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An *In Silico* Study: Phytochemical Compounds Screening of *Garcinia atroviridis* Griff. ex T. Anders as Anti-DENV

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Abstract

Dengue virus (DENV) is still global problem and infecting millions of people a year. This virus belongs to *Flavivirus* and consists of the structural and non-structural proteins including envelop (E), capsid (C), NS2B/NS3, and NS5. *Garcinia atroviridis* Griff. ex T. Anders is traditional plant that has broad potential as antioxidant, antibacterial, and anti-cancer activities. However, the anti-DENV potential of this plant is uncertain. The objective of this research is to find out the potential of the phytochemical compounds of *G. atroviridis* as DENV antiviral drugs targeting E, C, NSB2/NS3, and NS5 proteins using molecular simulation approach. Sample retrieval was obtained from PubChem and RCSB PDB. Drug-likeness analysis has been assessed with Swiss ADME based on the pharmacology and pharmacokinetics aspects. Toxicity prediction was done by pkCSM webserver. PyRx was carried out to screen ligand-protein interaction virtually. Visualization of the best interaction was displayed by BIOVIA Discovery Studio. CABS-flex 2.0 version webserver was performed to predict stability interaction. Atroviridin was determined as the most promising as DENV antiviral to be tested by the wet laboratory approach.

Keywords: DENV, *Garcinia atroviridis*, Structural Proteins, Non-structural Proteins, Bioinformatics

INTRODUCTION

Dengue virus (DENV) is the frequent arthropod-borne infection that infecting human worldwide.[1] It is reported infects over 400 million people each year. DENV is capped-single stranded RNA, positive sense virus that classified into the *Flavivirus*.[2] This virus has 5 serotypes, the most recent of which was found.[3,4] That condition complicated dengue control particularly in tropical climate countries where epidemic occurs regularly. DENV infects human via *Aedes sp*. mosquito's transmission.[5]

DENV has proteins act significant roles from viral entry to viral release in human cell. Proteins are classified into two types: structural and non-structural proteins. Structural and non-structural proteins have various roles in the virion's existence. Envelop (E), capsid (C), NS2B/NS3, and NS5 are parts of DENV proteins that play important roles in viral entrance, immune system recognition, growth and maturation, genome synthesis, and viral release.[6-11]

Garcinia atroviridis Griff ex T. Anders. is native to and widely dispersed throughout South and Southeast Asia regions including India, Thailand, Myanmar, and Indonesia.[12] This plant belongs to Guttiferae family. This plant is known as asamgelugur in Indonesia and commonly utilized as cooking spices especially in Aceh and other Sumatra regions.[13] Previous researches have shown that the extract has antioxidant, antibacterial, and anti-tumour activities.[14,15,16,17] There have been no researches regarding the potential of *G. atroviridis* as DENV antiviral drugs. The objective of this research is to find out the potential of the phytochemical compounds of *G. atroviridis*as DENV antiviral drugs targeting E, C, NSB2/NS3, and NS5 proteins using molecular simulation approach.

MATERIALS AND METHODS

Sample Retrieval

Various phytochemical compounds derived from *G. atroviridis* and specific synthetic drugs were yielded from PubChem (https://pubchem.ncbi.nlm.nih.gov/).

The compound structures have been compiled in *.sdf* file as ligands.[18] Therefore, conversion to be protein data bank (PDB) was done to produce flexible 3D structure using PyRx version 0.9 software.[19] The target proteins used were obtained from RCSB PDB (https://rcsb.org/) consists envelop (PDB ID 3UZV), capsid (PDB ID 6VSO), NSB/NS3 (PDB ID 2FOM), and NS5 (PDB ID 2J7U). Removal of water and native ligands was conducted using BIOVIA Discovery Studio 2016 16.1.0 ' 64 (Dassault Systems France).[20] Synthetic drugs were added to the later step as a control for each target protein.[21]

Drug-likeness Analysis

Drug-likeness analysis was done to analyze pharmacological and pharmacokinetics similarities in each drug using SwissADME (https://

www.swissadme.ch/index.php). The Lipinski, Ghose, Veber, Egan, Muege, bioavailability score (BA), and gastrointestinal absorption (GI abs) were included in this analysis. Drug-likeness analysis results must be no violation and ≥0.50 as well as high score for pharmacokinetics.[22] Positive predictions are distinguished to fulfill the criteria of each category with check mark (√) and will be continued to the next step.[21]

Toxicity prediction

The phytochemical compounds were filtered on the drug-likeness properties basis with toxicity prediction using Predicting Small-Molecule Pharmacokinetic Properties using Graph-Based Signature (pkCSM) (https://biosig.lab.uq.edu.au/pkcsm/).[23] Toxicity predictions are vital because their relations with pharmacokinetics on prospective drug analysis.[24] Several endpoint parameters were applied including Ames test, maximum recommended tolerated dose (MRTD), hERG I/II inhibitors, lethal dose 50 (LD50), and hepatotoxicity. The results of toxicity prediction should have one and/or no violation on Ames test, hERG I/II inhibitors, and hepatotoxicity categories.[25] For MRTD and LD50 are quantitative parameter with MRTD endpoint for human is 0.477 log(mg/kg/day) and LD50 is stated in mol/kg.[26] Positive predictors would mark as check mark (√) before they continue in docking analysis.

Docking analysis and interaction visualization

Docking analysis was carried out to investigate the ligand-protein interaction with computational screening. In recent years, this approach has been significant technique apart

Table 1. References of DENV target proteins

Protein	Control	Active sites	Center	Dimension	Ref.
Envelop (E)	NITD448 (CID13903 10)	A: Ile308, Val309, Gln325. B: Thr33, Gly100, Trp101, Glu102	X: -8.701 Y: 6.916 Z: 21.773	X: 43.458 Y: 27.357 Z: 28.788	31
Capsid (C)	ST-148 (CID29099 14)	A: Arg32, Phe33, Gly36, Met37, Leu38, Glu39, Leu44, Thr62, Ala63, Gly64, Arg68, Ile72, Arg82, Arg85, Leu92. B: Val26, Arg41, Leu57, Arg82, Arg85, Lys86, Leu92, Asn96 C: Arg32, Gln39, Pro43, Leu44, Leu46, Arg68, Ile72, Lys73, Arg82, Arg85, Leu92, Asn96. D: Gln39, Arg41, Leu44, Arg68, Ile72, Lys73, Arg82, Arg85, Leu92, Asn93, Asn96. E: Arg32, Phe33, Gly36, Met37, Leu38, Gln39, Lys45, Thr62, Ala63, Gly64, Arg68, Lys73, Arg82, Arg83, Lys86,Gly89, Leu92, Asn96. F: Val26, Gln39, Arg41, Leu44, Arg68, Ile72, Lys73, Arg82, Arg85, Lys86, Gly89, Leu92, Asn93, Asn96, Asn97. His51, Asp75, Ser135	X: 32.720 Y: 77.020 Z: 1.427	X: 55.925 Y: 74.438 Z: 79.230	32
NS2B/NS3	ARDP0006 (CID 3378440)	His51, Asp75, Ser135	X: 0.643 Y: -6.045 Z: 13.947	X: 17.381 Y: 23.658 Z: 43.862	33,34
NS5	SAH (CID 439155)	Glu37, His441, Cys446, Cys449, Asn492, Gly604, Gly607, Asp663, Asp664, His714, Cys728, Trp823	X: 23.702 Y: 58.239 Z: 12.627	X: 49.338 Y: 36.839 Z: 34.549	35

Table 2. The results of the analysis of drug-likeness analysis

Compound (PubChem ID)	Lipinski	Ghose	Veber	Egan	Muegge	BA score	GI abs	Status
Absorbic acid (54670067)	Yes (0)	No (2)	Yes (0)	Yes (0)	No (1)	.56	High	×
Citric acid (311)	Yes (0)	No (2)	Yes (0)	No (1)	No (1)	.56	Low	×
Malic acid (525)	Yes (0)	No (4)	Yes (0)	Yes (0)	No (2)	.56	High	×
Succinic acid (1110)	Yes (0)	No (3)	Yes (0)	Yes (0)	No (2)	.85	High	×
Tartaric acid (875)	Yes (0)	No (4)	Yes (0)	Yes (0)	No (2)	.56	Low	×
Hydroxycitric acid (123908)	Yes (0)	No (3)	No (1)	No (1)	No (2)	.11	Low	×
Pentadecanoic acid (13849)	Yes (0)	Yes (0)	Yes (0)	No (1)	No (1)	.85	High	×
Nonadecanoic acid (12591)	Yes (1)	No (1)	Yes (0)	Yes (0)	No (2)	.85	High	×
Dodecanoic acid (3893)	Yes (0)	Yes (0)	Yes (0)	Yes (0)	Yes (0)	.85	High	√
Atroviridin (11267348)	Yes (0)	Yes (0)	Yes (0)	Yes (0)	Yes (0)	.55	High	√
Atrovirisidone (10342405)	Yes (0)	Yes (0)	Yes (0)	Yes (0)	No (1)	.55	High	×
Naringenin (932)	Yes (0)	Yes (0)	Yes (0)	Yes (0)	Yes (0)	.55	High	√
Morelloflavone (5464454)	No (3)	No (2)	No (1)	No (1)	No (3)	.17	Low	×
Fukugiside (73157060)	No (3)	No (2)	No (1)	No (1)	No (4)	.17	Low	×
Kaempherol (5280863)	Yes (0)	Yes (0)	Yes (0)	Yes (0)	Yes (0)	.55	High	√
Quercetin (5280343)	Yes (0)	Yes (0)	Yes (0)	Yes (0)	Yes (0)	.55	High	√
Garcinol (5281560)	Yes (1)	No (4)	Yes (0)	No (1)	No (2)	.56	Low	×
Isogarcinol (11135781)	Yes (1)	No (4)	Yes (0)	No (1)	No (2)	.56	Low	×
α-humulene (5281520)	Yes (1)	Yes (0)	Yes (0)	Yes (0)	No (1)	.56	Low	×
(-)-β-caryophyllene (1742210)	Yes (0)	Yes (0)	Yes (0)	Yes (0)	No (1)	.55	High	×
4-methylhydroatrovirinone (101249096)	Yes (0)	No (1)	Yes (0)	Yes (0)	No (1)	.55	High	×
Gentisein (5281635)	Yes (0)	Yes (0)	Yes (0)	Yes (0)	Yes (0)	.55	High	√
Stigmasterol (5280794)	Yes (1)	No (3)	Yes (0)	No (1)	No (2)	.55	Low	×
2,6-dimethoxy-p-benzoquinone (68262)	Yes (0)	Yes (0)	Yes (0)	Yes (0)	No (1)	.56	High	×

from *in vitro* and *in vivo* for computer-aided drug development.[27] This study step was carried out by PyRx version 0.9 due to the precision.[28] Specific docking was modified to cover only the active sides of target protein (Table 1). Favoured interactions were indicated to the most negative binding affinity then compared to the native ligands and synthesis drugs. After docking analysis, visualization of selected ligand-protein interactions was displayed using BIOVIA Discovery Studio. 2D and 3D interactions will be visualized to examine the interaction groups.[21]

Molecular dynamics analysis

Molecular dynamics was explored to know the stability of ligand-protein interactions.[29] This simulation conducted using CABS-flex 2.0 versionwebserver (http://biocomp.chem.uw.edu.

Table 3. Toxicity prediction results using pkCSM

Compound	AMES toxicity	MRTD	hERG I/II inhibitor	LD50	Hepatotoxicity
Dodecanoic acid	No	-0.340	No/No	1.511	No
Atroviridin	Yes	0.161	No/No	1.918	No
Naringenin	No	-0.176	No/No	1.791	No
Kaempherol	No	0.531	No/No	2.449	No
Quercetin	No	0.499	No/No	2.471	No
Gentisein	Yes	0.166	No/No	2.135	No

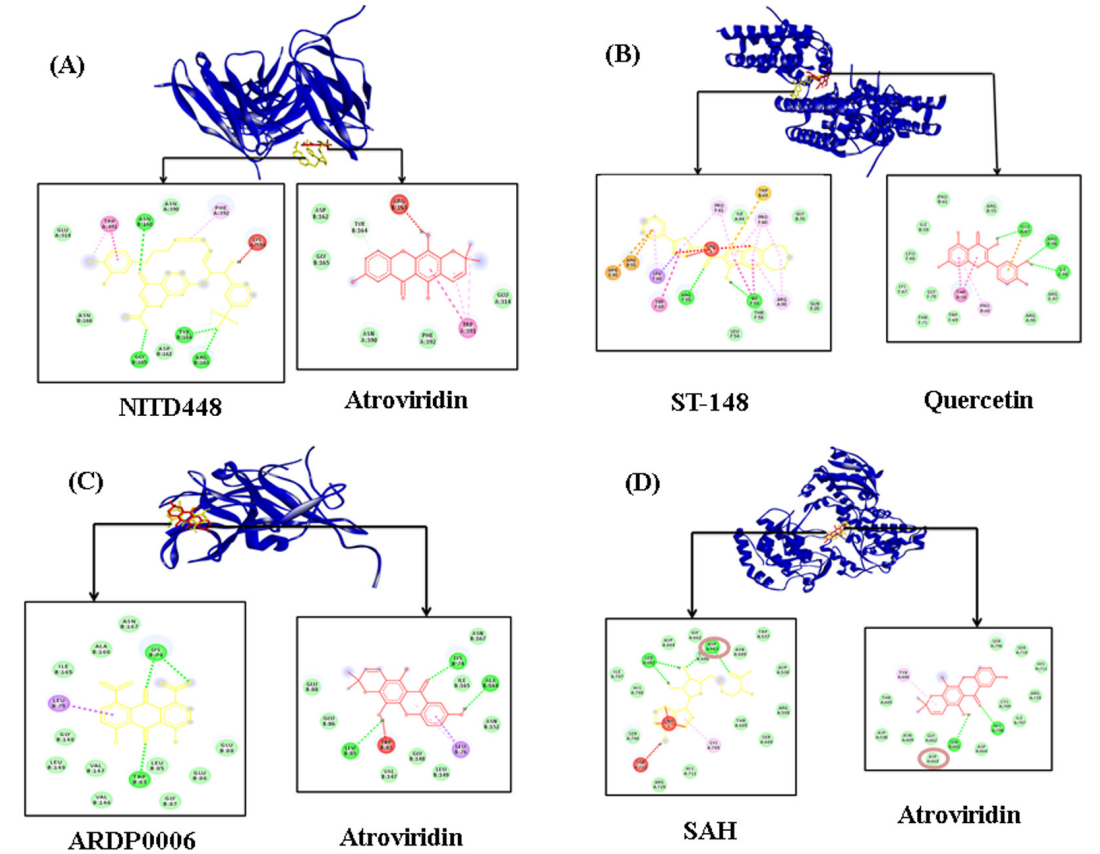

Figure 1. Visualization of docking analysis results against (A) envelop (E), (B) capsid (C), (C) NS2B/NS3, and (D) NS5 proteins. The pink circle indicates the same residue as the active site.

pl/CABSflex2/index) with protein rigidity (1.0), protein restraints (ss2 3 3.8 8.0), global c-alpha restraints weight (1.0), cycle number (50), cycle between trajectory (50), temperature range (1.4), and RNG seed (227) parameter. To maintain the stability, root mean square fluctuation (RMSF) results would be demonstrated with maximum distance of 1-3 Å.[30]

RESULTS

The optimal criteria of phytochemical compounds utilized as pharmaceutical compounds must meet the pharmacological and pharmacokinetics criteria before. Based on the drug similarity, there were 6 compounds matched the criteria consisting dodecanoic acid (lauric acid) (PubChem ID3893), atroviridin (PubChem ID11267348), naringenin (PubChem ID932), kaempherol (PubChem ID5280863), quercetin (PubChem ID5280343), and gentisein (1,3,7-trihydroxyxanthone) (PubChem ID5281635) (Table 2).

According to toxicity analysis from pkCSM, 6 compounds found match with all categories. Atroviridin and gentisein have may

Table 4. Docking analysis results against DENV proteins

Compound	Binding affinity (kcal/mol)			
	E	C	NS2B/ NS3	NS5
Dodecanoic acid	-4.1	-4.9	-4.6	-4.4
Atroviridin	-7.3	-8.5	-8.0	-7.8
Naringenin	-6.7	-7.8	-7.4	-7.0
Kaempherol	-7.1	-8.2	-7.3	-7.0
Quercetin	-6.8	-8.6	-7.6	-7.2
Gentisein	-6.9	-7.2	-7.7	-6.7
NITD448	-6.2			
ST-148		-8.9		
ARDP0006			-6.2	
SAH				-6.6

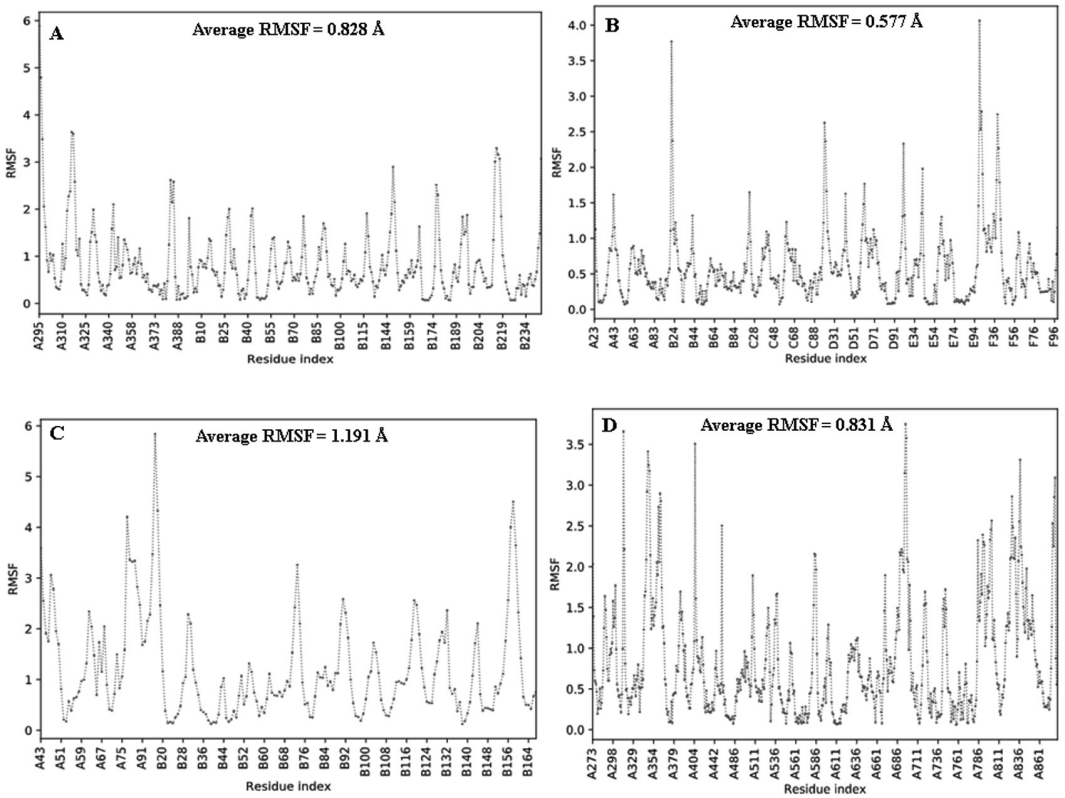

Figure 2. Molecular dynamics analysis results of (A) atroviridin-E, (B) quercetin-C, (C) atroviridin-NS2B/NS3, and (D) atroviridin-NS5 complexes. Each complex was calculated its average RMSF.

cause mutagenic and carcinogenic activities, whereas no compounds show the inhibitor mechanism toward hERG I and II as well as toxicity against liver. On the other hand, the highest MRTD and LD50 found in kaempferol (0.531 log(mg/kg/day) and 2.449 mol/kg and quercetin (0.499 log(mg/kg/day) and 2.471 mol/kg (Table 3).

Molecular docking analysis was utilized to determine the binding affinity of chosen phytochemical compounds from *G. atroviridis*, selected native ligands, and selected synthetic drugs with E, C, NS2B/NS3, and NS5 DENV proteins. The lowest binding affinity of each ligand is projected to play significant and stable biological roles. The results revealed that atroviridin (-7.3, -8.0, and -7.8 kcal/mol) has the most stable binding affinity compared to the native ligands (-3.0, -3.5, and -3.7 kcal/mol) and synthetic drugs (-6.2, -6.2, and -6.6 kcal/mol) against E, NS2B/NS3, and NS5 proteins. Meanwhile, quercetin demonstrated favourable interaction with C protein (-8.6 kcal/mol) although it was still more positive than ST-148 (-8.9 kcal/mol) as synthetic drug (Table 4).

Visualization of ligand-target protein interactions were displayed with different stain of protein and ligand. Protein was labeled yellow and ligand as blue for control and red for selected phytochemical compound. Based on the molecular interaction, atroviridin has less biochemistry interaction against E than the NITD448 as control ligand even though the former one has lower binding affinity value. Both atroviridin and NITD448 do not interact with active sites and have unfavorable bonds that influence the ligand-protein complexes. On the other hand, ligand-capsid protein interactions advantaged ST-148 as control ligand. ST-148 has more interactions than quercetin from *G. atrovridis*. Quercetin as well as ST-148 does not show interaction toward active sites of capsid protein. Atroviridin has more chemical interaction including the unfavourable donor-donor interaction compared to the ARDP0006 as control. However, neither active sites interaction was formed from complexes against NS2B/NS3 by atroviridin nor ARDP0006. SAH (S-adenocylhomocysteine) as control drug of NS5 has unfavourable bump and donor-donor interactions. Meanwhile, both SAH and atroviridin made up same active site Asp663 of NS5 (Figure 1).

Molecular dynamics results showed that NS2B/NS3-atroviridin has the most flexible result with mean of its RMSF around 1.191 Å. On the other hand, C-quercetin displayed more stable contact with 0.577 for its average RMSF. Apart of that, E-atroviridin has with average RMSF 0.828 and NS5-atroviridin stands with 0.831. Overall, the selected ligand-protein complexes have dominant RMSF value around 1-3 Å. (Figure 2)

DISCUSSION

DENV protein is made up both structural and non-structural proteins.[36] Envelop (E), capsid (C), and membrane proteins are included to the structural ones. Envelop is located outside the virus and contains three ectodomains and transmembrane segment.[37] Thus, this protein is in charge to recognize immune cell. DENV via its E protein will attach to several host receptors such as heparin sulphate, β-integrin, and Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin (DC-SIGN) or Cluster of Differentiation 2019 (CD209).[38] Meanwhile, the capsid protein (C) is involved in crucial functions of multiple processes such as structural maintenance, virus assembly, and viral genome release.[7] Recent study showed that C protein shuttles from and to the nucleus of infected cell.[8] Moreover, both of the structural proteins can be used as key targets for drug development.[6,8,39]

Other protein group that discovered in DENV is non-structural protein. This group is classified to NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5 that are transcribed by 11,000 bases genome.[40,41] NS2B, NS3, and NS5 are common proteins for classical targets dengue drug development.[42] NS2B/NS3 is one of the primary targets of dengue antiviral development in recent years.[43] It is trypsin-like serine protease which splits dengue polyprotein into the the separated proteins necessary for viral replication. NS3 plays essential roles for viral growth and maturation post-translation. It is boosted by NS3 that contributed as cofactor for cleavage process.[9] Besides, NS5 is the most enormous non-structural protein (±100 kDa) and highly conserved in DENV genome. It has key play in innate immune response impairment during evasion as well as RNA synthesis, capping, and methylation from

its N-terminal methyltransferase (MTase) and C-terminal RNA-dependent RNA polymerase (RdRp).[10,11,44] This finding raises the possibility of developing antiviral targeting NS2B/NES3 and NS5 as DENV drugs.

G. atroviridis showed numerous health properties as spices and herbal plant. There are 38 phytochemical compounds found from various parts of this plant based on the prior studies.[11] However, limited databases retrieved from PubChem webserver made this study only examine 24 compounds to asses for drug-likeness analysis. Based on the drug-likeness analysis, only 6 phytochemical compounds fulfilled the criteria. In order to analyze the toxicity, the filtered compounds passed with one or no violation of 5 criteria from pkCSM toxicity prediction. After that, selected compounds docked to investigate the interaction stability. The result showed that atroviridin was the most promising pyranoxanthone compounds as anti-DENV inhibits E, NSB/NS3, and NS5 proteins. The binding affinity scores were lower than the selective synthetic drug. Meanwhile, quercetin as a part of flavonoid compounds performed more positive result than ST-148 as the control for C protein. The lowest or the most negative binding affinity is needed to support the stability interaction during the cellular process and has capability as probable inhibitors.[45]

Atroviridin revealed as the most effective compound inhibitor of E protein compared to drug control. In comparison, atroviridin formed π-donor hydrogen bond with Asn390 from subunit A. There are other chemical interactions including hydrophobic (π-π stacked and π-alkyl) and van der Waals (vdw). Meanwhile, NITD448 demonstrated other chemical interactions including carbon hydrogen and conventional hydrogen bonds that known as the strongest chemical interaction.[46] However, the halogen interaction of fluorine and chlorine made this complex satisfied. Halogen can sustain inter- and intramolecular ligand-protein interaction and affect molecular folding but it is weaker than hydrogen bonds. As a result, 20% of drugs that approved by Food and Drug Administration (FDA) were halogenated compounds.[47] On the other hand, some of fluoride in biological interactions show that fluoride is highly oxidative that generate of reactive oxygen species, cell necrosis, and apoptosis.[48] Because of that, the binding affinity of NITD448 had a higher binding than the atroviridin. Both of the compounds exhibited unfavorable donor-donor interactions and not form any interactions towards active sites (Figure 1). But they share same interaction with Trp391 of subunit A with multiple hydrophobic interactions to help inhibit virion recognition to host cell with aromatic and electron clouds.[49]

According to the docking analysis, ST-448 displayed the most negative one among other compounds. ST-148 had hydrogen (conventional), hydrophobic (π-σ, π-π T-shaped, amide-π stacked, alkyl, and π-alkyl), electrostatic (π-cation), and unfavorable interactions. There is miscellaneous interaction towards Trp69 from subunit B namely π-sulphur. This interaction provides aromatic compounds that interact with single sulphur atom.[50] Sulphur gains specific function in biological activities consists folding stability and intermolecular interaction that larger than expected from vdw contacts.[51] Another research reported that S-arene interactions were preferred over O-arene ones due to the non-covalent bonds.[52] Meanwhile, quercetin formed only 3 hydrogen (conventional), 3 hydrophobic (amide-π stacked and π-alkyl), an electrostatic (π-anion), and a vdw interactions. Though quercetin did not possess unfavorable bonds, fewer groups of interaction provided more positive or less satisfied binding affinity via molecular docking.[20] Overall, neither chemical interaction with active sites from atroviridin nor quercetin interacted more intensively with various amino acid and C protein subunits.

NSB2/NS3 shares co-dependency to activate protease activities in dengue evasion.[42] ARDP0006 as control synthetic drug showed higher binding affinity than the atroviridin from *G. atroviridis*. It made this compound is preferred as anti-DENV drug candidate. Atroviridin has 3 conventional hydrogen (Lys74, Leu85, and Ala164), hydrophobic (both π-sigma and π-alkyl interact to Leu76), and one unfavorable donor-donor interaction (Trp83). Unfavourable interaction may indicate the presence of repulsive forces between ligand and target protein. It will affect to the more positive results after molecular screening.[53-55] Next, ARDP0006 demonstrated only 2 kinds of interactions: conventional hydrogen bonds (2

interactions against Lys74 and one interaction against Trp83) and π-sigma interaction (Leu76). Atroviridin as well as ARDP0006 indicated interactions with amino acid residues from subunit B and share same receptor toward Lys74, Leu76, and Trp83 with various bonds. Despite the lack of contacts with catalytic triad and unfavourable bond, atroviridin still revealed best inhibitory activity across the different interactions.[56]

Based on the molecular docking, atrovridin also developed the most efficient inhibitor for another non-structural protein, NS5. Conventional hydrogen bonds and π-alkyl assist stabilization of ligand-protein complex and triggering inhibitory responds against genome replication and disabling the innate immunity.[34] The results of control ligand showed the interaction against active site Asp663 via conventional hydrogen bonds. Besides, it possessed more hydrogen bonds and one hydrophobic interaction. Therefore, unfavourable donor-donor towards Ser710 made the binding affinity and desirable in computational study lower.[54]

Protein flexibility can be indicated by measuring the amplitude of atomic movements when it was simulated.[57] In this analysis, the protein flexibility was represented by RMSF value. Molecular dynamics showed that the most effective inhibitors of selected phytochemical compounds from *G. atroviridis* are significantly stable based on the predominantly RMSF value that fall between 1-3 Å.[58] However, several residue indexes from 4 selected ligand-target protein complexes demonstrated RMSF value >3 Å.

NITD448 is DENV fusion inhibitor that might attach to the ג-OG pocket in DENV E protein. But the antiviral effects only were observed during the initial viral entrance.[59] Besides, ST-148 proposed to impede viral assembly and release range in DENV-1, -3, and -4. The antivirus potentially beneficial work occurred after post infection and post entry stage.[38,60] Following that, ARDP0006 was identified suppress DENV-2 replication via virtual screening and cell culture.[61] In addition, SAH in combination with sinefungin, compound 10, and guanosine monophosphate (GMP) failed to block NS5 with good progress due to the cell non-permeability.[62] Some of the lack potential of synthetic antivirals above is required to address some of inhibitory functioned compounds towards specific target of DENV both targeting structural and non-structural proteins.[38,44] *G. atroviridis* has the potentials to be the next natural anti-DENV drugs. *In silico* analysis through molecular docking revealed that atroviridin has the most effective potential against E, NS2B/NS3, and NS5 proteins. Furthermore, *in vitro* and *in vivo* analyses still required further to confirm anti-DENV efficiency.

CONCLUSION

G. atroviridis Griff. ex T. Anders showed anti-DENV properties. Its phytochemical compounds have been discovered as DENV antiviral by inhibiting E, C, NS2B/NS3, and NS5 proteins. Atroviridin has the most negative binding affinity to the E, NS2B/NS3, and NS5 proteins according to the docking analysis. Besides, quercetin showed the second most effective compound by binding to the C protein after the ST-148 potential. Molecular dynamic simulation demonstrated the stable results for those two compounds. Further wet laboratory researches are required to establish the properties efficacy as anti-DENV.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved the final manuscript for publication.

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None.

DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

None.

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