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Anti-Dengue potential, Molecular Docking Study of Some Chemical Constituents in the leaves of *Isatis tinctoria*

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ABSTRACT

Dengue infection is a major public health challenge in several parts of the world, especially the subtropical and tropical regions. The development of agents that are able to inhibit the dengue virus (DNV) replication is therefore of utmost significance. *I. tinctoria* is one of the most investigated Chinese herbs, which has been recognised to be effective in the treatment of dengue fever. However, the mechanisms through which it exhibits such biological activity of great importance are still unclear. A total number of about 27 compounds isolated from *I. tinctoria* leaves which have been identified and reported in the literature to be effective against dengue fever were investigated for their inhibitory potencies against dengue virus as novel drugs for treating early attacks of dengue fever. The compounds were optimized by employing a method of Density functional theory (DFT) and a basis set of B_3LYP (6-31G**). The results of Molecular docking investigation between the compounds and the dengue viral protein (PDB: 6MO1) revealed that three of the compounds (GB-20, GB-19, and GB-6) possessing best binding energy in of -27.051, -26.193 and -24.664 kcal/mol respective were observed to inhibit the target through hydrogen bonds and hydrophobic interactions with amino acids residue of the protease binding site. The results of these studies would offer relevant insight into structural requirements for the development of effective and specific treatment against dengue virus infection.

1. Introduction

Dengue infection is a mosquito-borne infection caused by a virus called Dengue virus (DNV) which belongs to *Flavivirus* members commonly found in tropical regions of the world [1]. The virus is transmitted to persons by infested females especially *Aedes aegypti*, the Aedes genus [2-3]. The number of people infected with the dengue virus is over 390 yearly, with about 20–25% cases with clinically apparent symptoms [4].

These infections, in some cases, may also develop into a dengue hemorrhagic fever or dengue shock syndrome; a more acute phase of the fatal infection [5-7], these constitute a serious fatal threat in major dengue cases, about 2.5 % from 500,000 clinical cases [5]. The West Nile virus and the Zika virus are serotypes of DNV [8].The NS3-NS2B proteases, NS3 helicase, as well as the RNA polymerase of NS5, which are the essential proteins of the dengue virus, have been the drug able targets studied for the development of antiviral inhibitors in the past 4 years [9-12].

Currently, there is no reliable vaccine or antiviral treatment for dengue virus infection [13]. This necessitates the need to discover novel and highly potent drugs to battle the menace of this disease. In pursuant of this effort, several molecular drug targets have been identified to develop new drug candidates.

In 2016, Suganya and Mahendran carried out molecular docking studies of chemical compounds isolated from some selected plants of medicinal value against NS3 and NS5 protease of dengue virus. The

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results of their findings on the molecular docking performed on the 75 identified compounds showed 8 and 11 inhibitory molecules against NS3 and NS5 respectively; this led to the identification and design of dengue virus inhibitors using these novel plant compounds [11].

Isatis tinctoria is a well-known and one of the commonly studied Chinese herbs, which has been identified to be active against dengue fever. However, the mechanisms through which it exhibits such biological activity of great importance are still uncertain. *I. tinctoria* has shown potency against various viral infections such as influenza, hepatitis virus, and so on [14-16]. It has also been used for the management of other viral infections and for the treatment of dengue fever with remarkable effects [17].

This particular study is aimed at identifying chemical compounds in hydro alcoholic leaves extract of *I. tinctoria* through molecular docking simulations with dengue virus serotype 2 non-structural protein 2B and 3 (DNV2 NS2B-NS3) (PDB: 6M01) was used to evaluate the potential mode of action of the test compounds, molecular docking was used to establish their ability to act as protease inhibitors on the basis of their binding energy and interaction.

2. Material and Methods

2.1. *Experimental chemical dataset*

In this study, a chemical dataset of 27 compounds isolated from the leaves of *I. tinctoria* was collected from literature [18]. Spectroscopic data on the characterization of the Phytochemical constituents of the leaves of *I. tinctoria* already published revealed the presence of some important phytochemical compounds.

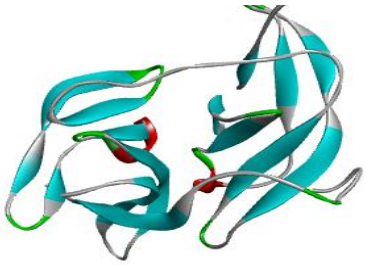
2.2. Molecular geometry optimization

Optimisation is the method of obtaining the equilibrium energy geometry. The 2D chemical structures of the 27 compounds identified in the leaves of *I. tinctoria* were drawn using Chemdraw software ultra-version 12.0 and subsequently imported into Spartan 14 software and converted to 3D before there were optimized [19-20].

The optimization was carried out using the density functional theory (D.F.T) level accompanied by Becks's three-parameter Lee-Yang-parr hybrid functional (B_3LYP) at 6-31G** level of theory [21-22] to obtain chemical structures of the molecules at their most stable conformation prior to the molecular docking process.

2.3. Preparation of ligand (compound) and target (protease)

All the compounds were optimized using Spartan software saved as SDF files and were appropriately later saved as Protein Data Bank (PDB) files. Subsequently, the PDB file of the receptor was downloaded from the RSCB site (http://www.rcsb.org/) with the PDB ID: 6MO1 for the crystal structure of DENV2 NS2B-NS3. The X-ray diffraction resolution for 6MO1 was given as 3.00 Å [23]. Figure 1 displays the structure of the receptor.



DNV2 NS2B-NS3 (PDB: 6MO1)

Figure 1: Structure of the target

2.4. Docking process

The molecular interactions studies were carried out on the HP computer system, with processor properties of Intel ® Core i3-5005U CPU Dual@2.00GHz, 8 GB (RAM) between the ligands and DNV2 protease (target); the X-ray Crystal Structure of the protease deposited in RSCB protein data bank. For proper identification of the most like active chemical compounds in the leave extract, and evaluation of the nature and type of interaction of the compound with the DNV2 NS2B-NS3 protease, molecular docking study was carried using ICM- pro software and also the visualization and the analysis of the interaction site was performed with the aid of Discovery Studio visualiser. This process was carried out using the method described by Neves and co-worker which involves removing all the water molecules present in the binding pocket of the protease and optimising all hydrogen as well as His. Pro. Asn. Gln. Cys. and also the construction of missing heavy atoms that are not described in the PDB (due to the lack of density), which are added based on the name of the residue and allocated zero occupancies. After docking, the result was saved as pdbqt file. The saved file was then moved into the discovery studio visualiser, where the 2-dimensional 2D and 3-dimensional 3D images of the interactions could be seen clearly. The score was calculated from equation 1 below:

$$Ebind = Eint. + \Delta STor. + Evw. + \alpha 1 Eel. + \alpha 2\ Ehb. + \alpha 3 Ehp. + \alpha 4 Esf. \quad (1)$$

Where, Evw., Eel., Ehb., Ehp., and Esf. are van der Waals, electrostatic, hydrogen bonding, and non-polar and polar atom solvation energy changes between complexed and uncomplexed states, respectively. Eint. is the compound internal strain, ΔS_Tor. is its conformational entropy loss upon complexing, T = 27°C, and αi. is compound and protease-independent constants. The score was apportioned to each compound according to the weighed factor of the ICM scoring function [24]. The smaller the ICM score value, the better the chance the compound is an inhibitor.

3. Results and Discussion

The results of this study is presented in terms of binding energy (kcal/mol) as reported in Table 1 together with their number of flexible bonds (Nflx), hydrogen bond energy (Hbnd), hydrophobic bond energy (Hphb) values and the compound IDs as obtained from the literature.All the compounds were docked with the crystal structure of dengue virus protease in order to evaluate their DENV inhibitory potentials.

Table 1: The ID of the dataset along with their Binding affinity result

Name	Score	Nflx	Hbnd	Hphb	Vwlnt	Eintl	Dsolv	SolEl	mfScore
GB-20	-27.051	2	-7.188	-4.343	-22.770	10.128	17.015	4.322	-59.425
GB-19	-26.193	0	-7.488	-3.352	-23.908	8.628	20.028	5.888	-51.260
GB-6	-24.664	8	-9.118	-5.253	-24.280	8.823	22.365	7.015	-48.205
GB-8	-23.864	12	-9.240	-6.768	-28.050	8.651	24.892	9.438	-64.099
GB-23	-22.372	2	-6.274	-5.458	-26.179	5.010	21.732	8.845	-83.354
GB-22	-21.161	1	-3.418	-5.666	-24.839	3.863	13.472	8.210	-97.448
GB-4	-20.777	5	-7.169	-2.905	-20.706	2.738	19.679	3.413	-33.371
GB-9	-20.522	8	-7.547	-3.542	-18.302	1.024	14.374	5.555	-16.314
GB-1	-20.249	8	-7.697	-4.756	-23.411	11.374	18.773	10.521	-61.723
GB-15	-19.608	10	-8.222	-5.175	-22.141	11.809	21.868	6.670	-62.304
GB-16	-18.774	10	-7.800	-5.860	-20.499	7.743	18.035	8.877	-60.668
GB-21	-18.545	0	-4.780	-3.866	-14.217	6.227	11.442	2.688	-4.835
GB-5	-17.599	1	-5.057	-3.522	-15.636	0.954	11.921	5.532	-30.904
GB-13	-17.275	4	-5.009	-4.239	-17.745	3.553	14.772	3.795	-30.399
GB-12	-17.241	4	-5.224	-4.582	-17.228	3.524	14.776	4.231	-24.360
GB-18	-15.950	10	-6.014	-5.481	-21.401	3.400	14.508	11.298	-65.683
GB-2	-15.913	2	-4.421	-3.619	-19.708	0.810	14.790	7.748	-33.772
GB-3	-15.549	0	-4.076	-2.713	-11.585	0.784	8.506	2.708	-61.905
GB-13	-14.418	4	-3.730	-4.721	-16.206	2.349	13.991	2.264	-31.691
GB-10	-14.278	7	-4.404	-4.690	-18.493	3.057	13.471	6.360	-59.530
GB-7	-13.681	3	-3.793	-3.503	-18.585	1.081	15.041	5.708	-44.030
GB-14	-13.363	12	-10.259	-4.464	-17.536	7.311	24.877	11.002	-72.027
GB-11	-11.477	6	-4.137	-4.039	-17.040	1.240	17.167	3.426	-37.612
GB-25	-11.019	12	-5.958	-3.879	-23.935	8.611	21.512	10.989	-56.797
GB-24	-10.594	5	-4.734	-3.671	-16.463	5.100	17.184	6.695	-21.742
GB-26	-10.466	6	0.000	-8.997	-21.806	7.988	9.688	9.851	-91.468
GB-17	-7.351	16	-6.151	-5.830	-24.808	4.923	28.077	9.495	-49.243
GB-14	-6.787	12	-5.624	-4.588	-19.771	6.334	22.883	8.975	-58.970
GB-27	-6.454	7	0.000	-8.857	-18.288	3.102	10.002	9.191	-64.991

The binding energy value of the protease (PDB: 6MO1) for all the studied compounds ranged between -6.454 to -27.051kcal/mol and were presented in Table 1. compounds GB-20, GB-19, and GB-6 had the best binding affinity values of -27.051, -26.193 and -24.664 kcal/mol respectively with the receptor (PDB: 6MO1). The Discovery Studio Visualizer was used to visualize complexes of the three ligands-protease interactions of the highest binding affinity that were presented in table 1 and were shown in Figure 2-7.

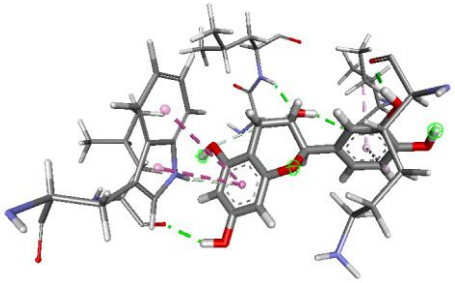


Figure 2: The 3D binding pose of ligand GB-20 with NS2B-NS3 displaying a hydrogen bond interaction surface.

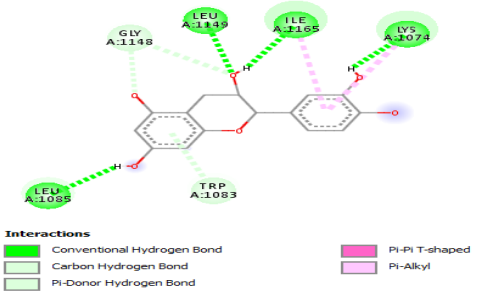


Figure 3: 2D interaction type of ligand GB-20 with the amino acids NS2B-NS3.

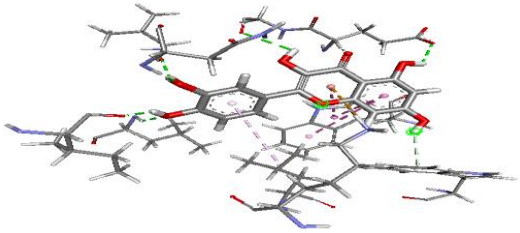


Figure 4: The 3D binding pose of ligand GB-19 with NS2B-NS3 protease displaying a hydrogen bond interaction surface

Table 2: Complete description of Hydrogen bonds and other interactions between GB-20 and DNV2 NS2B-NS3 protease

Distance (Å)	Types	From	From Chemistry	To	To Chemistry
2.088	Conventional Hydrogen Bond	A:LEU1149:HN	H-Donor	:RES1:O4	H-Acceptor
1.836	Conventional Hydrogen Bond	:RES1:H13	H-Donor	A:LYS1074: O	H-Acceptor
2.057	Conventional Hydrogen Bond	:RES1:H4	H-Donor	A: LEU1085: O	H-Acceptor
2.100	Conventional Hydrogen Bond	:RES1:H9	H-Donor	A: ILE1165:O	H-Acceptor
2.956	Carbon Hydrogen Bond	A:GLY1148:HA1	H-Donor	:RES1:O1	H-Acceptor
2.577	Carbon Hydrogen Bond	A:GLY1148:HA1	H-Donor	:RES1:O4	H-Acceptor
2.926	Pi-Donor Hydrogen Bond	A:TRP1083:HE1	H-Donor	:RES1	Pi-Orbitals
4.948	Pi-Pi T-shaped	A:TRP1083	Pi-Orbitals	:RES1	Pi-Orbitals
5.735	Pi-Pi T-shaped	A:TRP1083	Pi-Orbitals	:RES1	Pi-Orbitals
5.413	Pi-Alkyl	:RES1	Pi-Orbitals	A:LYS1074	Alkyl
4.534	Pi-Alkyl	:RES1	Pi-Orbitals	A:ILE1165	Alkyl

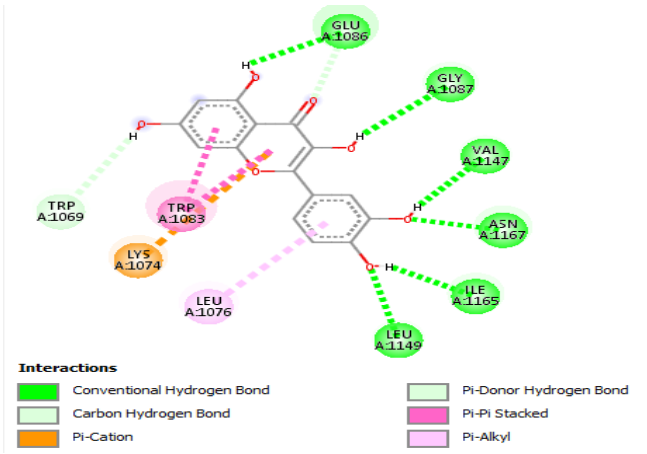


Figure 5: 2D interaction type of ligand GB-19 with different amino acids of NS2B-NS3.

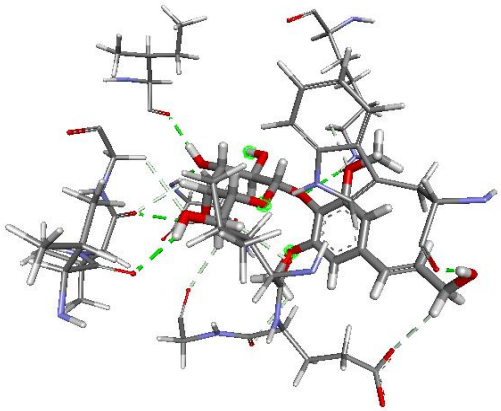


Figure 6: The 3D binding pose of ligand GB-6 with NS2B-NS3 protease displaying a hydrogen bond interaction surface.

Table 3: Complete description of Hydrogen bonds and other interactions between GB-19 and DNV2 NS2B-NS3 protease

Distance (Å)	Types	From	From Chemistry	To	To Chemistry
2.304	Conventional Hydrogen Bond	A:LEU1149:HN	H-Donor	:RES1:O6	H-Acceptor
1.905	Conventional Hydrogen Bond	A:ASN1167:HN	H-Donor	:RES1:O5	H-Acceptor
2.959	Conventional Hydrogen Bond	:RES1:H10	H-Donor	A: GLY1087:O	H-Acceptor
2.364	Conventional Hydrogen Bond	:RES1:H6	H-Donor	A:GLU1086:OE1	H-Acceptor
2.161	Conventional Hydrogen Bond	:RES1:H8	H-Donor	A: VAL1147:O	H-Acceptor
2.001	Conventional Hydrogen Bond	:RES1:H9	H-Donor	A: ILE1165:O	H-Acceptor
2.416	Carbon Hydrogen Bond	A:GLU1086:HA	H-Donor	:RES1:O2	H-Acceptor
4.979	Pi-Cation	A:LYS1074:NZ	Positive	:RES1	Pi-Orbitals
3.368	Pi-Donor Hydrogen Bond	:RES1:H7	H-Donor	A:TRP1069	Pi-Orbitals
4.432	Pi-Pi Stacked	A:TRP1083	Pi-Orbitals	:RES1	Pi-Orbitals
4.064	Pi-Pi Stacked	A:TRP1083	Pi-Orbitals	:RES1	Pi-Orbitals
5.928	Pi-Pi Stacked	A:TRP1083	Pi-Orbitals	:RES1	Pi-Orbitals
5.427	Pi-Alkyl	:RES1	Pi-Orbitals	A:LEU1076	Alkyl

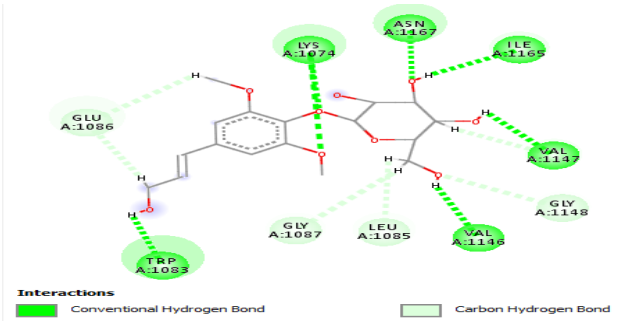


Figure 7: 2D interaction type of ligand GB-6 with the amino acids of NS2B NS3

Table 4: Complete description of Hydrogen bonds between GB-6 and DNV2 NS2B-NS3 protease

Distance (Å)	Types	From	From Chemistry	To	To Chemistry
2.616	Conventional Hydrogen Bond	A:LYS1074:HZ1	H-Donor	:RES1:O6	H-Acceptor
2.849	Conventional Hydrogen Bond	A:LYS1074:HZ1	H-Donor	:RES1:O7	H-Acceptor
1.729	Conventional Hydrogen Bond	A:ASN1167:HN	H-Donor	:RES1:O4	H-Acceptor
2.024	Conventional Hydrogen Bond	:RES1:H10	H-Donor	A: ILE1165:O	H-Acceptor
1.968	Conventional Hydrogen Bond	:RES1:H24	H-Donor	A: TRP1083:O	H-Acceptor
2.212	Conventional Hydrogen Bond	:RES1:H6	H-Donor	A: VAL1146:O	H-Acceptor
2.150	Conventional Hydrogen Bond	:RES1:H7	H-Donor	A: VAL1147:O	H-Acceptor
2.939	Carbon Hydrogen Bond	A:LYS1074:HE1	H-Donor	:RES1:O7	H-Acceptor
3.070	Carbon Hydrogen Bond	A:GLY1148:HA1	H-Donor	:RES1:O2	H-Acceptor
2.967	Carbon Hydrogen Bond	:RES1:H18	H-Donor	A: GLU1086:O	H-Acceptor

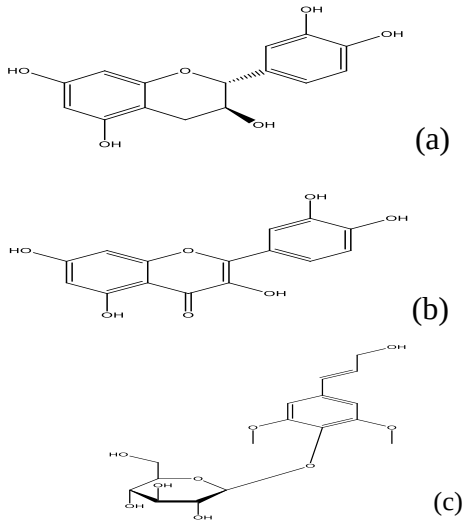


Figure 8: 2D chemical structures of compounds with the best binding energy GB-20 (a), GB-19 (b), and GB-6 (c).

The binding energy, hydrogen bond, hydrophobic and electrostatic interactions of the three ligands having the best binding energy with the receptor is reported in Tables 2, 3 and 4 respectively. Figure 2, 4 and 6 represent the 3dimensional view interactions of the compounds (GB-20, GB-19, and GB-6) with the protease's binding pocket (PDB ID 6MO1) respectively, while figure 3, 5 and 7 show the 2dimensional interaction of the compounds (GB-20, GB-19, and GB-6) with the protease (PDB ID 6MO1) respectively. All three compounds (GB-20, GB-19, and GB-6) with the highest binding energy of interaction were observed to inhibit the targets through hydrogen bonds and hydrophobic interactions with amino acids of the receptor as reported in Table 1. The three ligands (Compound GB-20, GB-19 and GB-6) were found to be firmly held within the binding pocket through hydrogen bonds with the protease's neighboring amino acids (LEU1149, LYS1074, LEU1085, and ILE1165), (LEU1149, ASN1167, GLY1087 GLU1086 VAL1147 and ILE1165) and (LYS1074, LYS1074 ASN1167 ILE1165 TRP1083 VAL1146 and VAL1147) respectively. The hydrogen bond, hydrophobic bond, and Vander Waal energies for the three ligands (Compound GB-20, GB-19, and GB-6) within the binding pocket of the protease also explain their high binding affinities as presented in table 1 (-27.051, -26.193 and -24.664) kcal/mol respectively.

Because there is no specific drug for the treatment of DNV infection, a well-known NS2B-NS3 inhibitor (Bz-Nle-Lys-Arg-Arg-H.) is stated to possess a significant level of interactions with some comparable residues of DNV2 NS2B-NS3 with a binding energy of -11.323 kcal/mol is even less potent than the one reported in this study [25]. This implies that there is a direct relationship between the binding energy and inhibitory activity of the studied compounds evidenced by a number of various interactions formed between the compounds and the receptor. Though high binding affinity is evidenced in the ligand GB-20 and this may be attributed to its multitude hydrophobic interactions and also the different nature of interactions, Conventional Hydrogen Bond, Carbon Hydrogen Bond, Pi-Donor Hydrogen Bond, Pi-Pi T-shaped Pi-Alkyl while GB-19 has Conventional Hydrogen Bond, Carbon Hydrogen Bond, Pi-Cation, Pi-Donor Hydrogen Bond, Pi-Pi Stacked Pi-Alkyl with GB-6 having Conventional Hydrogen Bond, Carbon Hydrogen Bond, with amino acid residues. It is also interesting to note that the first two compounds GB-20 and GB-19 with the best stability value with the protease have a significant structural relationship; however, these compounds had binding free energy values approximately close to each other, due to the similarity of the interactions with the amino acids residue and structural similarity also. In a study reported elsewhere, it has been shown that flavone significantly enhances DNV2 replication in Vero cells [26].

However, another study later showed that a class of flavone inhibits DNV replication and also reported the difference in structure between these two compounds lying in the presence of three hydroxyl groups in the studied compound in comparison to the flavone, signifying the potential relevance of the hydroxyl groups [27]. This possibility is further supported by the results of another study that has demonstrated the existence and the locations of the hydroxyl group in such compounds being vital for its activity against HIV relative to the flavone hydroxyl functional group [28].

4. Conclusion

This study aimed at identifying the compounds responsible for the therapeutic, In conclusion, the molecular docking study carried out on all the 27 compounds isolated from *I. tinctoria* using a crystal structure of dengue viral protein with a PDB ID 6MO1 revealed three ligands (compound GB-20, GB-19, and GB-6) with the best binding energy and so were found to inhibit the receptor by simple interaction through hydrogen bonds and hydrophobic interactions with amino acids of the protease. However, a higher number of hydrogen bonds were observed between the receptor and the ligand GB-6 when compared with the other ligand GB-20 and GB-19, although both compounds reported the binding energy in kcal/mol as -27.051, -26.193 and -24.664 respectively. Therefore, this suggests that both Ligands (Compound GB-20, GB-19, and GB-6) computationally proved to be the most promising inhibitors of dengue virus and could be used as lead compounds. The studies also revealed that these compounds isolated from *I. tinctoria* are the promising NS2B-NS3 protease inhibitors, in addition to another potential mechanism (s) of action instilled by the compounds.

Further investigations on these compounds are recommended to explore their potential as agents active against the dengue virus-related infections. The presence of important compounds in *I. tinctoria* can explain the pharmacological actions described in folk medicine. Therefore, it would be imperative to investigate the potential of this species of plants and the main compounds as a natural anti-dengue agent for use in the pharmaceutical industry.

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References

[1] S. S. Swain and D. Dude, Anti-dengue medicinal plants: a mini review. *Res. Rev. J Pharmacogn Phytochem.*, 1 (2013) 5-9.

[2] M. E. Beatty, A. Stone, W. D. Fitzsimons, J. N. Hanna, S. K. Lam and S. Vong, Best practices in dengue surveillance: a report from the Asia-Pacific and Americas Dengue Prevention Boards. *PLoS. Negl. Trop. Dis*., 4 (2010) 890.

[3] Z. Fatima, M. Idrees, M. A. Bajwa, Z. Tahir, O. Ullah and M.Q. Zia, Serotype and genotype analysis of dengue virus by sequencing followed by phylogenetic analysis using samples from three mini outbreaks-2007-2009 in Pakistan. *BMC Microbiol.*, 11 (2011)200.

[4] J. A. Ayukekbong, O. G. Oyero, S. E. Nnukwu, H. N. Mesumbe and C.N. Fobisong, Value of routine dengue diagnosis in endemic countries. *World. J. Virol.*, 6 (2017) 9-16.

[5] C. Nitsche, S. Holloway, T. Schirmeister and C. D. Klein, Biochemistry and medicinal chemistry of the dengue virus protease. *Chem Rev.*, 114 (2014) 11348–11381.

[6] A. J. Stevens, M. E. Gahan, S. Mahalingam and P. A. Keller, The medicinal chemistry of dengue fever. *J. Med. Chem.*, 52 (2009) 7911–7926.

[7] S. P. Lim, Q. Y. Wang, C. G. Noble, Y. L. Chen, H. Dong, B. Zou, F. Yokokawa, S. Nilar, P. Smith, D. Beer, J. Lescar and P. Y. Shi, Ten years of dengue drug discovery: Progress and prospects. *Antiviral Res.*, 100 (2013) 500–519.

[8] A. E. Sahili and J. Lescar, Dengue Virus Non-Structural Protein 5. *Viruses.*, 9 (2017) 9.

[9] J. Lei, G. Hansen, C. Nitsche, C. D. Klein, L. Zhang and R. Hilgenfeld. The Crystal structure of Zika virus NS2B-NS3 protease in complex with a boronate inhibitor. *Sci.*, 353 (2016) 503−505.

[10] C. Nitsche, L. Zhang, L. F. Weigel, J. Schilz, D. Graf, R. Bartenschlager, R. Hilgenfeld and C. D. Klein, Peptide–boronic acid inhibitors of flaviviral proteases: Medicinal chemistry and structural biology. *J. Med. Chem.*, 60 (2017) 511−516.

[11] J. Suganya and R. Mahendran. Molecular docking studies of selected medicinal plant compounds against NS5 and NS3 protein of dengue virus: a comparative approach. *Int. J. Pharm. Bio. Sci.*, 7 (2016) 1135 – 1144.

[12] Y. Yao, T. Huo, Y. Lin, S. Nie, F. Wu, Y. Hua, J. Wu, A. R. Kneubehl, M. B. Vogt, R. Rico-Hesse and Y. Song, Discovery, X-ray crystallography and antiviral activity of allosteric inhibitors of flavivirus NS2B-NS3 protease. *J. Am. Chem. Soc.*, 141 (2019) 6832-36.

[13] W. Schul, W. Liu, H. Y. Xu, M. Flamand and S. G. Vasudevan, A dengue fever viremia model in mice show a reduction in viral replication and suppression of the inflammatory response after treatment with antiviral drugs. *J. Infect. Dis.*,195 (2007) 665-674.

[14] W. J. Kassler, P. Blanc and R. Greenblatt, The use of medicinal herbs by human immunodeficiency virus-infected patients. *Arch. Intern. Med.*, 151 (1991) 2281-2288.

[15] H. C. Ko, B. L. Wei and W. F. Chiou, The effect of medicinal plants used in Chinese folk medicine on RANTES secretion by virus-infected human epithelial cells. *J. Ethnopharmacol.*, 107, (2006) 205-210.

[16] L. T. Lin, W. C. Hsu and C. C. Lin, Antiviral natural products and herbal medicines. *J. Tradit. Complement. Med.*, 4 (2014) 24-35.

[17] S. L. Woodward and J. A. Quinn, Encyclopedia of Invasive Species: From Africanized Honey Bees to Zebra Mussels, Greenwood Publishing Group, Santa Barbara, CA, USA, 1. 2011.

[18] B. Gao, J. Zhang and L. Xie, Structure analysis of effective chemical compounds against dengue viruses isolated from I. tinctoria. *Can. J. Infect. Dis. Med. Microbiol.*, 2018 https://doi.org/10.1155/2018/3217473.

[19] W. J. Hehre and W. W. Huang, Chemistry with Computation: An introduction to SPARTAN, Wavefunction, Inc; 1995.

[20] Z. Li, H. Wan, Y. Shi and P. Ouyang, Personal experience with four kinds of chemical structure drawing software: a review on ChemDraw, ChemWindow, ISIS/Draw, and ChemSketch. *J. Chem. Inform. Comput. Sci.*, 44 (2004) 1886-1890.

[21] E. R. Davidson and D. Feller, Basis set selection for molecular calculations. *Chem. Rev.*, 86 (1986) 681-696.

[22] A. Schäfer, H. Horn and R. Aldrichs, Fully optimized contracted Gaussian basis sets atoms Li to Kr. *The Journal of Chemical Physics*, 97 (1992) 2571-2577.

[23] A. El Sahili, T. S. Soh, J. Schiltz, A. Gharbi-Ayachi, C. C. She, P. Y. Shi and J. Lescar, NS5 from dengue virus serotype 2 can adopt a conformation analogous to that of its zika virus and Japanese encephalitis virus homologues. *J. Virol.*, 94 (2019) e01294-19.

[24] M. A. Neves, M. Totrov and R. Abagyan, Docking and scoring with ICM: the benchmarking results and strategies for improvement. *J. Comput. Aided Mol. Des.*, 26 (2012) 675-86.

[25] J. Joubert, E. B. Foxen and S. F. Malan, Microwave optimized synthesis of N-(adamantan-1-yl)-4-[(adamantan-1-yl)-sulfamoyl] benzamide and its derivatives for anti-dengue virus activity. *Molecules.*, 23 (2018) 1678.

[26] K. Zandi, R. Lani, P. E. Wong, B. T. Teoh, S. S. Sam, J. Johari, M. R. Mustafa, S. Abubakar, Flavone enhances dengue virus type-2 (NGC strain) infectivity and replication in Vero cells. *Molecules.*, 17 (2012) 2437-2445.

[27] K. Zandi, B. T. Teoh, S. S. Sam, P. F. Wong, M. R. Mustafa, S. Abubakar, Novel antiviral activity of baicalein against dengue virus. *BMC. Complement. Altern. Med.*, 12 (2012) 214.

[28] Ahn HC, Lee SY, Kim JW, Son WS, Shin CG, Lee BJ. Binding aspects of baicalein to HIV-1 intergrase. *Mol. Cells.*, 12 (2001) 127-130.

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