the range of -5.2 to -7.0 Kcal/mol. Therefore, naturally occurring metabolites can be studied in the future to design novel anti-IAV agents

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