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In silico discovery of drug compounds against envelope protein of Zika virus

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Abstract
Zika virus (ZIKV) is one of important emerged pathogen of the genus flavivirus causes Guillain-Barr´s syndrome and microcephaly in fetus and newborns, which is major concern across the globe. Envelope (E) protein is responsible for viral entry, represents a major target for neutralizing antibodies and, hence, could serve as potential target for drug screening. As there are no approved drugs available for treatment of Zika virus till today, this study was carried out with objective of discovery of novel drugs against this virus. The envelope protein (E) of the virus and 1050 phytochemicals was retrieved from protein database and pubchem database. The protein ligand interactions were performed through virtual screening by PyRx and Drug Discovery Studio. Further, *In silico* ADMET and Density function theory (DFT) studies were performed to find out the final hit compounds. Four compounds such as Catechin (-7.6 kCal/mol), Apegenin-7-O-beta-glucopyranoside (-7.5 kCal/mol), Baicalin (-7.4 kCal/ kCal/mol) and Madecassic acid (-7.1 kCal/mol) showed highest binding affinity against E protein. Therefore, this study would provide basic information to develop promising antiviral drugs against Zika virus in nearest future.

Keywords: Zika virus, envelop protein, PyRx, drug discovery studio

1. Introduction
Zika virus (ZIKV) is a mosquito-borne re-emerging deadly pathogen, belonging to the genus *Flavivirus* under the family *Flaviviridae*, causes global public health due to its association with significant neurological and developmental complications (Badshah *et al*., 2019) [1]. It is mainly transmitted by *Aedes aegypti*, widely distributed in tropical and subtropical regions; however the vertical transmission from mother to fetus was occurred through sexual contact, blood transfusion and organ transplantations (Barzon *et al*., 2016) [2]. This spherical enveloped virus is of 50 nm diameter with positive sense, single-stranded RNA of genome size of 10.8 kilobases. The viral RNA primarily translates a single polyprotein, that encodes three structural proteins including capsid (c), membrane (M) and envelope (E), along with seven non-structural proteins comprising NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5 (Li *et al*., 2022). The envelop (E) protein, being a major surface glycoprotein, serves as primary immunogenic determinant of the virus, contributing the binding and fusion of receptor with the host cell (Sangeetha *et al*., 2020) [16]. Heparan sulfate and C-type (calcium-dependent) lectin have been reported with an affinity to attach with the Zika virus receptor. The first Zika virus infection was detected in 1947 in a sentinel rhesus monkey, captivated in the Zika forest of Africa and subsequently isolated from *Aedes africanus* mosquito in 1948. In 2016, the World Health Organisation (WHO) declared Zika Virus infection associated with microcephaly and other neurological conditions, as a Public Health Emergency of International Concern (Sahoo *et al*., 2019) [6]. The zika virus infection is primarily characterized by fever, skin rash, conjunctivitis, arthralgia, myalgia and headache with major complications of microcephaly and congenital anomalies in newborns, stillbirth or premature birth in pregnant women and Guillain-Barré syndrome, neuropathy and myelitis in older children, posing a potential public health threat. Despite several serious health implications, the diagnosis, treatment and prophylaxis of Zika-Virus remain challenging (Sahoo *et al*., 2019) [6]. Further, only some non virus-specific drug such as galidesivir, BCX4430, and ribavirin have been identified against this disease (Sahoo *et al*., 2022) [18], but these drugs don't provide specific effect against ZIKV. As there is no specific antiviral treatment against ZIKV, this study was carried out with objective of development of a specific and reliable antiviral drug against the Zika virus.

2. Materials and Methods

2.1 Preparation of protein targets and phytochemicals

The three dimensional structure of envelop (E) protein (PDB 5JHM) of Zika virus was retrieved from Protein Data Bank (PDB). Similarly, three dimensional structures of drug compounds (1054) were retrieved from various databases such as Pubchem and Drug bank (Sahoo *et al*., 2021) [12].

2.1 Virtual screening

Virtual screening was performed to filter the drug compounds upon PyRx 0.8. All the drug compounds were retrieved from Drug bank in SDF format through open babel of PyRx and energy minimization of all ligands were performed with conversion ligands into AutoDock PDBQT format. Further, these ligands were subjected to docking against E protein of ZIKV using AutoDock Vina in PyRx 0.8 (Sahoo *et al*., 2020) [10].

2.2 **Estimation of ADMET properties:** The absorption, distribution, metabolism, excretion and toxicity of the drugs were assessed through ADMETlab 2.0. "Lipinski's Rule of Five" and Parameters like polar surface area (PSA), cytochrome P450, hepatotoxicity, blood brain barrier (BBB), and atom-based Log P98 (A LogP 98) were also determined to determine the best antiviral compound against Zika virus (Xiong *et al*., 2021) [17].

3. Result

Virtual screening of 1054 drug compounds showed promising hydrogen bond interaction with amino acids of the E protein at the active site and it was found that apigenin-7-O-beta-D-glucopyranoside, baicalein catechin curcumin, ellagic acid, lopinavir, madecassic_ acid, ponapensin, and neoandrographolide showed binding energy of more than -6.0 kcal/mol. Among 9 compounds, four compounds such as apigenin-7-O-beta-D-glucopyranoside, baicalein, catechin and madecassic acid resulted docking energy of more than -7.0 kcal/mol suggesting potential drug compounds against Zika virus (Table 1).

Table 1: Binding energy for the interaction of compounds with ZIKV Envelope (E) protein

No	Ligand	Binding Energy Score		Inhibition Constant (µM)
		Active site based virtual screening (kcal/mol)	Molecular docking (kcal/mol)	
1.	Apigenin-7-O-beta-D-glucopyranoside	-10.1	-7.5	2.54
2.	Baicalin	-8.5	-7.3	3.03
3.	Catechin	-10.4	-7.6	1.80
4.	Curcumin	-7.5	-6.6	10.76
5.	Ellagic_Acid	-7.6	-6.7	11.41
6.	lopinavir	-7.1	-6.0	34.35
7.	Madecassic_acid	-8.2	-7.1	3.67
8.	Neoandrographolide	-7.0	-6.3	22.55
9.	Ponapensin	-7.9	-6.7	9.56

Apigenin-7-O-beta-D-glucopyranoside showed intearction with the amino acids Asn 134, Thr 170, Ser 173, Ala 176, Glu 136, Leu 135, Glu 177 of E protein. Similarly, Baicalin interacted with aminoacids such as Gln 131, Pro 132, Ser 199, Ile 130, Leu 196, Pro 171, Pro 192. However, Catechin interacted with aminoacids such as Thr 366, Phe 183, His 144, Ala 361, Asn 362, Lys 373, Met 374, Val 143 and Madecassic acid showed interaction with Leu 196, Asn 172, Arg 193, Pro 171 aminoacids (Table 2).

Table 2: Molecular Interaction of compounds with ZIKV E protein

No	Drug Compunds	Predicted amino acid residues within active site of COMT (distance ≤3 Å	Predicted H-bond residues	Bond	Distance between atoms (Å)
1.	Apigenin-7-O-beta-D-glucopyranoside	Asn 134, Thr 170, Ser 173, Ala 176, Glu 136, Leu 135, Glu 177	Asn 134	HN---O	3.22
			Thr 170	OH---O	2.80
			Glu 136	O----HO	2.44
2.	Baicalin	Gln 131, Pro 132, Ser 199, Ile 130, Leu 196, Pro 171, Pro 192	Gln 131	HN---O	3.23
3.	Catechin	Thr 366, Phe 183, His 144, Ala 361, Asn 362, Lys 373, Met 374, Val 143	His 144	HN---O	1.93
			Ala 361	HN---O	2.39
			Asn 362	HN---O	2.04
			Lys 373	HN---O	2.71
4.	Curcumin	Gln 261, Ala 268, Trp 217, Pro 222, His 214, Ala 264	Gln 261	HN---O	2.52
5.	Ellagic_Acid	Asn 163, Tyr 305, Asn 362, His 144, Lys 301, Phe 183, Val 364, Lys 301, Val 143	Asn 163	HN---O	3.23
6.	lopinavir	Trp 217, Ala 272, Val 213, Ile 221, Ala 264, Val 265, Ala 268	Trp 217	N---O	2.90
			Ala 272	N---O	3.16
7.	Madecassic_acid	Leu 196, Asn 172, Arg 193, Pro 171	Leu 196	N---O	2.40
			Asn 172	HN---O	3.63
			Arg 183	HN---O	3.58
8.	Neoandrographolide	Ser 199, Glu 191, Pro 132	Ser 199	OH---O	3.03
			Glu 191	OH---O	2.22
9.	Ponapensin	Asp 197, Pro 132, Pro 174, Pro 192, Arg 193	Asp 197	OH---O	4.2

Further, apigenin-7-O-beta-D-glucopyranoside, baicalein, catechin and madecassic acid resulted 3,1,4,3 number of classical hydrogen bonds with E protein. The two and three dimensional autodock result of nine drug compounds with E protein was visualized and presented in Fig 1 & 2 respectively.

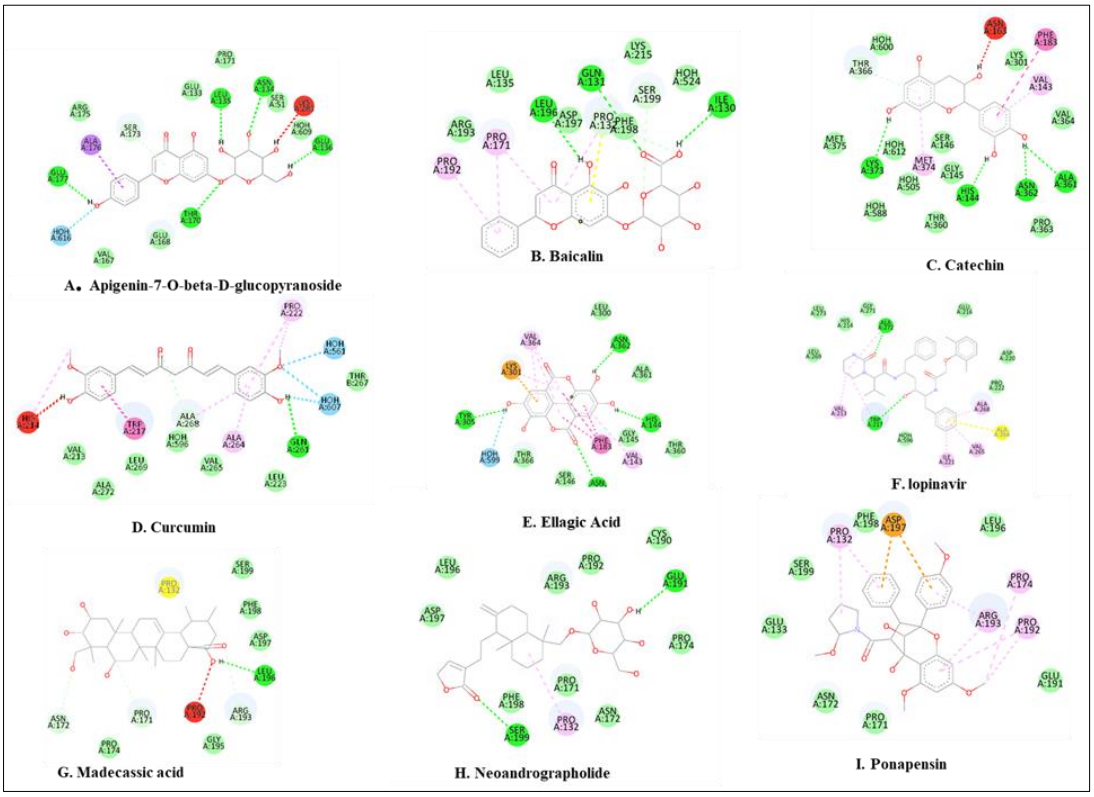

Fig 1: 2 D diagram model showing interactions drug compounds with E protein

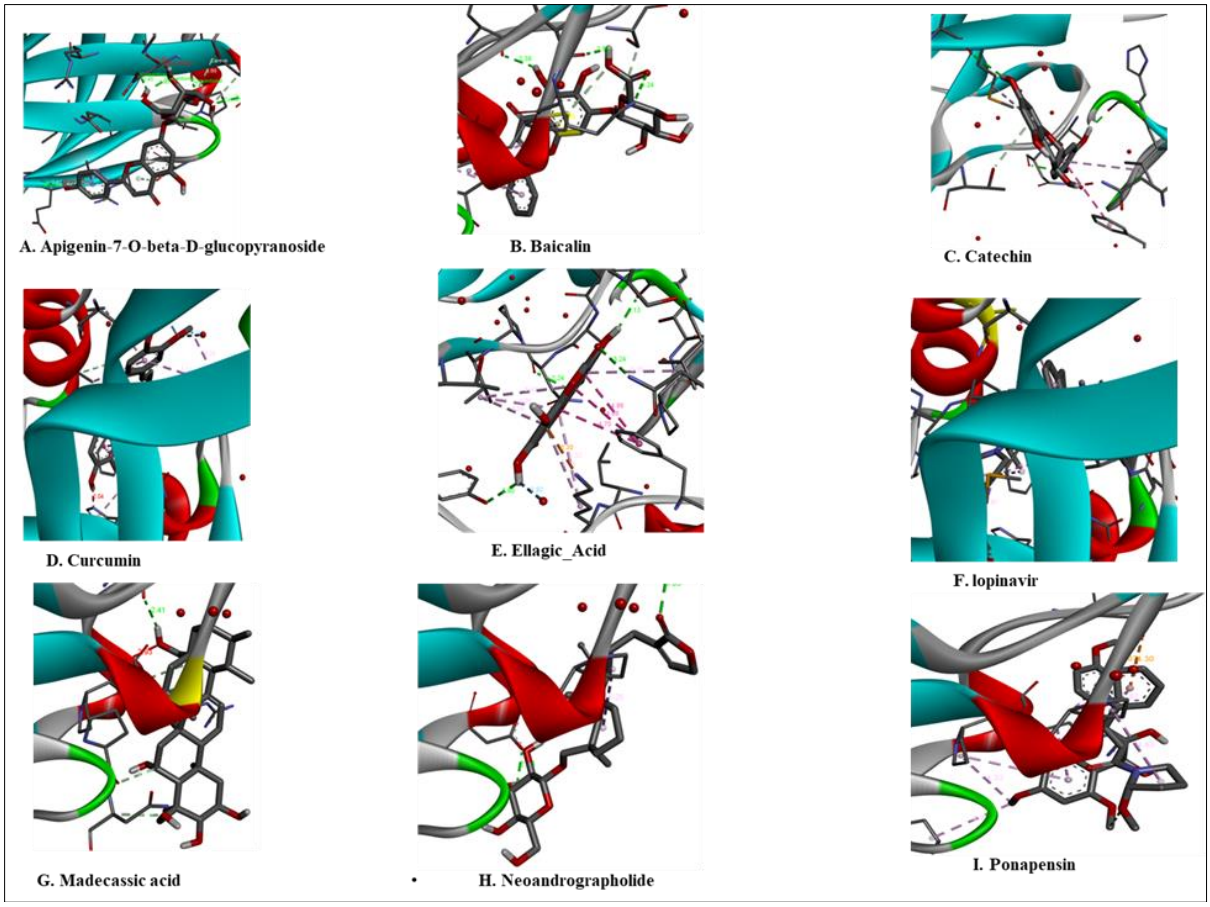

Fig 2: 3 D diagram model showing interactions of drug compounds with E protein

Further, four screened compounds showed normal PSA limits and optimal Lipinski Rule (Table 3).

Table 3: Physiochemical properties of identified lead compounds

Ligand	Molecular Weight (g/mol)	Hydrogen bond acceptor	Hydrogen Bond donor	Topological Polar Surface Area (TPSA) (Å²)	Lipinski Rule	Pfizer Rule	Consensus Log PPo/w
Apigenin-7-O-beta-D-glucopyranoside	432.11	10	6	170.05	Accepted	Accepted	1.731
Baicalin	446.08	11	6	187.12	Accepted	Accepted	1.288
Catechin	290.08	6	5	110.38	Accepted	Accepted	1.343
Curcumin	368.13	6	2	93.06	Accepted	Accepted	2.596
Ellagic_Acid	302.01	8	4	141.34	Accepted	Accepted	0.796
lopinavir	628.360	9	4	120.0	Accepted	Accepted	4.943
Madecassic_acid	504.35	6	5	118.22	Accepted	Accepted	1.504
Neoandrographolide	480.27	8	4	125.68	Accepted	Accepted	2.252
Ponapensin	561.24	9	2	106.92	Accepted	Accepted	3.742

Additionally, all four drug compounds resulted optimal ADME properties like PSA, Alog P98, absorption, aqueous solubility, blood brain barrier level, hepatotoxicity, and CYP2D6 within the limit (Table 4). The tested compounds were found to be moderately hydrophilic, hence suggesting a good bioavailability of the compounds. On the other hand, all the compounds showed non-hepatotoxic, non skin allergy and no AMES toxicity.

Table 4: ADMET and toxicity profile of the leads identified against E protein

	Absorption			Distribution		Metabolism		Excretion	Toxicity		
	Water solubility Log S	Caco-2 Permeability x 10-6	Human Intestinal Absorption (%)	VDss (human)	BBB Permeability	CYP450 1A2 Inhibitor	CYP450 2C9 Substrate	Total clearance (ml/min/kg)	AMES toxicity	Skin sensitization	Hepatoxicity
Apigenin-7-O-beta-D-glucopyranoside	-3.582	6.231	65.7	0.904	0.022	0.046	0.06	2.901	No	No	No
Baicalin	-3.813	6.283	48.8	0.72	0.038	0.05	0.143	1.013	No	No	No
Catechin	-2.739	6.052	85.0	0.656	0.029	0.036	0.818	17.03	No	No	No
Curcumin	-4.611	4.852	63.0	0.321	0.148	0.792	0.976	12.8	No	No	No
Ellagic_Acid	-4.027	5.394	43.7	0.693	0.014	0.922	0.473	3.724	No	Yes	Yes
lopinavir	-4.46	5.438	58.8	1.312	0.009	0.324	0.345	9.19	No	No	Yes
Madecassic acid	-3.583	5.757	71.34	0.497	0.067	0.009	0.153	1.919	No	No	No
Neoandrographolide	-3.663	4.996	39.9	1.25	0.088	0.021	0.047	1.539	No	Yes	No
Ponapensin	-5.137	5.155	23.89	1.032	0.249	0.014	0.315	7.836	Yes	No	Yes

4. Discussion

The ZIKV virus poses a major risk to the public, and the lack of effective antiviral medications highlights the necessity of finding new leads. *In silico* identification of potential drug candidates against the Zika virus (ZIKV) represents a promising avenue for addressing the challenges posed by this re-emerging pathogen (Baz & Boivin, 2019) [3]. Envelop protein is crucial for the synthesis of viral polyproteins and the zika virus entry into the host (Saiz & Martín-acebes, 2017) [15]. This study found apigenin-7-O-beta-D-glucopyranoside, baicalein, catechin and madecassic acid demonstrated significant binding interactions with the E protein (Sahoo & Singh, 2014) [13]. It might be due to presence of conserved amino acid residues in E protein that revealed critical interactions with drug compounds suggesting their potential to inhibit viral replication (Sahoo *et al*., 2023) [14]. These four compounds exhibit higher interaction energy than the other compound with E protein. It might be due to release of more exothermic energy during protein drug interaction (Sahoo, Mohapatra, *et al*., 2018) [7]. Additionally, the evaluated leads demonstrated significant molecular interactions, quantum chemical properties, and desirable pharmacokinetic characteristics by ADMET. It highlighted the drug-like properties including high solubility, low toxicity, and good bioavailability of these four compounds, suggesting remarkable drug against ZKV (Julander *et al*., 2021) [4]. Notably, apigenin-7-O-beta-D-glucopyranoside exhibited highest target affinity and minimal predicted off-target effects, underscoring its potential as a lead candidate (Sahoo, *et al*., 2018) [7]. Despite these encouraging findings, several challenges are still there during development a specific antiviral against zika virus.

5. Conclusions

This insilco method provides a cost-effective and efficient means of drug discovery; the predictions require experimental validation to confirm efficacy and safety. Future work should be carried in invitro and *in vivo* model to validate the inhibitory effects of the identified compounds against ZIKV replication and their pharmacokinetics and toxicity profiles should be accessed in biological systems. Additionally, structural variability in ZIKV strains and potential drug resistance mechanisms should be considered to ensure the robustness of the identified candidates

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7. References

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