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ORIGINAL ARTICLE

Molecular Docking and Density Function Theory Studies of Compounds from *Euphorbia hirta* and *Bacopa monnieri* to Zika Virus Structural and Nonstructural Proteins

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ABSTRACT

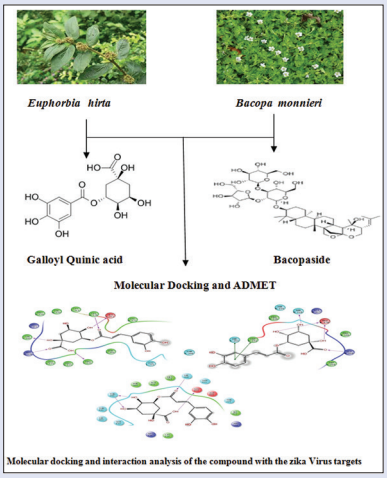
Background: Zika virus is an arbovirus belongs to the genus flavivirus and pose a serious global threat. The recent 2015 outbreak in Brazil was associated with a significant increase in microcephaly cases and other neurological complications in newborn babies and WHO declared Zika to be an international public health emergency. Currently, there is no specific treatment or Vaccine available for the Zika virus, and thus due to the unavailability of the antiviral drugs, the need for the identification of novel drugs is paramount. **Materials and Methods:** The compounds from two medicinal plants (*Bacopa monnieri* and *Euphorbia hirta*) were selected for the *in silico* molecular docking studies against the structural and nonstructural proteins of Zika virus. Quantum–chemical parameters density functional theory and absorption, distribution, metabolism, and excretion-toxicity (ADMET) was performed to identify the drug-likeliness properties. **Results:** Among the tested compounds, galloylquinic acid, Bacopaside III, and Bacopaside A were identified as leads against multiple targets of Zika virus. The identified compounds also exhibited desirable quantum chemical and ADMET properties. **Conclusion:** Hence, the compounds hampering the active site of the three different proteins playing a prime role in replication and fusion with desirable pharmacokinetic properties could be suggested for further *in vitro* and *in vivo* analysis of Zika virus.

Key words: Absorption, distribution, metabolism, and excretion-toxicity, density function theory, molecular docking, Zika virus

SUMMARY

- About 32 compounds from two plants namely, Bacopa monneri and Euphorbia hirta were subjected for molecular docking against Non Structural proteins (NS1 and NS3) and the structural protein (Envelope protein Domain III) in Discovery studio V 4.0. Pharmacokinetic properties were predicted by ADMET. The compounds Galloylquinic acid, Bacopaside III and Bacopaside A were identified as leads against multiple targets and hence could be suggested for further *in vitro* and *in vivo* analysis.

Abbreviations used: WHO: World Health Organization; DFT: Density function theory; ADMET: Absorption, distribution, metabolism, and excretion-toxicity; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; HSV: Herpes simplex virus; PDB: Protein data bank; OPLS: Optimized potential for liquid simulations; RMSD: Root-mean-square deviation; IFD XP: Induced fit docking extra precision; XP: Extra precision; PSA: Polar surface area; BBB: Blood brain barrier; A LogP 98: Atom-based Log P98; HOMO: Highest occupied molecular orbital; LUMO: Lowest unoccupied molecular orbital; DS V 4.0: Discovery Studio version 4.0; NS3: Nonstructural protein 3; NS1: Nonstructural protein 1



Molecular docking and interaction analysis of the compound with the zika Virus targets

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INTRODUCTION

Zika virus ,an arbovirus belongs to the genus flavivirus poses a serious global threat. Zika virus was first isolated from a Macaca monkey in 1947 in Zika Forest near Entebbe, Uganda.[1] Zika virus generally causes mild disease with most common symptoms of fever, rash, joint pain, and conjunctivitis, however, microcephaly and Guillain-Barre syndrome are reported in the fetuses of the infected mother through prenatal transmission.[2-5]

During the Zika outbreak in French Polynesia, an unusual increase in the number of neurological and autoimmune complications was identified. The French Polynesian outbreak spread to other Pacific islands, and autochthonous cases have been reported in New Caledonia (1400 confirmed cases), Cook Islands (932 suspected cases, 50 confirmed)

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Fiji, Samoa, and Solomon Islands.[6-10] The lack of antiviral drugs and the licensed vaccine to treat the disease necessitates the development of drugs to ZIKA virus.

Medicinal plants in the treatment of specific ailments have been in existence for several centuries. The novel scaffolds of the plants and their wide complex chemical constituents provide the source for the synthesis of new drugs. Antiviral studies of certain Indian plants specific to particular viruses, namely, *Phyllanthus niruri (HBV), Glycyrrhiza glabra (HCV), Phyllanthus niruri, Aristolochia indica, Cassia occidentalis, Phyllanthus niruri, Withania somnifera, Tinospora cordifolia, Camellia sinenis, Calophyllum spp, Glycyrrhiza glabra, Phytolacca americana, trichosanthes, Kirilowii, Calophyllum, lanigerum (HIV), Sarracenia purpurea, Glycyrrhiza glabra, Rhus chinensis and Rhus javanica, Punica granatum (HSV), Phyllanthus emblica,* and *Sophora* spp. (Coxsackie B virus) has been carried out for few viruses, however, this cannot be concluded as exhaustive.[11-23] Thus, it is constructive to identify the antiviral compounds against emerging Zika virus where the approved drug is unavailable. Hence, the compounds from two medicinal plants already in medicinal practice in India were selected for the *in silico* molecular docking studies against the structural and nonstructural proteins of Zika virus.

Bacopa monnieri is a perennial plant and possesses triterpenoid saponins called bacosides. It had proven antioxidant, hepatoprotective, and neuroprotective activity. Furthermore, earlier studies had demonstrated mechanism of action in acetylcholinesterase inhibition, choline acetyltransferase activation, β-amyloid reduction, increased cerebral blood flow, and monoamine potentiation.[24]

Euphorbia hirta belongs to the genus Euphorbiaceae and possess wide pharmacological activities such as antibacterial, antimalarial, anti-inflammatory, antiasthmatic, antidiarrheal, antioxidant, antifungal, and antiamoebic activity.[25] Thus, in this study, the compounds reported in the plants of *B. monnieri* and *E. hirta* were subjected for *in silico* molecular docking against the structural and nonstructural targets of Zika virus and furthermore absorption, distribution, metabolism, and excretion-toxicity (ADMET), density function theory (DFT) were undertaken to study the suitability of the compounds both in the biological and chemical standpoint.

MATERIALS AND METHODS

Compounds

Structures of Bacopaside I, Bacopaside II, Bacopaside III, Bacopaside IV, Bacopaside V, bacoside, pseudojujubogenin reported in *B. monnieri* and the structures of β-Sitosterol, campesterol, stigmasterol, geranin, 1,2,3,4,6-penta-O-galloyl-β-D glucose, euphorbin-B, euphorbin–D, heptacosane, nonacosane, shikimic acid, choline, camphol, alpha-amyrin, beta-amyrin, campesterol, cycloartenol, euphorbol hexacosaote, friedelin, galloylquinicacid, geranin, leukocyanidin, quercitol, taxaxerol, taxaxerone, tetramethyl-2 hexadecen-ol from *E. hirta* were retrieved from PubChem, ChemSpider in Mol format. For each ligands, conformational search and optimization were carried out using CharmMM Force field.

Molecular docking

Receptor grid generation

The proteins for NSP3 (PDB ID: 5JRZ), NSP1 (PDB ID: 5K6K), and envelope protein Domain III (PDB ID: 5KVD) were retrieved from PDB and prepared. The prepared proteins were calculated for the receptor grids so that the ligands could bind within the predicted active site. The parameters of van der Waals scaling factor 1.00 and charge cutoff 0.25 were kept as default subjected to optimized potential for liquid simulations 2001 force field. A cubic box of specific dimensions was set around the centroid of the active site residues. The bounding box dimensions of 14 Å ×14 Å ×14 Å was placed for docking experiments.

Induced fit docking extra precision

Induced fit docking (IFD) extra precision (XP) was performed using the module-Induced Fit Docking of Schrodinger-Maestrov 9.1, LLC, New York. The entire receptor molecule constrained minimized with a root-mean-square deviation cutoff of 0.18 Å was selected for generation of centroid of the residues, and the box size was generated automatically. The initial Glide docking for each ligand was carried out. Side chains were trimmed automatically based on B-factor, with receptor and ligand van der Waals scaling of 0.70 and 0.50, respectively, and the number of poses generated were set to be 20. Prime side chain prediction and minimization were carried out in which residues were refined within 5.0 Å of ligand poses and side chains were optimized. This leads to a ligand structure and confirmation that is induced fit to each pose of the receptor structure. Finally, Glide XP redocking was carried out into structures within 30.0 kcal/mol of the best structure, and within the top 20 structures overall. The ligand was rigorously docked into the induced-fit receptor structure and obtained the XP score.[26,27]

Absorption, distribution, metabolism, and excretion-toxicity

ADME and toxicity studies was performed in Discovery studio(DS) v4.0 ,Dassault systems,BIOVIA by considering the parameters such as Atom-based Log P98 (A LogP 98), polar surface area (PSA), blood-brain barrier (BBB), cytochrome P450, and hepatotoxicity.[28-32]

Density functional theory studies

DFT was carried out for the screened compounds to study the orbital energies (highest occupied molecular orbital [HOMO] and lowest unoccupied molecular orbital [LUMO]), energy gap and the dipole moment using $DMOL^3$/B3 LYP in DS V 4.0.[33-36]

RESULTS

Molecular docking

Among the compounds that were subjected for molecular docking using Schrodinger, 1,2,3,4,6-penta-O-galloyl-b-D-glucose showed highest Glide energy to the targets nonstructural protein 3 (NS3), nonstructural protein 1 (NS1), and E1 domain and XP bond followed by galloylquinic acid to NS3 and NS1. Likewise, compounds bacoside A and leukocyanidin showed higher binding energy and XP bond to envelope protein. Besides, the other compounds also exhibited equally higher binding energies, and the amino acid interaction profile of the compounds are represented in Tables 1 and 2.

Interaction analysis of compound -1,2,3,4,6-penta-O-galloyl-b-D-glucose virus proteins

The compound 1,2,3,4,6-penta-O-galloyl-b-D-glucose interacted with a promising docking score of −11.32 and the Glide binding energy of −72.277 against the target NS3 of Zika virus protein. The backbone amino acids Arg 211, Glu 213 interacted by hydrogen bond interactions with the galloyl moiety of the compound. Side-chain hydrogen bond interactions occurred with the OH group of other galloyl moieties at Glu 187 and Glu 123. The Glide energy against the target envelope protein was −94.77 and Glide score of −13.24 and backbone hydrogen bond interaction was observed between the galloyl moiety and Lys 277. Furthermore, other six side chain interactions occurred between the OH group of galloyl moieties and the amino acids Glu 224, Lys 206, Asp 208, Ser 176, and Ser 228. Likewise, for the target NSP1, two hydroxyl groups and one oxygen group of galloyl moiety interacted with aminoacid

Table 1: Molecular docking of the compounds against the Zika virus protein targets

Compounds	NS3			NS1			Envelope protein domain III		
	Glide Gscore	Glide energy	XP Gbond	Glide Gscore	Glide energy	XP Gbond	Glide Gscore	Glide energy	XP Gbond
1,2,3,4,6-penta-o-galloyl-b-D-glucose	−11.382	−72.277	−5.355	−11.620	−75.777	−4.058	−13.248	−94.775	−7.462
Galloylquinic acid	−8.292	−55.274	−4.615	−7.368	−39.026	−2.029	−7.972	−42.958	−3.360
Bacopaside IV	−7.236	−39.216	−3.907	−6.391	−47.341	−2.791	-	-	-
Bacopaside V	-	-	-	−6.485	−48.976	−3.595	−7.441	−56.612	−3.840
Leucocyanidin	−6.593	−42.121	−3.109	-	-	-	−8.772	−43.560	−3.089
Bacoside A	−6.485	−48.380	−4.192	-	-	-	−11.038	−68.709	−3.607
Geranin	−6.294	−53.670	−2.716	−5.521	−47.427	−3.377	−7.353	−53.911	−2.620
Bacopaside III	−5.909	−36.625	−1.920	-	-	-	−7.998	−63.525	−3.016
Quercitol	−5.904	−27.604	−2.662	−5.316	−26.770	−1.920	-	-	-
Shikimic acid	-	-	-	−5.038	−21.708	−1.326	-	-	-

NS3: Nonstructural protein 3; NS1: Nonstructural protein 1; XP: Extra precision

Table 2: Hydrogen bond interaction profile of the compounds against the Zika virus protein targets

Compound	NS3	NS1	Envelope protein domain III
1,2,3,4,6-penta-o-galloyl-b -D-glucose	Glu 123, Ser 122, Arg 228, Arg 211, Glu 187	Glu 224, Lys 206, Asp 208, Ser 228, Lys 227	Leu 430, Arg 226, Asp 410, Glu 413, Glu 392, Arg 388, Asp 291, Asp 540
Galloylquinic acid	Tyr 186, Arg 228, Cyc 128, Glu 213, Pro 120	Glu 178, Ser 228, Lys 206	Thr 290, Hie 288, Glu 413
Bacopaside IV	Ser 116, Ile 117, Ser 208, Thr 131	Lys 206, Asp 208, Asp 240, Tyr 260, Arg 257	
Bacopaside V	-	Glu 178, ser 176, Lys 206, Arg 191, Asn 207, Asp234, Lys 227	Ser 293, Ser 218, Asp410, Asp 540
Leucocyanidin	Glu 213, Arg 228, Val 229, Arg 211	-	Thr 290, Leu 430, Asp 410
Bacoside A	Ser 208, ASN 201, VAL 127, Glu 213	-	Leu 430, Arg 226, Asp 410, Hie 484, Ser 452, Thr 449, Thr 290, Asp 540
Geranin	Arg 228, Glu 213, Pro 227, Val 229	Glu 156, Val 155, Arg 191, Glu 178, Arg 172, Ser 176.	Asp 540, Arg 388
Bacopaside III	Asn 212		Asp 410, Asp 602, Ser 601
Quercitol	Arg 211, Arg 228, Tyr 186.	Trp 210, Trp 232	-
Shikimic acid	-	Trp210, Glu 178, Lys 206	-

NS3: Nonstructural protein 3; NS1: Nonstructural protein 1

residue Leu 430. Other side chain interactions were observed between hydroxyl groups and aminoacids Asp410, Glu 413, Glu 392, Asp 540, ASP 291, and the oxygen group with Arg 388. π–cation interaction was observed between the galloyl moiety and Arg 388 [Figure 1].

Interaction Analysis of compound - galloylquinic acid with Zika virus proteins

Galloylquinic acid interacted with high energy score of −8.292 and Glide energy of −55.274 against NSP3. It extended 5 hydrogen bond interaction with NSP3 of Zika virus. Hydroxyl group of quinic acid moiety interacted both by backbone and side chain interaction with Pro 120, Glu 123, and Tyr 186, respectively. Galloylquinic acid interacted with envelope protein Domain III of ZIKA virus with Glide score of −7.972 and Glide energy of −42.958 and showed hydrogen bond interactions at three different sites. Hydroxyl groups of the quinic acid formed side chain hydrogen bond interactions with amino acids Ser 228 and Glu 178. Galloylquinic acid interacted with NS1 of Zika virus with low Glide energy of −39.026 and Glide score of −7.368. Three hydroxyl groups of quinic acid interacted with Thr 290 and GLN 413 and an oxygen group of gallic acid extended its interaction with HIE 288 [Figure 2].

Interaction analysis of compound - leukocyanidin with Zika virus proteins

Leukocyanidin interacted with NS3 protein of Zika virus with Glide score of −6.593 and Glide energy of 42.12. In addition, it interacted with 5 hydrogen bond interactions. 2-hydroxyl groups of phenyl moiety interacted with Arg 211 through hydrogen bond side chain interaction whereas the two hydroxyl groups of chromene interacted by both backbone and side chain interaction with Glu 213 and Val 229, respectively. In addition, oxygen group of chromene interacted with Arg228.

Similarly, it exhibited higher binding energy and Glide score of −94.775 and −13.24, respectively, against envelope protein Domain III. The hydroxyl group of phenyl moiety interacted by hydrogen bond backbone with Leu 430. Furthermore, a pi-pi stacking was observed at HIS 486. Similarly, 3 hydroxyl groups of chromene interacted with the aminaocid Thr 290 by side chain interaction and with Asp 410 by backbone hydrogen bond interaction and another pi-pi stacking was observed with Phe at 299 [Figure 3].

Interaction analysis of bacopasides with Zika virus proteins

Bacopaside III interacted with NSP3 of Zika virus with higher interaction energy of −36.625 and Glide score of −5.909. The hydroxyl and oxygen group of pseudojujubogenin moiety of the compound interacted with Asn 212 both by backbone and side chain interactions. Furthermore, the OH group of β-D-glucopyranosyl–(1-3)-α-L-arabinopyranosyl interacted with Val 229 [Figure 4].

The hydroxyl group of jujubogenin of Bacopaside A interacted with Glu 213 of NSP3 and ASP 540 of NSP1 by side chain interactions. Likewise,

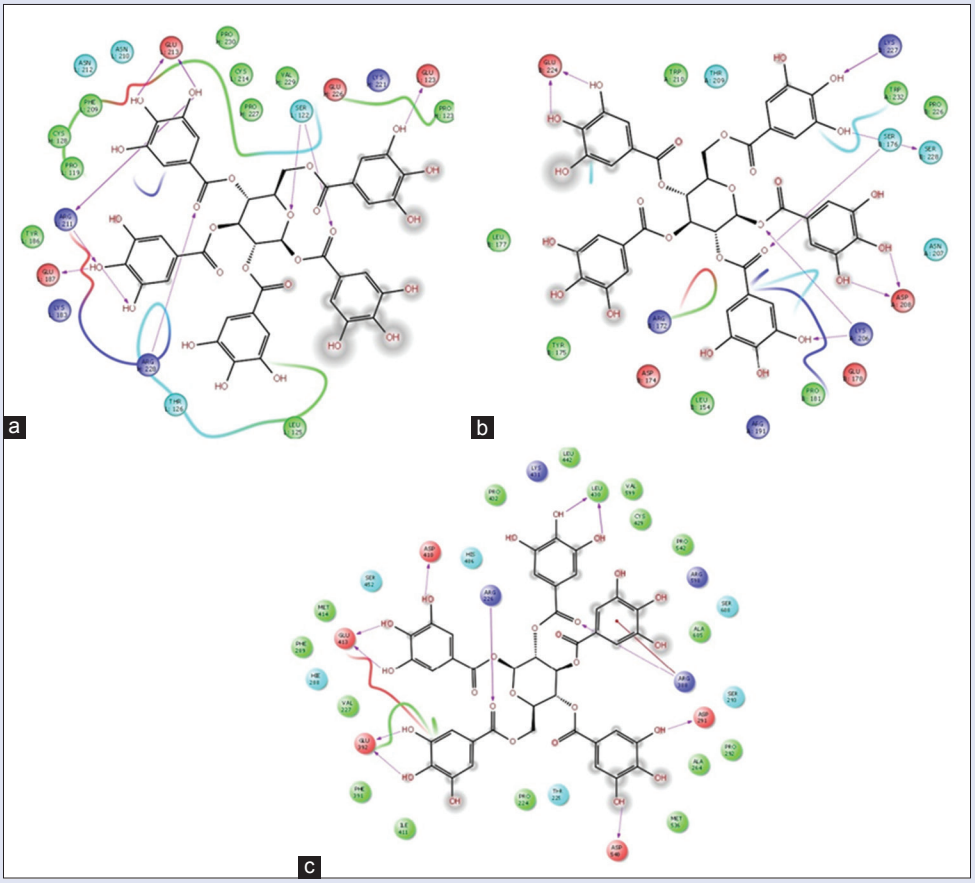

Figure 1: Molecular docking and interaction analysis of compound 1,2,3,4,6-penta-O-galloyl-b-D-glucose with the targets nonstructural protein 3 (a), nonstructural protein 1 (b), and envelope (c) respectively. Hydrogen bond interactions between the amino acids and the ligand molecules are represented by arrows in magenta color

the hydroxyl groups of sugar moieties interacted with Ser 208, Asn 201, Val 127 of NS3 and with ASP 410, Leu 430, Ser 452, and Thr 449 of NSP1 by both side chain and hydrogen bond interaction. Bacopaside IV interacted with both NS3 and NS1whereas Bacopaside V interacted with NS1 and envelope protein Domain III of ZIKA virus and the detailed interaction has been tabulated in Tables 1 and 2.

Thus, in Bacopasides, both the jujobogenin and pseudojujubogenin moiety along with the sugar moieties extended interactions with the multitargets of ZIKA virus.

Interaction analysis of compound quercitol with Zika virus proteins

Quercitol exhibited Glide energy of −26.77 and Glide score of −5.316 against the target NS1 and Glide energy of −27.604 and Glide score of −5.904 to NS3, however, has not shown any interaction with the envelope protein Domain 3 of ZIKA virus. Specific hydrogen bond interactions were observed both at the backbone and side chain between the amino acid residues Arg 211, Tyr 186, Arg 228 of NS1, and OH group of quercitol. Furthermore, both the Arg 211 and 228 interactions were positively charged. Similar interactions were observed between Trp210, Thr 256, and HIE 253 of NSP3 and the hydroxyl group of quercitol.

Density function theory

DFT studies were carried out for the compounds that showed higher binding energies. The Energy gap (ΔE) represents the function of reactivity and thus lower separation energy signifies the higher reactivity of the compounds. The top-ranked or lead compounds 1,2,3,4,6-penta-O-galloyl-b-D-glucose, Bacopaside III, IV, A, galloylquinic acid showed very low separation energies in comparison to other molecules (0.1665, 0.099, 0.192,0.150, 0.156) whereas quercitol and leukocyanidin showed a modest increased energy (0.2981, 0.2022). Hence, the results obtained from molecular orbital energies were highly in association to binding energies of the compounds obtained during molecular docking. The parameters such as HOMO, LUMO, energy gap, dipole movement of the compounds are presented in Table 3.

Absorption, distribution, metabolism, and excretion-toxicity

ADME properties such as PSA, Alog P98, absorption, aqueous solubility, BBB level, hepatotoxicity, and CYP2D6 were studied for the compounds. The intestinal absorption models are represented by 95% and 99% confidence ellipses in the ADMET_PSA_2D and ADMET_Alogp98 plane in which the upper limit are 131.62 and 148.12, respectively. In addition, the absorption of compounds is represented as good (0), moderate (1), poor (2), and very poor (3). Plasma surface area influences the drug transportation and permeability, and the lipophilicity is represented as the logarithm of the partition coefficient between n-octanol and water. Compounds with PSA <140 $A^{°2}$ and A logp98 <5 showed optimum cell permeability. Thus, the compounds leukocyanidin, quercitol, shikimic acid showed the value of PSA (133.82, 104.07, and 100.56, respectively). Similarly, all the compounds showed good log *P* value. Leukocyanidin

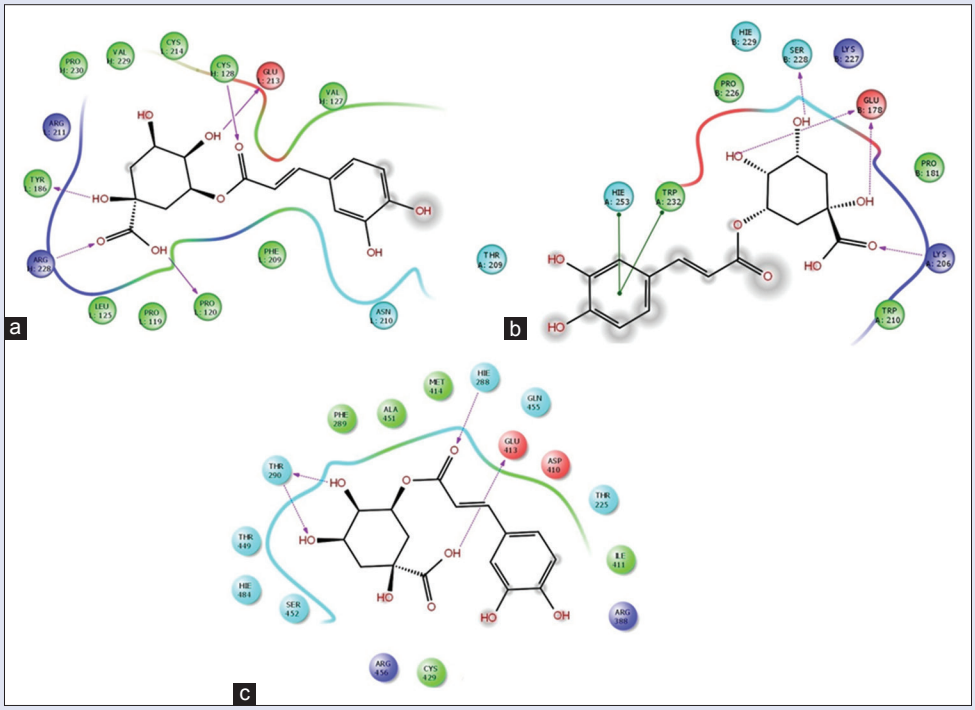

Figure 2: Molecular docking and interaction analysis of compound galloyl quinic acid with the targets nonstructural protein 3 (a), nonstructural protein 1 (b) and envelope (c) respectively. Hydrogen bond interactions between the amino acids and the ligand molecules are represented by arrows in magenta color. Green color arrow represents the pi-pi stacking interactions

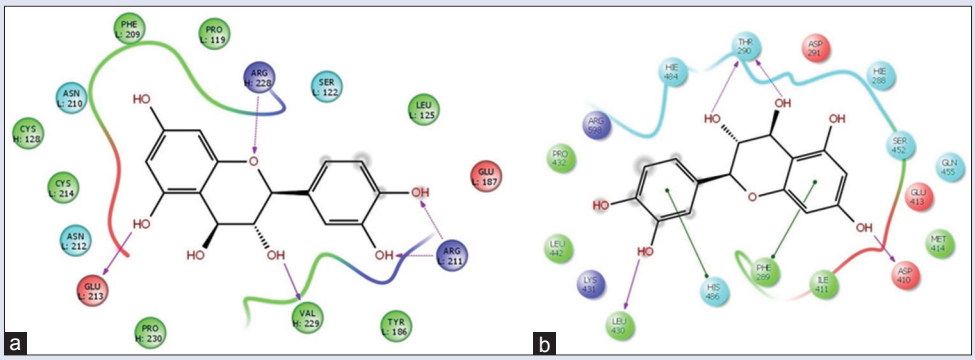

Figure 3: Molecular docking and interaction analysis of compound Leukocyanidin with the targets nonstructural protein 3 (a) and envelope (b) respectively. Hydrogen bond interactions between the amino acids and the ligand molecules are represented by arrows in magenta color. Green color arrow represents the pi-pi stacking interactions

Table 3: Quantum chemical parameters obtained from density function theory/B3LYP for the compounds

Name	Total energy (kcal/mol)	Binding energy (kcal/mol)	HOMO energy (kcal/mol)	LUMO energy (kcal/mol)	Dipole mag	Band gap energy (kcal/mol)	Dipole X	Dipole Y	Dipole Z
1,2,3,4,6-penta-o-galloyl-b-D-glucose	−3509.3	−20.544	−0.194021	−0.0870968	1.16491	0.16659263	1.07696001	0.55897352	0.34675882
Galloylquinic acid	−1287.08	−8.42136	−0.192136	−0.0973097	1.3858	0.15025675	1.47903555	0.38626659	−0.31022587
Bacopaside IV	−2557.95	−21.7874	−0.178497	−0.0624107	5.72305	0.19264761	−5.12279105	−2.37987197	−1.92136978
Leukocyanidin	−1097.56	−7.30912	−0.173361	−0.0324727	2.45302	0.20223728	1.24783941	−2.23585315	−6.606125e-002
Bacoside A	−2558.73	−21.6192	−0.155264	−0.0695827	3.33345	0.15697959	−3.32608362	−4.176119e-002	0.93544973
Geranin	−1968.58	−13.5521	−0.179389	−0.0696464	3.30602	0.17225299	−2.5842299	2.1111219	9.250406e-002
Bacopaside III	−3178.77	−22.0462	−0.197321	−0.155617	2.76174	0.09973013	−2.98632578	−2.58099914	0.15360391
Quercitol	−607.125	−4.02422	−0.200975	0.0109457	2.86611	0.29816200	1.78040269	−2.33114184	0.18126397
Bacopaside V	−2557.88	−21.7223	−0.189075	−0.0837576	3.27189	0.18138551	−1.84115797	0.51922157	2.80118346
Shikimic acid	−643.69	−4.08152	−0.216582	−0.104548	1.32352	0.18848524	0.44482849	−0.87955706	0.95721965

HOMO: Highest occupied molecular orbital; LUMO: Lowest unoccupied molecular orbital

and shikimic acid showed increased absorption activity while the other compounds showed poor absorption. Admet aqueous solubility predicts the solubility of each compound in water at 25°C. The tested compounds were found to be hydrophilic except quercitol and shikimic acid exhibiting lipophilic properties hence suggesting the good bioavailability of the compounds.

Except 1,2,3,4,6-penta-O-galloyl-b-D-glucose, other compounds were non hepatotoxic and showed the value <1. The BBB penetration levels of the compounds were 4 without any violations and also non-inhibitors of CYP2D6 suggesting the possible good metabolization by CYP2D6. The tested compounds were both noncarcinogenic and nonmutagenic and exhibited moderate to no ocular irritancy except for the compounds Bacopaside IV, V, leukocyanidin, and shikimic acid that exhibited severe ocular irritancy. The ADME and toxicity properties of the compounds are represented in Table 4.

DISCUSSION

Of the 32 compounds subjected for screening against the ZIKA virus structural and nonstructural protein targets, 10 compounds showed promising interaction with at least one of the targets or to all the three targets. The compounds 1,2,3,4,6-penta-O-galloyl-b-D-glucose, Bacopaside III, IV, V, bacoside A, geranin, galloylquinic acid, leukocyanidin, quercitol, and shikimic acid interacted with the ZIKA targets.

Furthermore, the quantum chemical parameters of the compounds were estimated based on the three components that the polar molecules dissociate better than nonpolar molecules which is expressed by dipole movement. Second, the Dipole movement is also an index of lipophilicity and ability of drug molecule to cross various biological membranes. Third, the smaller energy gap (ΔE) between HOMO and LUMO permits the transfer and exchange of electron which leads to an increase in the reactivity of the compounds.

Based on that the compounds 1,2,3,4,6-penta-O-galloyl-b-D-glucose, galloylquinic acid, shikimic acid, and leukocyanidin showed the lowest dipole movement (1.16491, 1.323, 1.385, 2.453) when compared to the other subjected compounds. This suggested that the inhibitors were found to be more hydrophobic (lipophilic) and hence could possibly show increased biological activities on further *in vitro* evaluation.

Although the compound 1,2,3,4,6-penta-O-Galloyl-β-D-glucose showed higher binding energy, lowest dipole moment, the ADMET analysis revealed it as hepatotoxic. Thus, based on the molecular docking, quantum chemical parameters and the ADMET properties, galloylquinic acid from *E. hirta*, Bacopaside III, Bacopaside A from *B. monnieri* were identified as potential lead molecules that could be tested for further *in vitro* analysis.

CONCLUSION

The study has identified the compound galloylquinic acid, Bacopaside III, and Bacopaside A as potential inhibitors of Zika virus protein targets. The screened compounds were effective against multiple targets (NS1, NS3, and envelope protein domain III of ZIKA virus) involved in genome replication, RNA synthesis and the fusion with the host cell. Hence, the compounds hampering the active site of the three different protein playing prime roles in replication with acceptable pharmacokinetic properties could be suggested for further *in vitro* and *in vivo* analysis.

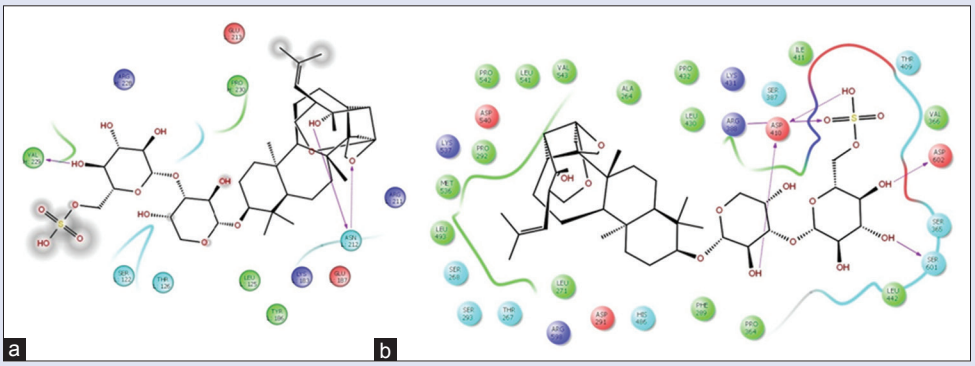

Figure 4: Molecular Docking and interaction analysis of compound Bacopaside III with the Targets nonstructural protein 3 (a) and envelope (b) respectively. Hydrogen bond interactions between the amino acids and the ligand molecules are represented by arrows in magenta color. Green color arrow represents the pi-pi stacking interactions

Table 4: Absorption, distribution, metabolism, and excretion and toxicity profile of the compounds

Name	Carcinogenicity	Mutagenicity	Ocular irritancy	Solubility	CYP2D6	Hepatotoxic	Absorption	AlogP98	PSA-2D	Blood brain barrier level
Bacopaside	Noncarcinogen	Nonmutagen	Severe	−3.969	−10.927	−16.9822	3	1.409	199.289	4
Bacopaside III	Noncarcinogen	Nonmutagen	None	−4.28	−13.6831	−14.1045	3	1.067	242.82	4
Bacopaside V	Noncarcinogen	Nonmutagen	Severe	−3.849	−9.92295	−16.2789	3	1.277	199.289	4
Bacoside	Noncarcinogen	Nonmutagen	Moderate	−3.61	−7.8831	−11.7874	3	1.74	219.545	4
1,2,3,4,6-penta-o-galloyl-b-D-glucose	Noncarcinogen	Nonmutagen	None	−21.899	−5.21568	12.1644	3	4.073	452.317	4
Galloyl quinic acid	Noncarcinogen	Nonmutagen	Moderate	−1.261	−7.10652	−6.61985	3	−0.34	168.424	4
Leukocyanidin	Noncarcinogen	Nonmutagen	Severe	−2.039	−0.642779	−2.8066	1	1.189	133.823	4
Geranin	Noncarcinogen	Nonmutagen	Mild	−7.251	2.35433	−2.8066	3	4	193.314	4
Quercitol	Noncarcinogen	Nonmutagen	Moderate	2.639	−3.83659	−2.8066	3	−2.492	104.077	4
Shikimic acid	Noncarcinogen	Nonmutagen	Severe	1.184	−5.01285	−4.77352	1	−1.154	100.562	4

PSA: Polar surface area

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Conflicts of interest

There are no conflicts of interest.

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