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Molecular Docking of Bioactive Components of Tawa-Tawa (*Euphorbia hirta l.)* Leaves as Inhibitor Against the NS2B-NS3 Protease of DENV-2

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From January 1 to August 20, 2022, the Philippines recorded 128,346 dengue cases and 422 deaths, a significant increase from the 50,982 cases in 2021, according to the World Health Organization. This study aims to simulate the inhibition of the NS2B-NS3 protease of DENV-2 (PDB Code: 2FOM) using bioactive compounds from Tawa-Tawa and analyzing the toxicity properties of these compounds. The methods include AutoDock Vina for molecular docking, Biovia for interaction visualization, SwissADME for predicting oral bioavailability via Lipinski Analysis, and admetSAR for assessing blood-brain barrier permeability and toxicity. Ribavirin was used as a control drug. Out of over 200 phytochemicals present in Tawa-tawa, 18 were identified with binding affinities ranging from -10.50 to -5.76 kcal/mol, all surpassing the control drug Ribavirin's affinity of -5.41 kcal/mol. Further analysis using Lipinski's rule and ADMET tests narrowed these 18 candidates down to three potential drug candidates. Three compounds—Corchoionoside C, Luteolin-7-O-beta-D-glucopyranoside, and Corilagin — exhibit promising binding affinities and hydrogen bond interactions with the protease This study provides a deep understanding of Tawa-Tawa's bioactive components interacting with the catalytic triad of the NS2B-NS3 protease of DENV-2 and predicts the ADMET profiles to assess potential toxicity.

1. Introduction

The primary transmission of dengue, which is the Dengue Fever Virus (DENV), is the Aedes aegypti mosquito. It may result in minor symptoms or serious illnesses like Dengue Shock Syndrome (DSS) and Dengue Hemorrhagic Fever (DHF) (Nanaware et al., 2021). Even though dengue has spread widely throughout the Philippines since 1958, there isn't a vaccination that fights against all four DENV serotypes (Undurraga et al., 2017). As of September 2022, the WHO reported 128,346 cases from January 1 to August 20, a 152 % increase from 2021 (World Health Organization, 2022). Plants have several phytochemicals that could inhibit the Dengue virus thus extraction of phytochemicals is optimized using several methods (Laina et al., 2021). The pharmacological properties of tawa-tawa (Euphorbia hirta l.) include antibacterial, antimalarial, and anti-inflammatory properties (Kumar et al., 2010). According to recent research, it might suppress viruses including malaria (Shah et al., 2019) and SARS-CoV-2(Cayona and Creencia, 2022). There are 298 identified phytochemicals present in Euphorbia hirta L. (Cayona and Creencia, 2022). The efficacy of these phytochemicals against the Dengue virus has not yet been studied. Current research lacks the identification of Tawa-Tawa bioactive compounds that may inhibit DENV replication. This study aims to fill this gap by utilizing bioactive compounds from Tawa-Tawa to mimic the inhibition of the NS2B-NS3 protease of DENV-2. The approach employs AutoDock Vina for ligand interaction analysis, virtual screening, and molecular docking. AutoDock Vina is widely recognized as a standard tool for drug screening due to its efficiency and accuracy in molecular docking (Gaillard, 2018). It is frequently used in modern drug discovery for predicting the binding of small molecules to protein targets. Biovia will also be used to visualize the intermolecular forces of attraction between the ligand and the Dengue virus.The study will also utilize ADMETox to screen potential drugs for oral viability, carcinogenicity, hepatotoxicity, Blood-Brain Barrier (BBB) penetration, and LD50 category. In silico

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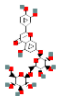
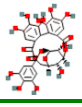
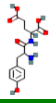
ADME-Tox prediction remains crucial in aiding pharmaceutical companies to select suitable candidate drugs before investing in costly clinical trials (Alqahtani, 2017)

2. Methodology

2.1 Ligand Preparation

Eighteen high scoring (based on docking score) bioactive components of Tawa-Tawa (*Euphorbia hirta l.*) leaves and the control drug *Ribavirin* were identified. These compounds were downloaded in 3D conformer SDF file format from PubChem, converted to PDB files using Cygwin and Open Babel, and prepared for molecular docking using AutoDockTools by adding Gasteiger charges and saving them as PDBQT files. The retrieved eighteen bioactive components CID and 2D structure were presented in Table 1.

Table 1: The 18 bioactive components of Euphorbia hirta L. with PubChem CID and 2D chemical structure.

Compounds (CID)	2D Structure	Compound (CID)	2D Structure	Compounds (CID)	2D Structure
24-hydroperoxycycloart-25-en-3beta-ol (15293070)		Cycloart-23-ene-3beta,25-diol (5470009)		Kaempferol-3-O-glucuronide (74315888)	
2-coumaroylquinic acid (6441280)		Ellagic acid (5281855)		Luteolin-7-O-beta-D-glucopyranoside (14032967)	
Brevifolin carboxylic acid (9838995)		Epicatechin (72276)		Syringin (5316860)	
Chelidonic acid (7431)		Feruloyl malate (71694479)		Trigallic Acid (90470472)	
Corchoionoside C (10317980)		Hyperoside (5281643)		Tryptophan (6305)	
Corilagin (73568)		Isojaponin A (101836940)		Tyrosylglutamate (19816750)	

2.2 Protease Preparation

The NS2B-NS3 protease (PDB Code: 2FOM) was prepared using AutoDockTools by removing water molecules and attached ligands and adding polar hydrogens and Kollman charges to improve prediction accuracy (Sunani et al., 2022). The protease was saved in PDBQT format. CavityPlus identified the best binding sites, with grid box coordinates for the binding site XYZ coordinates (96, 70, 76) and the center grid box coordinates (-8.972, 4.389, -4.444).

2.3 Molecular Docking

The 18 high scoring bioactive components and *Ribavirin* were docked against the NS2B-NS3 Protease (2FOM) using AutoDock Vina, which provided 3D ligand positions and binding affinity results in kcal/mol (Trott and Olson, 2010). PyMOL is used for verification to find out whether the process is valid. If the RMSD results are less than 2Å then the parameters used are considered correct (Ruswanto et al., 2022).

2.4 Scoring Function and Energy Calculation

Binding energy is based on Gibbs free energy (ΔG in kcal/mol). An unfavorable ΔG indicates a powerful bind between the NS2B-NS3 Protease (2FOM) and Tawa-Tawa components (Forli et al., 2016). The predicted ΔG value comes from the scoring function Eq(1):

$$S1 = \Delta^{o}G = g(c_1\text{-}c_{intra1}) = g(c_{inter1}) \quad (1)$$

In this Eq(1) S1 refers to the scoring function used in molecular docking to calculate Gibbs free energy change score $\Delta^{o}G$. Where c1 represents the conformation or interaction resulting from either intramolecular (cintra1) or

intermolecular (cinter1) both hydrophobic reactions and hydrogen bonds, and g is a non-linear function (Sukmanadi and Mustofa, 2021).

2.5 ADME and Toxicity Analysis

The 18 high scoring bioactive components were used to predict druglikeness using the SwissADME's Lipinski Rule and toxicity using admetSAR.

3. Results and Discussion

Molecular docking, ADME predictions, and toxicity analysis was carried out on Tawa-Tawa bioactive compounds (*Euphorbia hirta L.*) against the NS2B-NS3 protease of DENV-2. The bioactive components docking score and binding features is shown in Table 2. The docking scores ranged from -10.50 to -5.76 kcal/mol and all compounds have higher binding affinity than the control drug Ribavirin. Using LigPlot+ hydrogen bond interactions of *Euphorbia hirta l.* with 2FOM amino acid residues was discovered. The hydrogen bonds are formed with Gly153, Gly151, Asp75, Trp50, His51, Val155, Ser135, Thr120, Asn119, Asp17, and Asn152. The 18 bioactive components and the control drug Ribavirin interacted with the catalytic triad His-51, Asp-75, and Ser-135 via hydrogen bonding or hydrophobic contacts.

Table 2: NS2B-NS3 Protease (2FOM) and Euphorbia hirta L. calculated docking score (in kcal/mol) and interactions based on hydrogen bond analysis.

Compound	Docking Score (kcal/mol)	Binding Features (Hydrogen bond in Å)	Compound	Docking Score (kcal/mol)	Binding Features (Hydrogen bond in Å)
Corchoionoside C	-10.50	Gly153 (3.13 Å)	Brevifolin carboxylic acid	-7.64	Gly153 (3.07 Å), (3.11 Å)
Luteolin-7-O-beta-D-glucopyranoside	-9.05	Val155 (3.14), His51 (2.96 Å), (2.67 Å), (2.86 Å)	24-hydroperoxycycloart-25-en-3beta-ol	-7.58	Asn119 (3.13 Å), Gly153 (2.91 Å)
Ellagic acid	-8.85	Gly153(3.28 Å)	2-coumaroylquinic acid	-7.55	Thr120 (2.95 Å), Asn119 (3.14 Å), His51 (3.18 Å), (2.57 Å), (2.89 Å)
Corilagin	-8.55	Gly153 (3.18 Å), Trp50 (3.12 Å)	Isojaponin A	-6.80	Ser135 (2.92 Å), His51 (3.00 Å), Asp75 (2.57 Å)
Cycloart-23-ene-3beta,25-diol	-8.49	Asp17 (2.57 Å), (2.86 Å)	Syringin	-6.61	Thr120 (2.99 Å)
Kaempferol-3-O-glucuronide	-8.37	His51 (2.98 Å), (2.86 Å)	Feruloyl malate	-6.41	Gyl153 (3.14 Å)
Trigallic Acid	-8.32	His51 (3.12 Å), (2.57 Å), (2.86 Å), Gly153 (2.94 Å), Val155 (2.91 Å)	Tyrosylglutamate	-6.37	Gly151 (2.80 Å), Asp75 (2.96 Å)
Hyperoside	-8.19	His51 (2.96 Å), (2.57 Å), (2.86 Å), Gly153 (3.30 Å), (2.09 Å)	Tryptophan	-5.80	Asn152 (3.06 Å)
Epicatechin	-8.10	Gly153 (3.07 Å), (3.11 Å)	Chelidonic acid	-5.76	Gly151 (3.16 Å)
Ribavirin	-5.41	His51 (3.05 Å), Arg54 (3.18 Å)			

Three bioactive components, including Corchoionoside C, Luteolin-7-O-beta-D-glucopyranoside, and Ellagic acid show promising binding affinities. Several hydrogen bonds are formed in the active site between the hydroxyl and carbonyl groups of these phytochemicals and the residues of various amino acids. Another three bioactive components, Hyperoside, Corilagin, and Kaempferol-3-O-glucuronide, also exhibit high binding affinities to the protease with the formation of hydrogen bonding and hydrophobic bonding to the oxygen and nitrogen atoms of the bioactive components and 2FOM itself. Corchoionoside C and Ellagic Acid exhibited a binding affinity of –10.50 kcal/mol and –8.85 kcal/mol that inhibits the Ser-135 amino acid through hydrogen

bonding. Luteolin-7-O-beta-D-glucopyranoside showed a binding affinity of –9.05 kcal/mol that inhibits the catalytic triad (Asp-75, His-51, and Ser-135) due to its abundance of oxygen atoms present in the bioactive component that binds to the catalytic triad. Corilagin showed a binding affinity of –8.55 kcal/mol that inhibits some parts of the catalytic triad through hydrophobic bonding with His-51 nad Asp-75. Kaempferol-3-O-glucuronide exhibits a binding affinity of –8.37 kcal/mol that also inhibits some parts of the catalytic triad by hydrogen bonding of Asp-75 and His-51 due to its abundance of oxygen atoms within the bioactive component. Hyperoside showed a binding affinity of –8.19 kcal/mol that also inhibits all three of the amino acids that are present in the catalytic triad through hydrogen bonding. It shows that high abundance of oxygen atoms within the bioactive components result in higher binding affinities and higher chance of inhibiting the catalytic triad whether through hydrogen bonding or hydrophobic bonding.

Table 3: Blood-Brain Barrier, Toxicity Analysis and Lipinski Result of the 18 bioactive components of Euphorbia hirta L.

Compound	Blood-Brain Barrier (BBB)		Acute Oral Toxicity		Carcinogenicity (Binary)		Hepatotoxicity		Lipinski Result
	Value	Probability	Value	Probability	Value	Probability	Value	Probability	
24-hydroperoxycycloart-25-en-3beta-ol	+	0.6500	III	0.4576	-	0.6306	-	0.6968	Orally viable
2-coumaroylquinic acid	-	0.5250	III	0.7858	-	0.9064	+	0.6243	Orally viable
Brevifolin carboxylic acid	-	0.6750	IV	0.4155	-	1.0000	+	0.6000	Orally viable
Chelidonic acid	-	0.7500	III	0.5236	-	0.8434	+	0.6750	Orally viable
Corchoionoside C	-	0.5500	III	0.7159	-	0.9800	-	0.8000	Orally viable
Corilagin	-	0.7750	III	0.4887	-	0.9900	-	0.6750	Not orally viable
Cycloart-23-ene-3beta,25-diol	+	0.7000	III	0.6549	-	0.8400	-	0.6125	Orally viable
Ellagic acid	-	0.8250	II	0.6020	-	1.0000	+	0.6948	Orally viable
Epicatechin	-	0.6750	IV	0.6433	-	0.9700	-	0.7375	Orally viable
Feruloyl malate	-	0.6000	III	0.6197	-	0.8018	-	0.7000	Orally viable
Hyperoside	-	0.7750	III	0.4045	-	1.0000	-	0.5196	Not orally viable
Isojaponin A	-	0.7000	I	0.4630	-	0.9800	+	0.5825	Orally viable
Kaempferol-3-O-glucuronide	-	0.8250	II	0.4816	-	1.0000	-	0.6782	Not orally viable
Luteolin-7-O-beta-D-glucopyranoside	-	0.7500	IV	0.4763	-	0.9900	-	0.8821	Not orally viable
Syringin	-	0.5250	III	0.7551	-	0.6989	-	0.7822	Orally viable
Trigallic acid	-	0.7000	III	0.8285	-	0.7997	+	0.7125	Not orally viable
Tryptophan	+	0.8500	IV	0.6272	-	0.7800	+	0.5166	Orally viable
Tyrosylglutamate	-	0.5500	III	0.6636	-	0.8122	-	0.6146	Orally viable

The Blood-Brain Barrier (BBB) is crucial in preventing neuroinvasion by viruses, including the four DENV serotypes, which can cause neurological issues by entering the central nervous system via the bloodstream. DENV-2 and DENV-3 are most associated with BBB infection (Calderon-Pelaez et al., 2019). Neurological effects are seen in all age groups in dengue-endemic areas (Hapuarachchi et al., 2015). Microvascular endothelial cells protect the CNS from toxins, provide nutrients, and filter harmful compounds (Persidsky et al., 2006). In Table 3 predicts the BBB penetration of compounds: bioactive components with a (+) value are likely to cross the BBB, while those with a (-) value are not. Out of 18 bioactive components, three are predicted to penetrate the BBB: 24-hydroperoxycycloart-25-en-3beta-ol, Cycloart-23-ene-3beta,25-diol, and Tryptophan. The toxicity analysis evaluates the predicted toxicity of *Euphorbia hirta l.* bioactive components. Acute oral toxicity is classified into four categories based on LD50 values: I (danger, LD50 less than or equal to 50 mg/kg), II (warning, LD50 greater than 50 mg/kg and less than or equal to 500 mg/kg), III (caution, LD50 greater than 500 mg/kg and less than or equal to 5,000 mg/kg), and IV (non-required, LD50 greater than or equal to 5,000 mg/kg) (Lipinski, 2001). Most components fall into categories III and IV, with only Isojaponin A in category I, and Ellagic acid and Kaempferol-3-O-glucuronide in category II. Carcinogenicity is assessed using binary model. The binary model predicts whether compounds are carcinogenic (+) or not (-) (Syahputra et al., 2021). All *Euphorbia hirta l.* bioactive components are non-carcinogenic. Hepatotoxicity is the ability of the compound to damage the liver. Compounds with a (+) value are hepatotoxic, while those with a (-) value are not (Syahputra et al., 2021). Seven bioactive compounds are predicted to have hepatotoxicity: Brevifolin carboxylic acid, Chelidonic acid, Ellagic acid, Isojaponin A, Tryptophan, 2-Coumaroylquinic acid, and Trigallic acid. The others are predicted to be non-hepatotoxic. The substantial presence of toxic components in medicinal plants like Tawa-tawa, as indicated by ADMETox results, suggests that it is not advisable to simply boil the plant in water and consume the solution orally (Farzaei, 2020).

Pharmacokinetic solubility and permeability predictions were performed using SwissADME's Lipinski parameters, shown in Table 3. The Lipinski rule determines the drug-likeness of compounds for absorption based on four guidelines: 1) Molecular weight must be less than or equal to 500 g/mol, 2) Hydrogen bond acceptors must be less than or equal to 10, 3) Hydrogen bond donors must be less than or equal to 5, and 4) MlogP be less than or equal to 4.15. Compounds should not violate more than one guideline to ensure good absorption and permeability (Lipinski et al., 2001). Compounds with molecular weight > 500 g/mol diffuse slowly across lipid membranes, hindering absorption. Hydrogen bond donors must be ≤ 5 and acceptors ≤ 10 to permeate through the lipid membrane, as they interact with water due to their aquaphilic nature. MlogP, the Moriguchi octanol-water partition coefficient measures the compound solubility and lipophilicity. The higher MlogP values improve lipid membrane permeation but can hinder dissolution in gastric or intestinal fluid, affecting absorption (Lipinski et al., 2001). Lipinski's 1997 publication of the 'Rule of 5' (Ro5) stands as one of the most influential works in recent medicinal chemistry (Walters, 2012)

4. Conclusion

Based on our simulations, Corchoionoside C exhibits the highest binding affinity score and successfully passes both the Lipinski Oral Viability test and all ADMETsar tests. Therefore, Corchoionoside C emerges as the most promising candidate for a potential Dengue drug. Six of the *Euphorbia hirta l.* bioactive components were identified as potential inhibitors of the NS2B-NS3 Protease (2FOM) of DENV-2: Corchoionoside C (-10.50 kcal/mol), Luteolin-7-O-beta-D-glucopyranoside (-9.05 kcal/mol), Corilagin (-8.55 kcal/mol), Kaempferol-3-O-glucuronide (-8.37 kcal/mol), Epicatechin (8.10 kcal/mol), Syringin (-6.61 kcal/mol). These compounds are proven to bind at the catalytic triad of the protease through hydrogen bonding with high binding affinities. Only three bioactive components (Corchoionoside C, Epicatechin, and Syringin) have passed the Lipinski Test, Blood-Brain Barrier, and Toxicity analysis while the other three bioactive components (Luteolin-7-O-beta-D-glucopyranoside, Corilagin, Kaempferol-3-O-glucuronide) have not passed the Lipinski Test but passed the Blood-Brain Barrier and Toxicity Analysis. This means the latter 3 bioactive components would only be administered through injection within the human body. Other bioactive components from *Euphorbia hirta l.* should still be considered. Lipinski analysis applies only to oral absorption, so other administration routes like injection are possible. For the BBB, unless the target is the central nervous system the blood-brain barrier value should be negative. Further research must be verified if these six bioactive components can inhibit the NS2B-NS3 protease of DENV-2 through clinical trials whether it is *in-vitro* or *in-vivo and* examine other possibilities of drug-likeness in the bioactive components of *Euphorbia hirta l.*

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