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In Silico Analysis of Antiviral Activity and Pharmacokinetic Prediction of Brazilein Sappan Wood (*Caesalpinia sappan* L.) Against SARS-CoV-2 Spike Glycoproteins

Dwi Krihariyani[1], Edy Haryanto[1], Retno Sasongkowati[1]

[1]Department of Medical Laboratory Technology, Poltekkes Kemenkes Surabaya, Indonesia

Correspondence:
Dwi Krihariyani,
Jl. Wiguna Tengah XIX No.19,
Surabaya, East Java, Indonesia
Zip Code: 60294

Email: dwikrihariyani@gmail.com

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Abstract

Brazilein is one of the secondary sappan wood metabolites which can be used empirically as an antivirus. The SARS-CoV-2 spike (S) glycoproteins play significant roles in attaching and entering the virus into the host cell. This study aims to predict the antiviral activity and pharmacokinetic properties of brazilein of the sappan wood against the in silico SARS-CoV-2 S glycoproteins with vitamin C as the reference compound. Molegro Virtual Docker 5.5 was used to predict antiviral activity by docking process. SARS-CoV-2 S glycoprotein with NAG ligand available in Protein Data Bank (PDB) (PDB ID: 7C01) was the receptor used. The pkCSM online tool was used to predict the pharmacokinetic properties and toxicity of brazilein. Data were analyzed on the target receptors by comparing the docking bond energies between NAG, brazilein, and vitamin C. The smaller the ligands' bond energy to the target receptor, the more stable the bonds are. The bond energy of NAG, brazilein, and vitamin C was –59.2864 kcal/mol, –65.8911 kcal/mol, and –53.9093 kcal/mol, respectively. These results suggested that brazilein has a greater capacity as an antivirus compared to NAG and vitamin C. In silico test using the pkCSM online tool demonstrated that brazilein had strong pharmacokinetic properties and relatively low toxicity.

Keywords

ADME, Brazilein, NAG, Toxicology, Vitamin C.

INTRODUCTION

In December 2019, mysterious cases of pneumonia were first recorded in Wuhan, Hubei Province, China (1,2). This disease was initially referred to as the 2019 novel coronavirus (2019-nCoV). On February 11, 2020, World Health Organization (WHO) declared a new name which was coronavirus disease 2019 (COVID-19). The disease was caused by severe acute respiratory syndrome

coronavirus 2 (SARS-CoV-2) (3). To date, COVID-19 has become a pandemic.

Coronavirus is one of the significant pathogens that can infect the human respiratory system and cause mild to severe symptoms. Seven coronaviruses are known that can infect humans. Four of them (HCoV-NL63, HCoV-229E, HCoV-OC43, and HCoV-HKU1) can infect immunocompetent patients with only moderate symptoms. In contrast, Middle East Respiratory Syndrome Coronavirus (MERS-CoV), Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), and SARS-CoV-2 cause severe symptoms in patients (4,5).

The pathogenesis of SARS-CoV-2 is still unknown, although it is believed not too different from that of SARS-CoV. SARS-CoV-2 mainly infects alveoli-lining airway cells (6,7). Host tropism is the key for virus infection. If SARS-CoV-2 has identified the host cell according to its viral tropism, it will bind to the host cell via spike (S) glycoprotein (8,9). The S glycoprotein binds to the host cell receptor which is the angiotensin-converting enzyme 2 (ACE2). ACE2 is also present in other organs, such as the oral and nasal mucosa, nasopharynx, lung, stomach, small intestine, large intestine, skin, thymus, bone marrow, spleen, liver, kidney, brain, pulmonary alveolar epithelial cells, enterocyte cells of the small intestine, endothelial cells of the venous artery, and smooth muscle cells (9,10). Therefore, SARS-CoV-2 does not only infect the human respiratory system, but also other organs.

The host cell receptor for SARS-CoV-2 is the same as SARS-CoV which is ACE2. The receptor-binding domain (RBD) sequences include the SARS-CoV-2 receptor-binding motif (RBM) that specifically contacts the ACE2. SARS-CoV-2 RBM interacts with ACE2 in humans with residual effects (Gln493), thereby making SARS-CoV-2 capable of infecting human cells (10,11,12).

COVID-19 pandemic is a major health concern which requires immediate treatment. One of the efforts that can be made to combat this disease includes enhancing the humans' immune systems. Flavonoids, curcumin, limonoids, vitamin C, vitamin E (tocopherol), and catechins are good candidates which can strengthen the immune system (13,14).

Sappan wood (*Caesalpinia sappan* L.) consists of five flavonoid compounds, namely brazilin, brazilein, 3'-O-methylbrazilin, sappanin, chalcone, and sappancalchone. Brazilein is the major constituent in sappan wood that is used empirically as an antivirus. The five compounds can be used as anti-stressants, growth promoters, appetite stimulants, antiviral drugs, aphrodisiacs, and antimicrobial agents (13,15).

In silico test to determine the potential use of brazilein as an antivirus is an attractive

method due to several reasons. This test is safe, free of chemical waste, simple, cost-effective, and can shorten research time (16,17). This test is an approach to the prediction of chemical properties of molecular physics, pharmacokinetic properties (absorption, distribution, metabolism, and excretion (ADME)), the interaction of compounds with receptors, mechanisms of action, compound selectivity, and compound toxicity.

Vitamin C, which has been demonstrated to have a role in the treatment of COVID-19, was used as a reference in this study (18). The Protein Data Bank (PDB) 7C01 (molecular basis for a potent human neutralizing antibody targeting SARS-CoV-2 RBD) was used for ligands that have demonstrated good biological activities and are able to bind to the desired biological target (receptor) of the docking.

Here, we present a study on the prediction of the antiviral activity and pharmacokinetic properties of brazilein of the sappan wood against the in silico SARS-CoV-2 S glycoprotein with vitamin C as the reference compound.

MATERIALS AND METHODS

The materials included the 3D structures of 7C01 which were downloaded from RCSB PDB. The 3D structures of 2-acetamido-2-deoxy-beta-D-glucopyranose (NAG), brazilein, and vitamin C were downloaded from PubChem®. The tool used in this study was a computer with processor specifications: Windows 8 64-bit. The software used was ChemDraw Professional 16.0, Chem3D 16.0, and Molegro Virtual Docker 5.5.

Prediction of Operation (Molecular Docking)

ChemDraw Professional 16.0 was used to draw the 2D structures of the NAG, brazilein, and vitamin C ligands. Chem3D 16.0 was then used to convert them to 3D structures. This software was also used to find the most stable conformation. After the minimum energy of NAG, brazilein, and vitamin C ligands were calculated, {SYBYL2 (*. Mol2)} was stored in the format of mol2. The results were in the form of rerank score (RS), which was the energy needed in the process of ligand-receptor interaction. From this score, the antiviral activity of brazilein can be predicted.

Physicochemical, pharmacokinetic, and toxicity prediction of compounds (pkCSM)

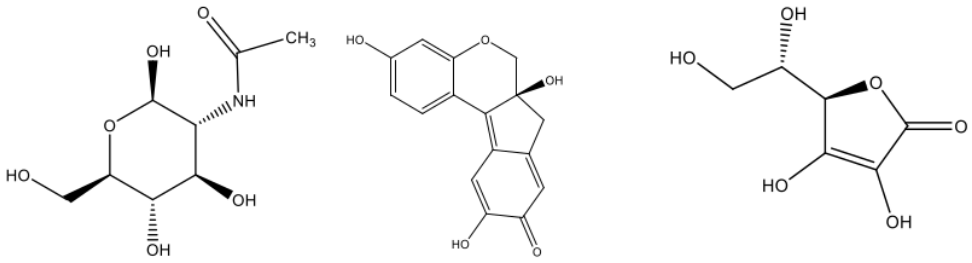
The pkCSM online method has been used to predict physicochemical properties, such as the molecular weight (MW), octanol/water partition coefficient logarithm (Log P), the number of bonds between atoms that can rotate (torsion), hydrogen bond acceptors (HBA), hydrogen bond donors (HBD), and polar surface area (PSA). In this study, the pkCSM online tool was used to predict the

pharmacokinetic properties and toxicity of NAG, brazilein and vitamin C. Firstly, the 2D molecular structures of NAG, brazilein, and vitamin C were drawn with the ChemDraw Professional 16.0 program. Secondly, they were copied to the Chem3D 16.0 program to be converted into 3D structures (saved as *.sdf files). Thirdly, online SMILES Translator was used to transform the structures of NAG, brazilein, and vitamin C into SMILES format. Compounds are subsequently processed in SMILES format using the pkCSM online tool to predict the ADME and toxicity. Protox online tool (http://tox.charite.de/tox/) was used to predict the oral toxicity (LD50) in the Globally Harmonized System (GSH) (17,19).

RESULTS

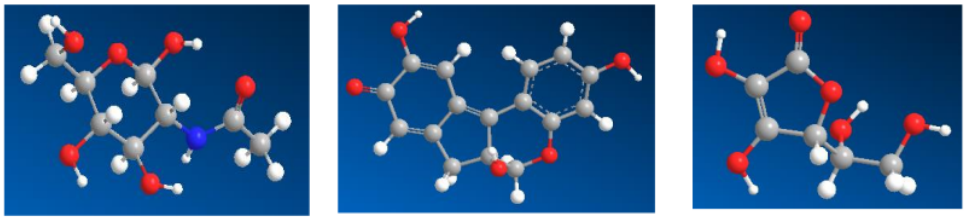
Prediction of Operation (Molecular Docking)

The 2D structures of NAG, brazilein, and vitamin C are depicted in Figure 1, whereas the 3D structures of NAG, brazilein, and vitamin C are depicted in Figure 2.



(a) (b) (c)

Figure 1. 2D structures. (a) NAG, (b) brazilein, (c) and vitamin C (ChemDraw Professional 16.0)



(a) (b) (c)

Figure 2. 3D structures. (a) NAG, (b) brazilein, (c) and vitamin C (Chem3D 16.0)

Prediction of Docking and Amino Acid

The protein structures of PDB 7C01 are depicted in Figure 3, whilst the interaction between the ligands (NAG, brazilein, and vitamin C) and receptors on the 7C01 protein is depicted in Figure 4.

Figure 5 and Table 1 indicate the amino acids involved in the interactions of NAG, brazilein, and vitamin C compounds with the 7C01 protein receptor. Table 2 displays the redocking effects of NAG, brazilein, and vitamin C with 7C01 protein receptor.

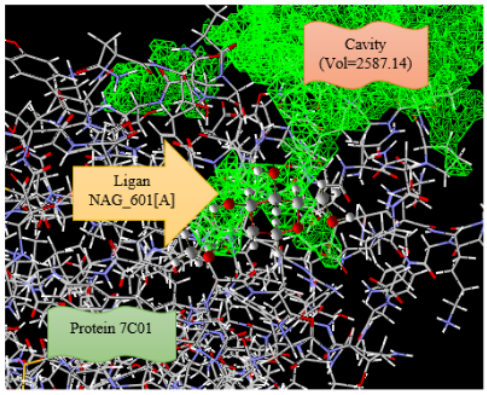


Figure 3. Protein structures (PDB 7C01) (Molegro Virtual Docker 5.5)

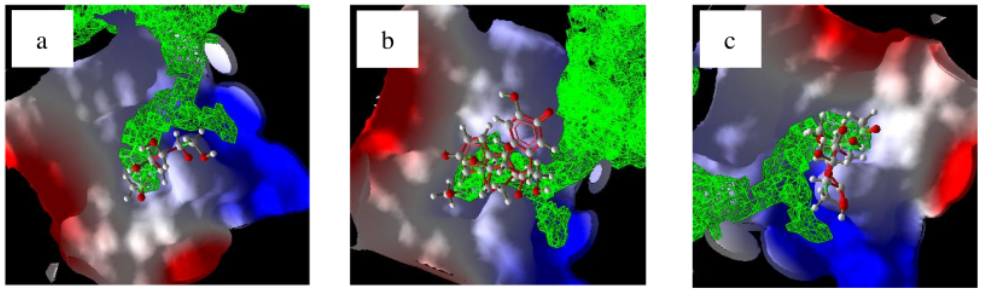


Figure 4. Receptor interactions between the ligands of
(a) NAG, (b) brazilein, (c) and vitamin C (Molegro Virtual Docker 5.5)

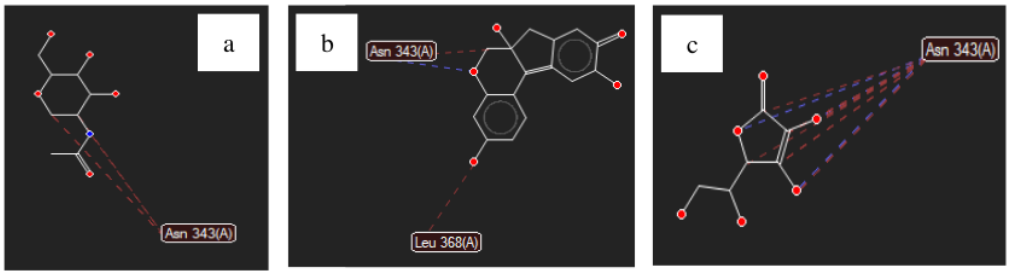


Figure 5. Amino acids involved in the interactions of (a) NAG, (b) brazilein, (c) and vitamin C (c) with 7C01 protein receptor (H-bond, electrostatic, and steric)
(Molegro Virtual Docker 5.5)

Table 1. Amino acids involved in the interactions of NAG (a), brazilein (b), and vitamin C (c) with 7C01 protein receptor (H-bond, electrostatic, and steric).

Ligands	Hydrogen bonds and amino acid residues		Electrostatic interactions and amino acid residues		Steric interactions and amino acid residues	
NAG	0	–	0	–	1	Asn 343(A)
Brazilein	1	Asn 343(A)	0	–	2	Asn 343(A) Leu 368(A)
Vitamin C	1	Asn 343(A)	0	–	1	Asn 343(A)

Table 2. Redocking results using the Molegro Virtual Docker 5.5.

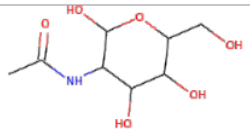
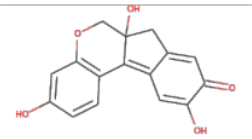
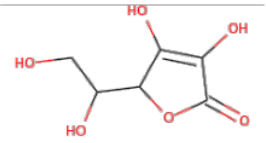
Redocking/Ligand	NAG	Brazilein	Vitamin C
I	–51.5568	–58.0565	–45.9314
II	–59.2864	–65.8911	–53.9093
III	–51.2831	–55.7692	–46.8643

Physicochemical, pharmacokinetic, and toxicity prediction of compounds (pkCSM)

The results of the in silico predictions for physicochemical parameters of NAG, brazilein, and vitamin C are presented in Table 3.

The in silico predictions of pharmacokinetic properties and toxicity of NAG, brazilein, and vitamin C are presented in Table 4.

Table 3. In silico predictions for physicochemical parameters of NAG, brazilein, and vitamin C.

Struktur SMILES	 NAG	 Brazilein	 Vitamin C
MW	221.209	284.267	176.124
Log P	–3.0776	1.624	–1.4074
Torsion	2	0	2
HBA	6	5	6
HBD	5	3	4
PSA (A^2)	86.290	119.652	67.321

MW = molecular weight; log P = logarithm of the octanol/water partition coefficient; torsion = bonds between atoms that can rotate; HBA = hydrogen bond acceptors; HBD = hydrogen bond donors; PSA = polar surface area.

Table 4. In silico predictions of pharmacokinetic properties and toxicity of NAG, brazilein, and vitamin C.

Pharmacokinetic properties and toxicity	NAG	Brazilein	Vitamin C
Intestinal absorption (human) (%)	19.518	90.021	39.716
Skin permeability (log Kp)	–3.264	–3.498	–3.198
Vss (human) (log L/kg)	–0.101	0.194	–0.156
BBB permeability (log BB)	–1.023	–0.662	–1.031
CYP2D6 substrate (Yes/No)	No	No	No
CYP2D6 inhibition (Yes/No)	No	No	No
Total Clearance (log ml/min/kg)	0.718	0.264	0.631
OCT2 substrate (Yes/No)	No	No	No
Ames **toxicity (Yes/No)**	No	Yes	No
LD50 (mol/kg)	1.714	2.246	1.271

Vss: steady-state volume of distribution; BBB: blood-brain barrier; CYP2D6: cytochrome P2D6; OCT2: organic cation transporter 2.

DISCUSSION

Activity Prediction (Molecular Docking)

In this study, SARS-CoV-2 S glycoprotein with NAG_601[A] ligand (PDB 7C01) was the target molecular receptor. PDB 7C01 was selected since it is homologous with SARS-CoV-2 S glycoprotein. The host cell receptor for SARS-CoV-2 is the same as SARS-CoV which is ACE2. The RBD sequence involves SARS-CoV-2 RBM in direct contact with the ACE2 (20). NAG_601[A] ligand was selected since it demonstrated good biological activity and can bind to the desired biological target during the docking process to determine the molecules' physical and chemical properties. The functional groups of NAG, brazilein, and vitamin C responsible for pharmacophores which can reduce activity, as well as the lipophilic, electrostatic, and steric/geometric properties of the functional groups, were searched using Molegro Virtual Docker 5.5. This was conducted in order to design the minimum structural characteristics needed for further medicine production development (21).

Physical and chemical properties (e.g. lipophilic and electrostatic properties) of the drugs play an essential role in transporting the drugs to reach the virus (i.e. absorption and delivery). Only drugs that have a high specificity structure can interact and cause activity with the biological receptors. Furthermore, the drugs' electrostatic and steric properties play a role in promoting the precise orientation of the receptor surface molecule (21).

Docking and Amino Acid Analysis Activity Prediction

The protein receptor (PDB 7C01) that was downloaded and imported into the Molegro Virtual Docker 5.5 is presented in Figure 3. Figure 4 depicts the detection results of the interaction between the three ligands and S glycoprotein. Cavity (volume 2587.14) with active NAG_601[A] ligand was used because there is a region where the NAG ligand interacts with the S glycoprotein.

There was a ligand interaction with multiple amino acid residues from the 7C01 protein receptor in the interaction between the ligands and receptors. Figure 5 and Table 1 indicate the amino acids involved in the NAG, brazilein, and vitamin C interaction pathway with the 7C01 protein receptor. The lipophilic/hydrophobic bond, electronic, and steric interactions of the amino acid residues of the protein receptor with these compounds take place. There were variations in the interactions with the S glycoprotein receptor between each of the NAG, brazilein, and vitamin C compounds (Figure 5 and Table 1) since there were differences in the spatial arrangement of the three compound structures.

The effects of redocking with the 7C01 protein receptor for NAG, brazilein, and vitamin C are displayed in Table 2. The binding energy of brazilein with the 7C01 protein receptor was lower than NAG and vitamin C ligands. Brazil had a RS of –65,8911 kcal/mol, whereas NAG and vitamin C had RSs of –59,2864 kcal/mol and –53,9093 kcal/mol, respectively. It indicated that brazilein supplied lower energy than NAG and vitamin C, hence binding to the receptor would be more stable compared to NAG and vitamin C.

Physicochemical, pharmacokinetic, and toxicity prediction of compounds (pkCSM)

The results of the in silico prediction of NAG, brazilein, and vitamin C physicochemical parameter values are displayed in Table 3. Lipinski et al. (1997) analyzed 2,245 drugs from the baseline World Drugs Index and concluded that if the molecular weight is greater than 500 Da, the compounds would be difficult to be absorbed, have low permeability, have a log value of +5 octanol/water (log P) partition coefficient, have HBD expressed by the number of groups O-H and N-H greater than 5, and have an H-bond. Since all values are the multiplication of five, this analysis is known as Lipinski's Rule of Five (20). It can be analyzed from Table 3 that NAG, brazilein, and vitamin C had molecular weight of less than 500 Da, logP values of less than 5, acceptor and donor values of less than 10, hence it can be inferred that it is easy to absorb these three compounds.

The in silico pharmacokinetic properties and toxicity predictions of NAG, brazilein, and vitamin C are presented in Table 4. According to Chander et al. (21), a compound is categorized as having strong absorption capacity if the absorption value is > 80%, whereas it has poor absorption capacity if the absorption value is < 30%. The primary site for absorption of oral medications is the intestine (22). Table 4 shows that NAG's human intestinal absorption value was less than 30%, whereas brazilein's and vitamin C's were more than 80%. These results suggested that brazilein and vitamin C had better absorption capacity than NAG.

Pires et al. (20) stated that a compound is described to have relatively low skin permeability if its value is log Kp > –2.5 (23). Table 4 displays that the skin permeability (log Kp) of NAG, brazilein, and vitamin C was lower than –2.5, hence these three compounds were supposed to have strong skin permeability.

The volume of distribution (Vd) refers to the theoretical volume that is required to distribute the total dose of the medicine equally in order to give the same concentration as in the blood plasma. The higher the Vd value, the more drugs than blood plasma are distributed to the body's tissues. Pires et al. (20) stated that a compound is described to have high Vd if the value of log Vd is > 0.45, but low Vd if the value of log Vd is < –0.15 (19). The steady-state volume of distribution (Vss) values for NAG, brazilein, and vitamin C were –0.101, 0.194, and –0.156 (Table 4), thus it could be estimated that all the derivatives of these compounds can be uniformly distributed to have the same concentration as in blood plasma.

Another significant parameter to consider is the ability of drugs to cross the blood-brain barrier (BBB) to help decrease side effects and toxicity, or to improve the effectiveness of drugs whose pharmacological activity is present in the brain. BBB permeability is calculated as log BB (the logarithmic ratio of brain-to-plasma concentrations) in vivo in an animal model. Pires et al. (20) stated that compounds are believed to be able to pass the BBB effectively if their log BB values are > 0.3, and cannot be adequately distributed if their log BB values are < –1 (23). The log BB values of NAG, brazilein, and vitamin C were –1.023, –0.662, and –1.031, respectively (Table 4). The log BB value of brazilein was higher than –1, while NAG's and vitamin C's were lower than –1, hence it was expected that brazilein was capable of penetrating the BBB moderately, while NAG and vitamin C compounds were less capable.

Most of the metabolic reactions require oxidation process. Cytochrome P450 is an essential detoxification enzyme in the body, and it is primarily found in the liver. Cytochrome P450 acts by oxidizing and

promoting the excretion of unidentified organic compounds, including narcotics. Enzyme inhibitors, such as grapefruit juice, are contraindicated against cytochrome P450 enzymes since it can affect drug metabolism. It is therefore important to assess the ability of compounds to inhibit cytochrome P450, which is represented as the cytochrome P2D6 (CYP2D6) isoform in this study. Table 4 displays that the CYP2D6 enzyme is not impaired or inhibited by NAG, brazilein, and vitamin C, thus it could be expected that these derivatives appear to be metabolized by the P450 enzyme (19).

The compound excretion process can be carried out by calculating the total clearance (CLtot) and renal organic cation transporter 2 (OCT2) substrate constants. CLtot is a mixture of liver clearance (liver and bile metabolism) and renal clearance (excretion through the kidneys). This is related to bioavailability. To achieve steady-state concentrations, it is necessary to determine the dosage level (19). CLtot values of NAG, brazilein, and vitamin C were 0.718, 0.264, and 0.631, respectively (Table 4). Therefore, the rate of compound excretion could be estimated from these values.

OCT2 is a kidney-based transporter that plays a significant role in drug and endogenous compound disposal and clearance. When given along with OCT2 inhibitors, OCT2 substrates also have the potential to cause side interactions. The three compounds did not affect the OCT2 substrates (Table 4), thus it could be interpreted that the NAG, brazilein, and vitamin C derivatives were not substrates of OCT2.

To assess the toxicity of the compounds, the Ames toxicity test was carried out. The Ames Toxicity Test is a commonly used method to determine the mutagenic ability of bacteria-based compounds. A positive test result indicates the mutagenicity of the compound and may thus serve as a carcinogen (19). Brazilein might cause mutagenic effects, while NAG and vitamin C were not expected to cause mutagenic effects (Table 4).

CONCLUSIONS

The bond energy of brazilein was lower than NAG and vitamin C. The comparison of the bond energy values showed that brazilein had higher antiviral capacity than NAG and vitamin C in silico using the molecular docking process. The physicochemical, pharmacokinetic, and toxicity properties of brazilein showed that it was projected to have strong skin permeability, be distributed uniformly to provide the same concentration as in the blood plasma, be penetrating the BBB moderately, be very well absorbed in the intestine, be metabolized by the P450 enzyme, and have relatively low toxicity.

AUTHOR CONTRIBUTIONS

Dwi Krihariyani: conceptualization, software, formal analysis, writing the original draft, and visualization. Edy Haryanto: methodology, validation, writing, review, and editing. Retno Sasongkowati: supervision, writing, review, and editing.

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CONFLICT OF INTEREST

None to declare.

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