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Original Article

In silico analysis of anti-dengue activity of faloak (*Sterculia quadrifida* R. Br) stem bark compounds

[Análisis *in silico* de la actividad anti-dengue de compuestos de corteza de tallo de faloak (*Sterculia quadrifida* R. Br.)]

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Abstract

Context: Dengue is one of the most common infectious diseases found in tropical and subtropical regions, particularly in urban and semi-urban areas. Management dengue until now has not had a specific therapy. The development of dengue therapy using traditional plants as the main source of dengue therapy is needed. *Sterculia quadrifida* R. Br stem bark is one of the traditional plants in Indonesia, widely used by local people to treat various diseases.

Aims: To identify the potency of *S. quadrifida* stem bark extract against the envelope protein and NS5 RdRp (RNA-dependent RNA polymerase) in dengue infection through *in silico* approach.

Methods: All ligands from *S. quadrifida* stem bark extract from the previous study and protein preparations were retrieved from the PubChem and RSCB data bank database, respectively. Drug-likeness using Lipinski's rule of five methods. Pyrx, PyMOL, and Discovery Studio 2.0 were used to analyze and visualize the potency of *S. quadrifida* stem bark-specific compounds against the envelope and NS5 RdRp.

Results: Epicatechin and scopoletin have the lowest affinity bond, some noncovalent interaction, and also similarity in the position of the amino acid interaction to the reference control ribavirin.

Conclusions: Epicatechin and scopoletin from *S. quadrifida* have antiviral potential against dengue by disposing of envelope protein and NS5 RdRp.

Keywords: dengue; envelope protein; faloak; molecular docking; NS5 RdRp; *Sterculia quadrifida*.

Resumen

Contexto: El dengue es una de las enfermedades infecciosas más comunes que se encuentran en las regiones tropicales y subtropicales, particularmente en áreas urbanas y semiurbanas. El manejo del dengue hasta el momento no ha tenido una terapia específica. Se necesita el desarrollo de la terapia contra el dengue utilizando plantas tradicionales como fuente principal para la terapia contra el dengue. La corteza del tallo *Sterculia quadrifida* R. Br. es una de las plantas tradicionales en Indonesia, ampliamente utilizada por la población local para tratar diversas enfermedades.

Objetivos: Identificar la potencia del extracto de corteza de tallo de *S. quadrifida* contra la proteína de la envoltura y NS5 RdRp (ARN polimerasa dependiente de ARN) en la infección por dengue mediante un enfoque *in silico*.

Métodos: Todos los ligandos del extracto de corteza de tallo de *S. quadrifida* del estudio anterior y las preparaciones de proteínas se recuperaron de la base de datos del banco de datos PubChem y RSCB, respectivamente. Semejanza a los fármacos utilizando la regla de los cinco métodos de Lipinski. Pyrx, PyMOL y Discovery Studio 2.0 se utilizaron para analizar y visualizar la potencia de los compuestos específicos de la corteza del tallo de *S. quadrifida* contra la envoltura y NS5 RdRp.

Resultados: La epicatequina y la escopoletina tienen el enlace de afinidad más bajo, alguna interacción no covalente y también similitud en la posición de la interacción de aminoácidos con la ribavirina como control de referencia.

Conclusiones: La epicatequina y la escopoletina de *S. quadrifida* tienen potencial antiviral contra el dengue al eliminar la proteína de la envoltura y la NS5 RdRp.

Palabras Clave: acoplamiento molecular; dengue; faloak; NS5RdRp; proteína de envoltura; *Sterculia quadrifida*.

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INTRODUCTION

Dengue is one of the most common infectious diseases found in tropical and subtropical regions, particularly in urban and semi-urban areas. Dengue is caused by the dengue virus (DENV) originating in the *Flaviviridae* family, consisting of five serotypes, namely DEN-1, DEN-2, DEN-3, DEN-4, and DEN-5, which are transmitted by the mosquitoes *Aedes aegypti* and *Aedes albopictus* (Mustafa et al., 2015) with DENV-2 is the most circulating and predominant serotypes that caused severe dengue (Renantha et al., 2022; Sirisena et al., 2021). Dengue has become a global problem as an estimated 100-400 million people are infected yearly. According to the WHO, the number of reported dengue patients has increased eightfold over the past two decades, from 505 430 cases in 2000 to more than 2.4 million in 2010, and 4.2 million in 2019 with 70% of cases found in Asia (WHO, 2021).

Dengue virus (DENV) is a single-stranded positive RNA virus that has a round virion with a size of 50 nm consisting of three structural proteins, namely capsid (C), pre-membrane/membrane (prM/M), and envelope (E), and seven nonstructural proteins (NS), namely NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5, which are directly involved in assembly and replication of DENV (Sindi, 2021). Protein E and NS5 can be used as targets for dengue infection. Protein E is a glycoprotein that belongs to a class II membrane fusion protein, has a length of about 400 amino acids, and is involved in the assembly, attachment, and internalization of viruses into the host cell through a pathway mediated by endosomes. NS5 protein is the largest protein produced by the dengue virus, with a size of 103 kDa. This protein, through the C-terminal domain RNA-dependent RNA polymerase (RdRP), plays a role in the transcription and replication of the dengue virus. Therefore, these two proteins are attractive drug targets for the development of anti-dengue therapy (Kampmann et al., 2009; Nasar et al., 2020; Shimizu et al., 2019).

Until now, the management of dengue has not had a specific therapy. The therapy used is only supportive and symptomatic to overcome clinical symptoms experienced by dengue patients. Therefore, therapeutic exploration for dengue is indispensable (Kadir et al., 2013). One source of treatment that can be used as an anti-dengue therapy is to use natural products. *Sterculia quadrifida* R. Br. (family *Malvaceae*) is a species that is widely used by the local people in Timor Island, East Nusa Tenggara, Indonesia, as traditional medicine. *S. quadrifida* known to the world as peanut tree or orange-fruited kurrajong (local name in Indonesia: Faloak), is a plant first identified in North Queensland and used by Aboriginal people to treat various diseases such as wound treatment, to treat eye pain, and insect bites (Australian Botanic Garden, 2021; Siswadi et al., 2016).

In Indonesia, *S. quadrifida* stem bark is widely used by local communities as a treatment for hepatitis C virus (HCV) infection. This is also supported by previous research studies that prove that stem bark extract has hepatoprotective activity because it is able to inhibit all stages in the life cycle of HCV (Dean et al., 2019). HCV is one of the viruses that bear some resemblance to the dengue virus because both viruses are from the *Flaviviridae* family. The two viruses have several similarities, as the viral genome is composed of positive ssRNA that replicates in the host cytoplasm, has the same replication mechanism, and HCV has one of the polyproteins that have similar amino acid sequences with NS3 DENV proteins (Chatel-Chaix et al., 2014; Gerold et al., 2017).

Research studies on the potential of *S. quadrifida* stem bark extract as a dengue antiviral have not been found in the literature reviewed. This study will be predicted the potential of *S. quadrifida* stem bark extract as an antiviral agent of dengue through inhibition in two dengue virus proteins, namely envelope protein and NS5 RdRp. The bonding of specific compounds in *S. quadrifida* bark is expected to inhibit the activity and replication of the dengue virus.

MATERIAL AND METHODS

Ligand preparation

The ligands used in this study are based on specific compounds from previous studies (Dean et al., 2019; Lulan, 2020; Munawaroh et al., 2020; Siswadi and Saragih, 2021). All ligands and control samples in this study were taken through the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). PubChem is the world's largest database providing a wide range of chemical information, including freely accessible names, molecular formulas, structures, and other identifiers. The ligands used in this study, namely: epicatechin (Compound CID: 72276), scopoletin (CID: 5280460), β-sitosterol (CID: 2284), hexadecanoic acid methyl ester (CID: 8042), hexadecenoic acid (CID: 985), ethyl 9-hexadecenoate acid (CID: 5364759), 9.12-hexadecadienoic acid (CID: 5282787), 9.12-octadecadienoic acid (CID: 5280450), 1, Z-5, E-7-dodecatriene (CID: 5367454), and 1,2-benzenedicarboxylic acid (CID: 18972250), and ribavirin as control (CID: 37542), an antiviral therapy that is known to inhibit viral replication by inhibiting inosine monophosphate dehydrogenase, RNA transla-

tion, replication, and 5-capping of dengue virus (Nag and Chowdhury, 2020) All ligands are downloaded in 3D with structure data format (sdf) to be then minimized into protein data bank (pdf) format through OpenBabel in PyRx software (PyRx-Phyton Prescription 0.8, The Script Research Institute).

Target protein preparation

The target protein used as drug targets in the study were DENV-2 envelope protein (1OK8) and NS5 RdRp (6IZY). These two proteins were taken through the RSCB Data Bank database (https://www.rcsb.org/) in protein data bank (pdb) format.

Drug-likeness

Drug-likeness is a method that is carried out as an early stage to distinguish molecules that can be categorized as drugs and non-drugs so that they can predict the probability of success of the drug. The drug-likeness method in this study used Lipinski's rule of five: a molecular mass of less than 500 Da, hydrogen donor bond less than 5, hydrogen acceptor bond less than 10, lipophilicity (LogP) less than 5, and molar refraction between 40-130. A drug candidate has potential as a drug if it qualifies at least two or more rules in Lipinski (http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp).

Molecular docking and visualization

Molecular docking is a virtual method of predicting the interaction between one or more ligands and a target protein. This method can predict the bond energy between ligands and proteins and the complex structure of those bonds that are useful for optimizing a drug candidate (Wang and Zhu, 2016). In this study, molecular docking was conducted using PyRx software through the Autodock Vina Wizard feature (PyRx-Phyton Prescription 0.8, The Script Research Institute). After molecular docking, the docking results will be visualized in 3D through PyMOL software (Edu PyMOL v1.7.4, Schrodinger, LLC).

Molecular interactions

The ligand-protein complex produced through molecular docking will be identified as chemical bonds using Discovery Studio 2.0 software. The types of molecular interactions that will be identified are hydrogen bonds, hydrophobic bonds, van der Waals bonds, and Pi bonds (π) that aim to determine the type of interaction and amino acid similarity between ligands and control of target proteins.

Data analysis

The data analysis process was carried out in stages, including: (1) drug-likeness analysis of all compounds using Lipinski's Rule of Five method to identify compounds that could be utilized as drug candidates, (2) molecular docking to determine compounds with the lowest binding affinity, (3) after molecular docking, the compound with the lowest affinity was simulated to observe the molecular interaction between the compound and the two target proteins (compared to the control). This analysis aims to determine the similarity of binding sites between compounds and control binding to both target proteins.

RESULTS

Visualization of ligands, control, and target proteins

The visualization of all ligands and control, as well as target proteins analyzed with PyMOL software, can be seen in Figs. 1 and 2, respectively.

Drug-likeness

The results of drug-likeness predictions with Lipinski's showed that all compounds in *S. quadrifida* stem bark extract could be used as drug candidates because they qualify for drug-likeness. All compounds can be used for further analysis of their potential as anti-dengue (Table 1).

Molecular docking

Molecular docking in this study aims to determine the binding affinity between specific compounds from *S. quadrifida* bark extract that binds to the target protein, which was then compared with the binding affinity between control and target proteins. The grid position used in this study was envelope protein: center: X: -8.5360, Y: 31.6645, Z: -26.0561; dimension: X:56.7060, Y:40.6528, Z:116.8880; NS5 RdRp: center: X:6.7696, Y: -45.951, Z: 3.4144; and dimension: X: 41.6514, Y: 514269, Z: 57.9497.

The molecular docking results showed that the specific compounds epicatechin and scopoletin exhibited more negative binding affinity than the reference control, namely, -7.1 kcal/mol and -6.8 kcal/mol on envelope protein (control: -6.6 kcal/mol), respectively, and -7.9 kcal/mol and -6.3 kcal/mol in NS5 RdRp (control: -6.2 kcal/mol) (Table 2).

Molecular interactions between ligand-target proteins

In the results of simulations of molecular interactions between epicatechin and envelope proteins, it was found that these compounds interacted through

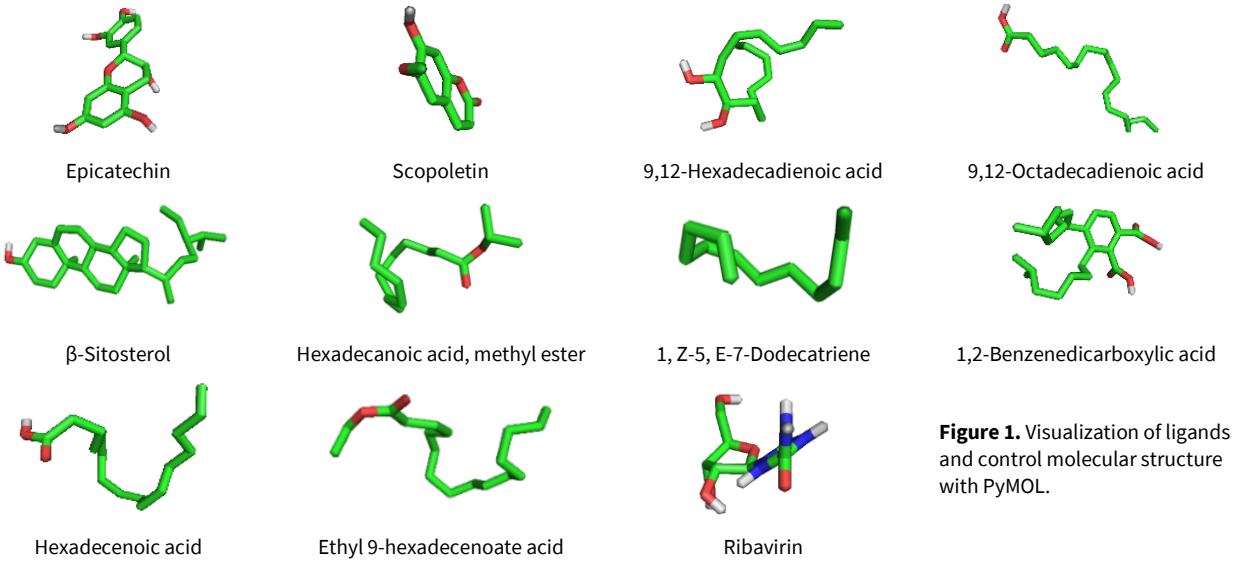

Figure 1. Visualization of ligands and control molecular structure with PyMOL.

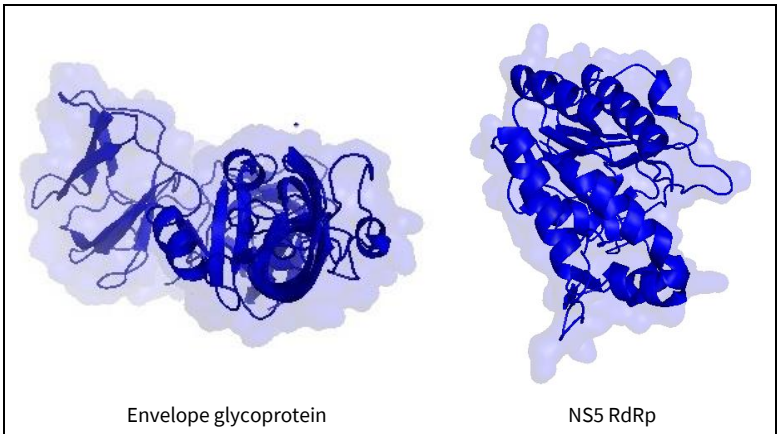

Figure 2. Visualization of the structure of the target protein molecule with PyMOL.

Table 1. Drug-likeness with Lipinski's rule.

Ligands	Lipinski's Rule of Five				
	MW <500 Da	H-bond donor <5	H-bond acceptor <10	LogP <5	MR: 40-130
Epicatechin	Yes	Yes	Yes	Yes	Yes
Scopoletin	Yes	Yes	Yes	Yes	Yes
B-sitosterol	Yes	Yes	Yes	No	Yes
Hexadecanoic acid methyl ester	Yes	Yes	Yes	No	Yes
Hexadecenoic acid	Yes	Yes	Yes	No	Yes
Ethyl 9-hexadecenoate acid	Yes	Yes	Yes	No	Yes
9,12-hexadecadienoic acid	Yes	Yes	Yes	Yes	Yes
9,12-octadecadienoic acid	Yes	Yes	Yes	No	Yes
1, Z-5, E-7-Dodecatriene	Yes	Yes	Yes	Yes	Yes
1,2-Benzenedicarboxylic acid	Yes	Yes	Yes	No	Yes

MW: molecular weight; MR: molar refraction; H: hydrogen.

Table 2. The molecular docking results of *S. quadrifida* stem bark extract compounds with envelope protein and NS5 RNA-dependent RNA polymerase.

Ligand	Binding affinity (kcal/mol)	
	Envelope	NS5 RdRp
Hexadecanoic acid	-5,4	-5
Ethyl 9-hexadcenoate acid	-5,3	-5,4
Scopoletin	**-6,8**	**-6,3**
Hexadecanoic-methyl esther	-5,0	-4,8
β-Sitosterol	-6,5	-7,8
Epicatechin	**-7,1**	**-7,9**
9,12-Octadecedienoic acid	-4,9	-5,1
9,12-Hexadecadienoic-acid	-5,2	-5,4
1,Z-5,E-7-Dodecatriene	-5,6	-5,2
1,2-Benzenedicarboxylic acid	-6,0	-6,6
Ribavirin (control)	**-6,6**	**-6,2**

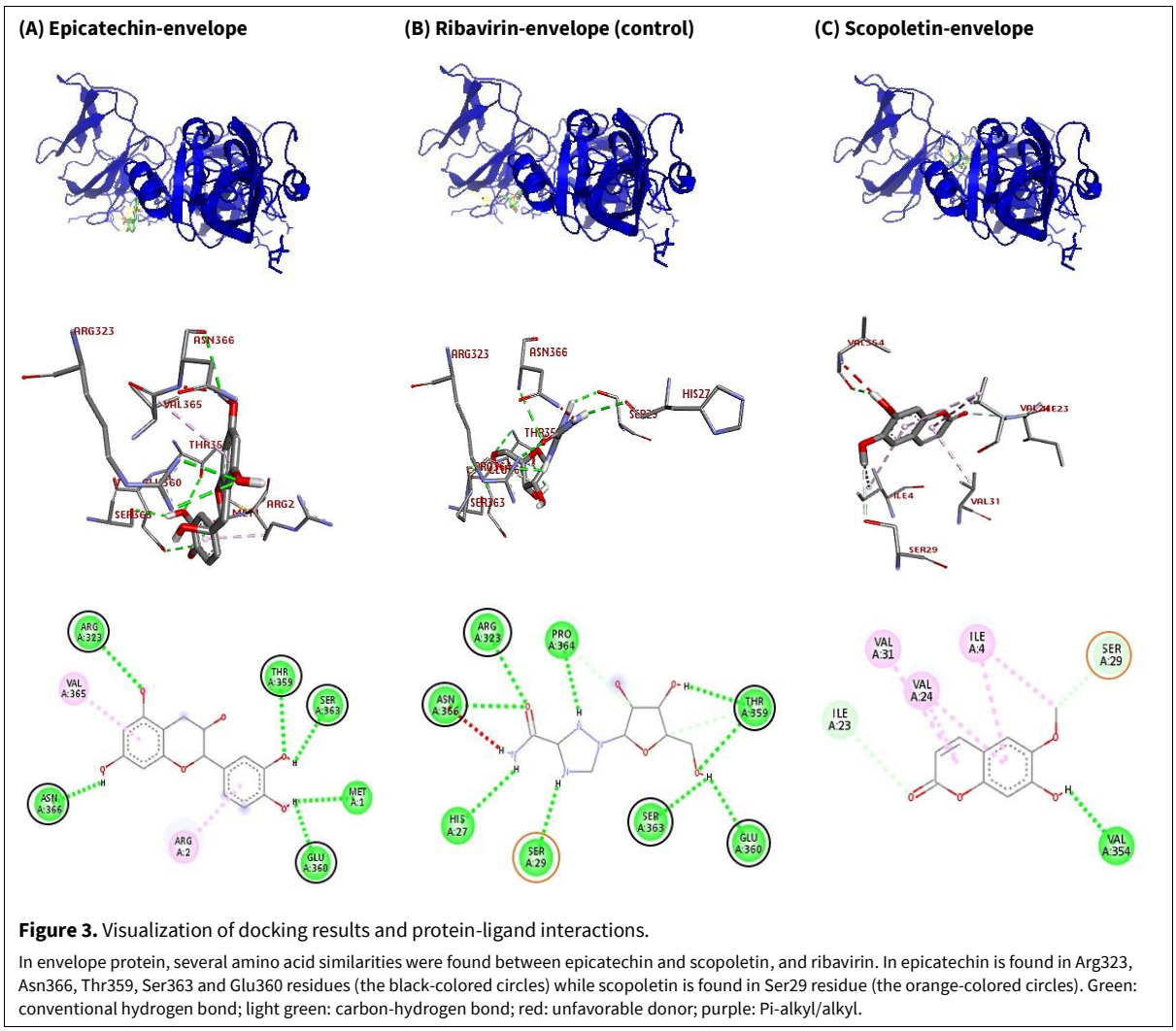

Figure 3. Visualization of docking results and protein-ligand interactions.

In envelope protein, several amino acid similarities were found between epicatechin and scopoletin, and ribavirin. In epicatechin is found in Arg323, Asn366, Thr359, Ser363 and Glu360 residues (the black-colored circles) while scopoletin is found in Ser29 residue (the orange-colored circles). Green: conventional hydrogen bond; light green: carbon-hydrogen bond; red: unfavorable donor; purple: Pi-alkyl/alkyl.

hydrogen bonds at active sites with Arg323, Thr359, Ser363, Met1, Glu360, and Asn366 residues, and Pi-alkyl interaction with Arg2 and Val 365 residues (Fig. 3A). While in scopoletin and envelope protein, it was found that six active sides formed, through hydrogen bonds with Val354, Ile23, Ser29, and Pi-alkyl/alkyl interaction with Val31, Val24, Ile4 residues (Fig. 3C). The compounds epicatechin and scopoletin were also

found to have some amino acid similarities with the reference control (ribavirin). In epicatechin, amino acid similarities were found in Arg323, Thr359, Ser363, and Glu360 residues, while in scopoletin, the amino acids were similar in Ser29 residue (Fig. 3B).

In the bond between epicatechin and NS5 RdRp, 6 active sites were found, namely Phe486, Ala408, Val604, Asn493, Lys402, and Asn406. The bonds formed are hydrogen bonds with Asn406, Lys402, and Val 604 residues, alkyl bonds with Val604 residues, Pi-alkyl bonds with Ala408 residues, Pi-Pi T-shaped bonds with Phe486 residues, Pi-cation bonds also with Lys402 residues, and unfavorable bonds with Asn 493 residues (Fig. 4A), while in scopoletin 5 active sites were found, through hydrogen bonds with Lys402 and Asn493 residues, Pi-alkyl bonds with Ala408 residues, Pi-sigma bonds with Val604 residues, and carbon-hydrogen bonds with Phe399 residue (Fig. 4C). The epicatechin and scopoletin compounds were also found to have some amino acid similarities with ribavirin as a control. In epicatechin, amino acid similarities were found in Val604, Asn493, Lys402, and Asn406, while in scopoletin in Val604, Asn493, and Lys402 (Fig. 4B).

Based on the results of molecular docking simulations, it is known that epicatechin and scopoletin compounds presented the most negative binding affinity compared to other compounds and the reference control (ribavirin). This shows that both compounds could have the potential to cause biological effects on both target proteins. The results of the molecular docking simulation were analyzed using Discovery studio 2.0 to find out the type of interaction produced.

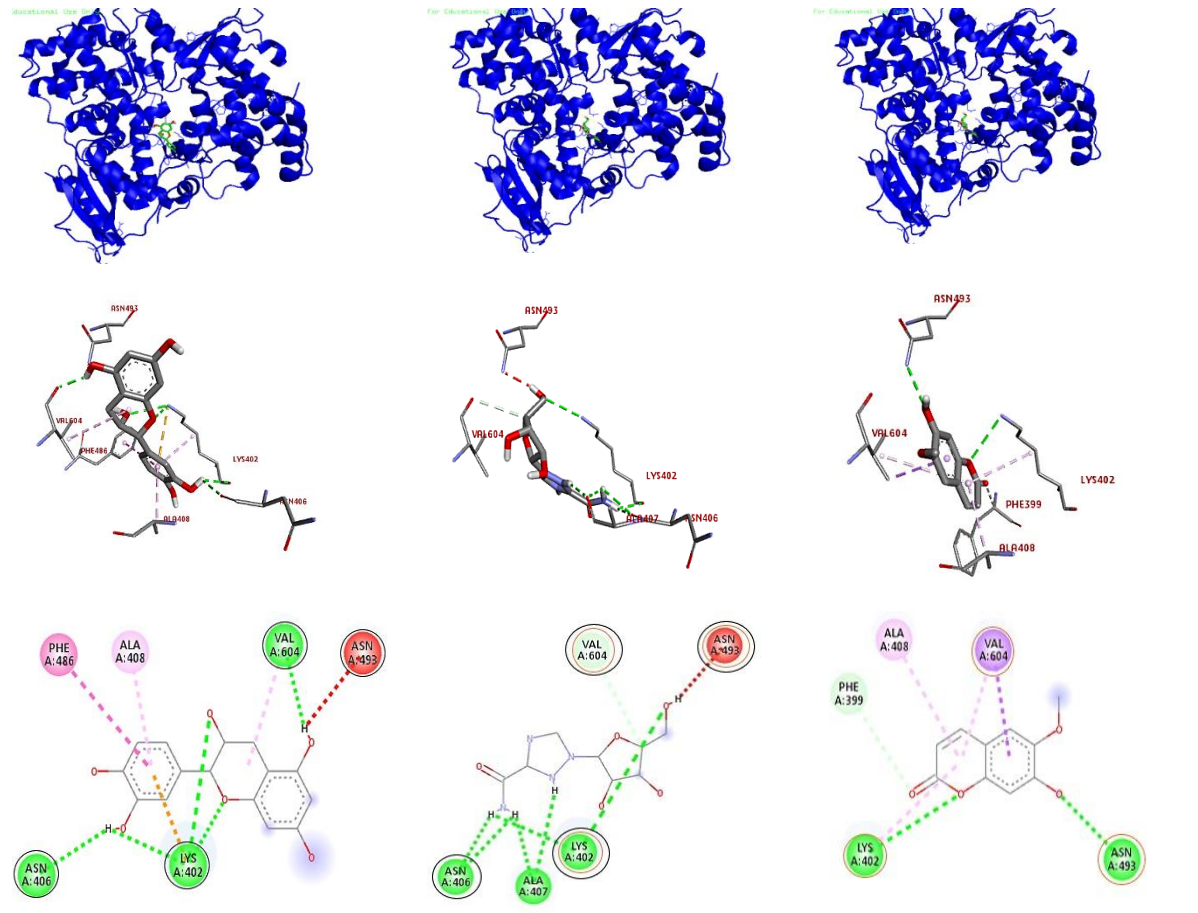

Figure 4. Visualization of docking results and protein-ligand interactions.

In the NS5 RdRp protein, several amino acid similarities were found between epicatechin and scopoletin with ribavirin. In epicatechin is found in Val604, Asn493, Lys402, and Asn406 residues (the black-colored circles) while scopoletin is found in Val604, Asn493, and Lys402 residues (the orange-colored circles). Green: conventional hydrogen bond; light green: carbon-hydrogen bond; red: unfavorable donor; purple: Pi-alkyl/alkyl; pink: Pi-Pi T shaped.

DISCUSSION

The structural envelope proteins and nonstructural proteins-5 (NS5) play an important role in the life cycle of the dengue virus (DENV). Protein E plays a role in binding to receptors on the surface of the host cell and mediating membrane fusion that causes the release of the viral genome into the cytoplasms, while NS5 through RdRp synthesizes *complementray minus* the RNA strand, which in turn produces many copies of the viral genome (Takahashi and Suzuki, 2017).

In this study, we carried out molecular docking between specific compounds (ligands) of *S. quadrifida* stem bark extract with target proteins, namely protein E and NS5 RdRp from the dengue virus, to see the potential of these ligands to affect the target protein. The ligands used were specific compounds from *S. quadrifida* R. Br stem bark obtained from previous studies (Dean et al., 2019; Lulan, 2020; Munawaroh et al., 2020; Siswadi and Saragih, 2021). Molecular docking can predict the bond formed between a protein with a ligand or protein with a protein and mention the model of the bond that plays a role in inhibiting protein. With the docking method, the ligand is inserted into the binding site by combining and optimizing variables such as steric complementarity, electrostatic, and hydrophobicity and predicting the binding affinity score (binding free energy) (Sethi et al., 2020).

In predicting the potential of a ligand to be used as a drug candidate, the drug-likeness method is needed to determine the ability of the ligand to absorb. Lipinski's rule of five is one of the drug-likeness methods that has been widely used in various *in silico* studies in terms of drug discovery to predict the ability of drug absorption orally in a compound. This rule has significantly reduced the adverse pharmacokinetic effects of drugs (Doak et al., 2014). Lipinski is used to predict and evaluate these molecules' similarity to drugs. These similarities include certain properties that can predict the success of these molecules as drug candidates. According to Lipinski's rule, an ideal drug must comply with the following rules: molecular weight of fewer than 500 Daltons, hydrogen bond donors less than 5, hydrogen bond acceptors less than 10, LogP less than 5, and molar refraction between 40-130 (Doak et al., 2014; Lipinski, 2004).

In Lipinski's rule, the molecular weight should not exceed 500 Da because if the molecular weight is too large, it will be difficult to absorb through biological membranes; The value of hydrogen donors and acceptors is related to the ability of interactions between molecules, especially water (increased hydrogen bonds make transportation through cell membranes thermodynamically unfavorable), the logP value is used to evaluate the lipophilicity and hydrosolubility of a compound (compounds with logP >5 are too lipophilic, so it is difficult to soluble in water and not easy to be absorbed), molar refraction is a parameter of steric properties affecting the compatibility of drug-receptor interactions (Giménez et al., 2010; Widiandani et al., 2013). The results of the drug-likeness analysis with Lipinski in Table 2 show that all ligands of the stem bark extract compounds qualify the drug-likeness parameters because they qualify at least two of Lipinski's rules. These results indicate that all compounds can be absorbed well if given orally.

In molecular docking, binding affinity is a very important indicator in predicting the ability of a compound to affect the target protein. Binding affinity is the negative energy produced when the interactions between molecules form a stable complex. The negative value of the binding affinity can predict the binding complex's stability between the ligand-protein. In a state of equilibrium, a negative value is a condition due to changes in the energy of ΔG, which reaches constant pressure and temperature (Kharisma and Septiadi, 2018). In addition, the more negative the value of ΔG, the higher the potential between the ligand and receptor to bind to each other and form a biological activity (Pannindriya et al., 2021). In this study, the compound epicatechin and scopoletin have more negative binding affinity than ribavirin, which is the control on both target proteins. These results indicate that epicatechin and scopoletin in *S. quadrifida* stem bark extract have the potential to affect the physiological properties of the target protein because they have the ability to bind to receptors higher than ribavirin. Compounds that have the same ability to bind to target proteins as controls indicate that these compounds have similar abilities to control (Kharisma and Septiadi, 2018).

In biological systems, molecular recognition depends on noncovalent interactions between molecules, such as electrostatic interactions such as hydrogen bonds, Pi-effects such as Pi-cations, Pi-anions, van der Waals bonds, and hydrophobic bonds (Liang and Li, 2018). These bonds contribute to form biological activity, which is specific to the target protein, and the ligand-binding domain in the query ligands and control compounds (Kharisma et al., 2021). In molecular interactions, a compound has the potential to bind to the target protein, and it is able to inhibit the target protein with high affinity if it has the same amino acid residue on the active site compared to the control (Sreelakshmi et al., 2017). Based on this, it can be said that epicatechin and scopoletin compounds have potential as inhibitors of the protein envelope and NS5 RNA-dependent RNA polymerase because they have more negative binding affinity than control, have

interactions through hydrogen bonds, Pi-alkyl/alkyl bonds, pi-cation bonds, pi-sigma bonds, also has the same binding position as ribavirin. Therefore, it is thought that the two ligands present in the *S. quadrifida* stem bark allow the resulting molecular complex to be more stable (Kharisma et al., 2021).

CONCLUSION

Specific compounds epicatechin and scopoletin in *S. quadrifida* stem bark extract have the potential as antiviral agents against dengue through their inhibitory activity on envelope protein and NS5 RNA-dependent RNA polymerase. The more negative affinity bonds, the formation of noncovalent bonds, and the similarity in several amino acid residues compared to ribavirin make this compound potentially produce stable molecular complexes.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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AUTHOR CONTRIBUTION:

Contribution	Riwu AG	Nugraha J	Purwanto DA	Triyono EA
Concepts or ideas	x	x	x	x
Design	x	x	x	x
Definition of intellectual content	x	x	x	x
Literature search	x		x	
Experimental studies	x	x	x	x
Data acquisition	x		x	
Data analysis	x	x	x	
Statistical analysis	x	x	x	
Manuscript preparation	x		x	
Manuscript editing	x		x	
Manuscript review	x	x	x	x

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