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RESEARCH ARTICLE

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In silico research of anti-CHIKF phytoconstituent-based from *Physalis peruviana* leaves via molecular docking and dynamics analyses

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Abstract

Chikungunya fever (CHIKF) is an infectious disease that has similar symptoms with dengue fever (DF). Several drugs have been offered to treat both dengue (DENV) and chikungunya virus (CHIKV). Investigating anti-CHIKF potential from nearby plants is one strategy to produce potential drug to reduce CHIKF in endemic countries. *Physalis peruviana* is one the promising object to be new anti-CHIKV drug candidate. This study aimed to analyze the anti-CHIKV agents from leaf parts of *P. peruviana*. Ligand and protein samples were collected from multiple sources. The phytoconstituents were evaluated their drug-likeness properties throughout SwissADME webservers. Selected ligands then docked via PyRX and measured the output by binding affinity. Visualization of the best outputs was carried out using BIOVIA Discovery Studio. CABS-flex was carried out to screen the RMSF of molecular dynamics activity of the best complex. The result showed that 1,2-benzenecarboxylic acid had the lowest binding affinity following suramin as control with -5.1 and -11.1 kcal/mol after targeting E2 domain protein of CHIKV. This led to the conclusion that 1,2-benzenecarboxylic acid could be forecast as predictive anti-CHIKF therapeutic candidate. Additional *in vitro* and *in vivo* studies are needed to validate this outcome.

Keywords: 1,2-benzenecarboxylic acid, Physalis peruviana, Chikungunya, CHIKV, Antiviral

Introduction

Chikungunya virus (CHIKV) is a single-stranded RNA virus cause's chikungunya fever (CHIKF)[1]. This virus belongs to the genus Alphavirus and is spread through bites from female *Aedes aegyptii* and *A. albopictus* bites[2]. The symptoms of CHIKF resembles of dengue fever (DF) which is caused by dengue virus (DENV) and spread by the same vector mosquitos[3–5]. Since both CHIKF and DF share common symptoms, CHIKF is frequently misdiagnosed as DF. Several studies identified FDA-approved drugs namely doxorubicin, lomibuvir, resveratrol, elvitegravir, and enalprilat with anti-DENV activity using system biology and in vitro experiments[6]. Investigating anti-CHIKF potential from surrounding plants is one way to develop potential drug to suppress CHIKF in endemic countries.

Physalis peruviana is one of the weed that produces high levels of antioxidant substances throughout the body[7]. Its roots have several phytoconstituents that have anti-inflammatory and diarrheal traditional medicine in several tribes worldwide[8,9]. However, no previous records found of *P. peruviana* treated as anti-CHIKF before were uncovered. These chemicals can be utilized to be simulated as a drug in various in silico technics. Thus, the objective of this study was to analyze the inhibitory activity of anti-CHIKF agents derived from *P. peruviana* leaf elements.

Materials and methods

Study area

This study conducted using *P. peruviana* phytoconstituents from the leaf portions and target protein were obtained from online database[7,10]. SMILES of the compounds were obtained in order to determine the drug similarity in public website. Selected phytoconstituents would be selective docked to CHIKV envelope domain 2 (E2) and evaluated the chemical interactions through different softwares. The most effective results would be simulated by molecular dynamics in open server[11].

Procedures

The compounds contained in leaves of *P. peruviana* and control ligand suramin (CID 5361) were retrieved from PubChem, Human Metabolome Database (HMDB), and ChemSpider, respectively. The information gathered from this database consisted of Compound Identifier (CID) and simplified molecular-input line-entry system (SMILES)[12]. In addition, E2 protein was downloaded in protein database (PDB file from RCSB PDB. Protein was cleaned to eliminate the water, native ligand, and other compartment contents for screening purpose through BIOVIA Discovery Studio 2020 software[13].

Selected constituents obtained from the database were screened using SwissADME webserver to medicinal qualities that combined with those of the Lipinski, Ghose, Veber, Egan, and Muegge rules. Filtered drug candidates would be reviewed by fulfilling with 0 and 1 violations[11]. Molecular docking simulation method is part of *in silico* strategy for determining the inhibitory of the ligands to the target protein. This method employed was blind docking and carried out using PyRx 0.9.9 version with academic license[14]. Molecular dynamics simulation was used for CABS-flex 2.0 webserver with the default setting. The result of root mean square fluctuation (RMSF) would be calculated to define the flexibility of ligand and target protein interaction. The optimal RMSF value is below 3Å[11].

Data analysis

Docking results were downloaded per interaction and analyzed throughout the binding affinity (kcal/mol) and chemical bonds. The position and interaction of docking analysis were established by

BIOVIA Discovery Studio. The best results of structure of ligand-protein interactions observed in 3 dimension (3D) and 2D structures consisted specific staining and interactions[12,13]. Molecular dynamics analysis was conducted using Microsoft Excel to average the RMSF value[11].

Results

According to the literature review, there were 18 phytochemicals revealed in leaves of *P. peruviana*[7]. Those compounds were tested in various webservers to get the CID and SMILE. However, only 11 compounds left alongside with sumarin (**Table 1**). On the other hand, envelope protein complex was retrieved using information from related sources (**Table 2**).

Table 1. Phytoconstituents from Leaves of *P. peruviana*

Phytoconstituent	CID	Source
(S)-4-Iodo-1,2-epoxybutane	-	-
1,1,1,5,7,7,7-Heptamethyl-3,3 bis(trimethylsiloxy)tetrasiloxane	6329081	PubChem
1,2,3-Tri(t-butyl)cyclopropenylium tribromide	-	-
1,2-Benzenedicarboxylic acid	1017	PubChem
3,3-Dimethyl-hexane	HMDB0031418	HMDB
3,3-Dimethyl-octane	121758	ChemSpider
3α-Tigloylnxytropane	-	-
3β-Acetoxytropane	-	-
Cuscohygrine	1201543	PubChem
Diethyl ester	7478	ChemSpider
Dimethyl-flubendazole	-	-
Docosane	12405	PubChem
Eicosamethylcyclodecasiloxane	453230	ChemSpider
Hygrine	440933	PubChem
N-Methylpyrrolidinylhygrine A	-	-
N-Methylpyrrolidinylhygrine B	-	-
Physoperuvine	443008	PubChem
Tropine	449293	PubChem

Drug-likeness identification chose phytoconstituents that have drug-like characteristics. Seven compounds were filtered and fulfilled the drug-likeness identification and proceeded to the next steps: molecular docking and molecular dynamics (**Table 3**).

Table 2. Envelope protein of CHIKV

Protein	PDB ID	Reference
Envelope	3N42	[10]

After filtering in previous steps, we got 7 phytoconstituents that matched drug-likeness parameters including 1,1,1,5,7,7,7-hepatomethyl-3,3 bis(trimethylsiloxy)tetrasiloxane, 1,2-benzenedicarboxylic acid, cuscohygrine, eicosamethylcyclodecasiloxane, hygrine, physoperuvine, and tropine. Those ligands would be simulated by computer with isoniazid as control. Molecular docking was carried out by blind docking and resulted 1,2-benzenedicarboxylic acid as the most potent inhibitors

after suramin. In contrast, other constituents had no binding affinity outcomes that exhibited the inappropriate structure for docking by PyRx (**Table 4 and 5**).

Table 3. Drug-Likeness Identification

Phytoconstituent	Lipinski	Ghose	Veber	Egan	Muegge	Status
1,1,1,5,7,7,7-Heptamethyl-3,3 bis(trimethylsiloxy)tetrasiloxane	Yes (0)	Yes	Yes	Yes	No (1)	√
1,2-Benzenedicarboxylic acid	Yes (0)	Yes	Yes	Yes	No (1)	√
3,3-Dimethyl-hexane	Yes (1)	No (1)	Yes	Yes	No (2)	×
3,3-Dimethyl-octane	Yes (1)	No (1)	Yes	Yes	No (3)	×
Cuscohygrine	Yes (0)	Yes	Yes	Yes	Yes	√
Diethyl ester	Yes (0)	No (3)	Yes	Yes	No (1)	×
Docosane	Yes (1)	No (1)	No (1)	No (1)	No (3)	×
Eicosamethylcyclodecasiloxane	Yes (1)	No (4)	Yes	No (1)	No (2)	√
Hygrine	Yes (0)	No (1)	Yes	Yes	No (1)	√
Physoperuvine	Yes (0)	No (1)	Yes	Yes	No (1)	√
Tropine	Yes (0)	No (1)	Yes	Yes	No (1)	√

1,2-benzenedicarboxylic acid was chosen to determine the chemical interactions and visualization with comparison by the suramin. According to the chemical interaction, 1,2-benzenedicarboxylic acid formed less hydrogen bond, hydrophobic interaction, and electrostatic interaction. In contrast, isoniazid had more interactions with CHIKV E2 by more hydrogen bond, hydrophobic interaction, electrostatic interaction as well as pi-sulfur interaction. These findings revealed Arg104 and Phe141 had most favorable interactions based on the virtual screening (**Table 5**, **Figure 1**).

Table 4. Molecular Docking Results of Selected Phytoconstituents of *P. peruviana* against CHIKV E2

Phytoconstituent	Binding affinity (kcal/mol)
Suramin (control)	-11.1
1,1,1,5,7,7,7-Heptamethyl-3,3 bis(trimethylsiloxy)tetrasiloxane	-
1,2-Benzenedicarboxylic acid	-5.7
Cuscohygrine	-5.2
Eicosamethylcyclodecasiloxane	-
Hygrine	-4.4
Physoperuvine	-4.7
Tropine	-4.9

After molecular docking, complex of suramin and 1,2-benzenedicarboxylic acid with CHIKV E2 had been simulated by molecular dynamics. The RMSF outcomes met below 3 Å in 0.97 and 0.89 Å respectively. It means that the interaction complex is quite stable to make inhibition activities (Figure 2).

Discussion

In silico approach to analyze antibacterial activity of *P. peruviana* phytoconstituents from leaves targeted with E2 of CHIKV revealed its inhibitory activity and pharmacological characteristics from 1,2-benzenedicarboxylic acid. This constituent was detected diversely in *P. peruviana* parts like in body,

fruits, leaves, roots, and seeds[15]. 1,2-Benzenedicarboxylic acid is phthalic acid esters acts as antifungal against Fusarium and primary roots supplementary metabolite in plant roots[16]. Furthermore, this constituent also contains antimicrobial, antioxidant, anticancer, thyroid inhibitor, and anti-inflammatory properties[17].

Table 5. Chemical Interaction of Docking Outcomes

Ligand	Residues	Interaction	
		Category	**Type**
Suramin	Arg86, Thr92, **Arg104**, **Arg104**, Ser122, Ile136, **Phe141**, Arg144	Hydrogen bond	Conventional
	Gly82, Ser122, Val135		Carbon-hydrogen
	Phe84, Phe84	Hydrophobic interaction	Pi-pi stacked
	Phe141		Pi-pi T shaped
	Pro106, Arg144		Pi-alkyl
	Phe141	Electrostatic interaction	Pi-anion
	Phe141	Others	Pi-sulfur
1,2-benzenedicarboxylic acid	Pro134, Ile136	Hydrogen bond	Conventional
	Asp43		Carbon-hydrogen
	Phe141	Hydrophobic interaction	Pi-pi stacked
	Arg104	Electrostatic interaction	Pi-cation

Note: same residues are written in bold.

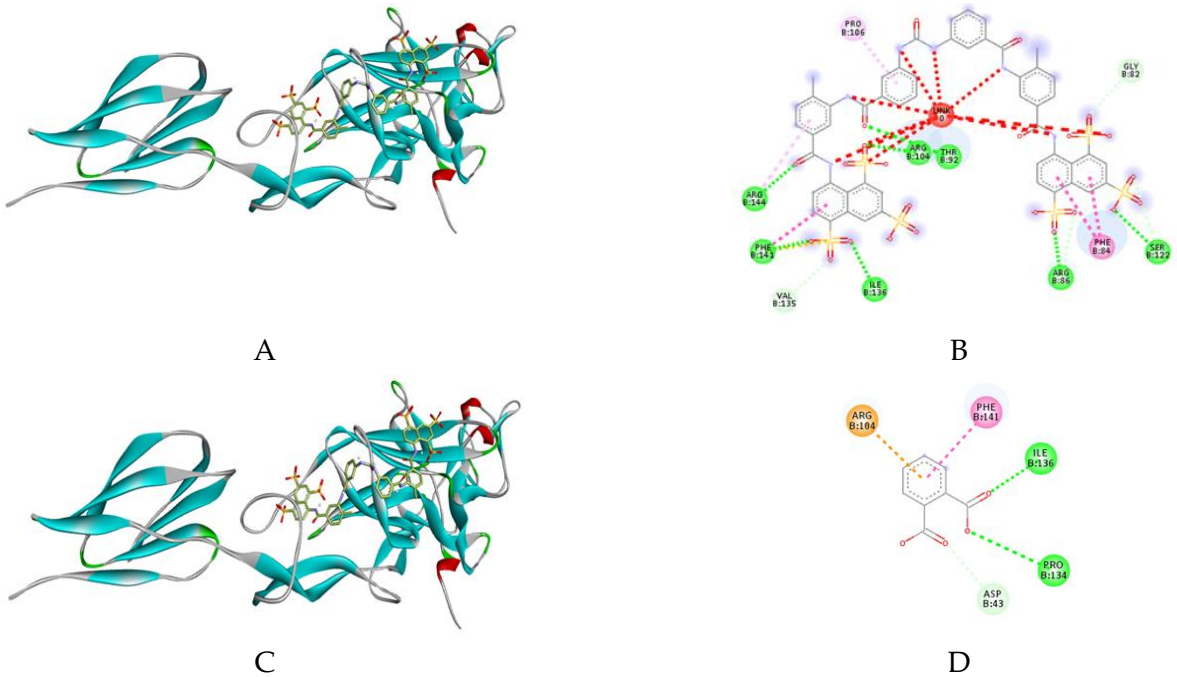

Figure 1. E2 of CHIKV interaction after molecular docking against suramin (A = 3D and B = 2D structure) and 1,2-benzenecarboxylic acid (C = 3D and D = 2D structure).

CHIKV enters cells via receptor-mediated endocytosis and the acidic endosomal environment triggers are irreversible rearrangement of the surface glycoprotein of mature virion. E2 is one of the CHIKV glycoprotein that carries primary antigenic determinants and forms icosahedral shell at the virion surface. This glycoprotein was produced from furin cleavage and is responsible for receptor binding[18]. As a potential, this domain has great prospective for vaccine design[10].

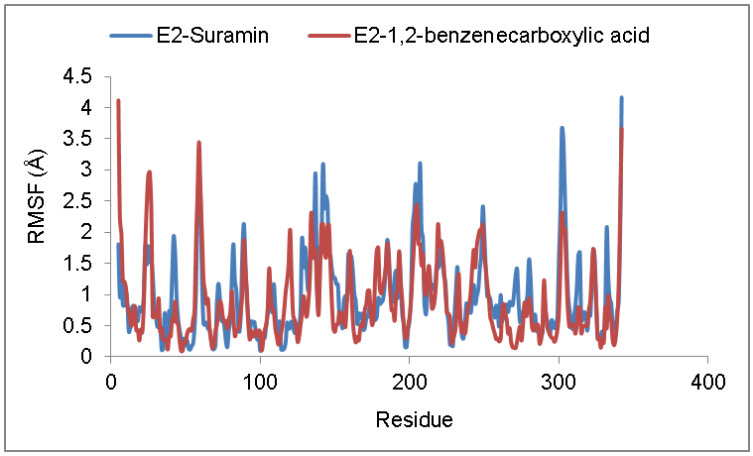

Figure 2. RMSF value of E2 complex with suramin and 1,2-benzenecarboxylic acid

Based on the molecular docking, 1,2-benzenedicarboxylic acid had the more positive result than the control drug, suramin. This conclusion is due to the lack of hydrogen bond, hydrophobic interaction, and electrostatic interaction as well as the absence of any extra interactions such as pi-sulfur (**Table 5**, **Figure 1**). These interactions play vitally in biological and cellular activities, resulting stability and turnover of proposed interaction[19–21]. In addition, Arg104 and Phe141 form favorable residues in ligand-protein complex (**Table 5**). Molecular dynamics revealed that suramin demosntarted more flexible finding due to the higher value of RMSF than the selected constituent (**Figure 2**). However, this data is still being considered in terms of of proposed drug interaction.

Conclusions

1,2-benzenedicarboxylic acid from *P. peruviana* has promise potential as anti-CHIKV agents due to its ability to block the interaction of E2 despite being outperformed by suramin. This outcome requires additional trials with *in vitro* and *in vivo* analyses to reinforce the evidence of *in silico* study.

Acknowledgments

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Conflicts of Interest

There are not potential conflicts of interest.

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