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Antibacterial Activity of *Streptococcus mutans* from Saga Herbaceous Plant (*Abrus precatorius*): *In Silico* Study

Richa Mardianingrum[a], Neta Ekayanti Suganda[a], Srie Rezeki Nur Endah[a], Ruswanto Ruswanto[b*]

[a]*Department of Pharmacy, Universitas Perjuangan Tasikmalaya*
Jalan Peta 177 Tasikmalaya, 46115, Indonesia
[b]*Faculty of Pharmacy, Universitas Bakti Tunas Husada*
Jalan Cilolohan 36 Tasikmalaya, 46115, Indonesia

[*]*Corresponding author: ruswanto@universitas-bth.ac.id*

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2HVW.

ABSTRACT. Antibacterial is a substance that can inhibit growth or can even kill bacteria that cause infection. One of them is infection with *Streptococcus mutans* bacteria that cause damage to teeth, such as dental caries. Dental caries is a disease that affects many adults and children, permanently damaging the tooth layer and forming small holes in the teeth. The purpose of this study was to find active compounds from the herb Saga plant (*Abrus precatorius*), which has the potential to be antibacterial of *S. mutans in silico*. The methods used are pharmacokinetics and toxicity screening, Lipinski's Rule of Five, as well as simulations of molecular docking and molecular dynamics. The Abruquinone D (-6.43) and Abruquinone F (-7.08) were predicted to have stable interactions and be similar to amoxicillin (-7.69) and native ligand (-8.56 kcal/mol) based on the results of screening and molecular docking simulations of active compounds from Saga herbaceous (*Abrus precatorius*) against deoxycytidylate deaminase receptors. Molecular dynamics findings confirmed by MMGBSA methods that Abruquinone D (-41.3876 kcal/mol) had a lower energy value than Abruquinone F (-24.8521 kcal/mol). It can be inferred that Abruquinone D has a higher potential as an antibiotic (*S. mutans*) than Abruquinone F.

INTRODUCTION

Antibacterial is a substance that can inhibit growth or can even kill bacteria that cause infection (Magani *et al*., 2020). One of the causes of infection is *S. mutans*, which is a Gram-positive anaerobic bacterium. Generally, *S. mutans* are found in the human oral cavity and can cause tooth decay, such as dental caries (Kementerian Kesehatan RI, 2012; Pramiastuti *et al*., 2020). Dental caries is a prevalent disease affecting both adults and children, causing permanent tooth damage and small holes (Norfai and Rahman, 2017). The World Health Organization reported that 90% of schoolchildren worldwide have caries, with the highest prevalence in Indonesia at 88.8%, primarily in the 55 – 64 age group (Khasanah *et al*., 2019; Kementerian Kesehatan RI, 2019). Dental caries can be reduced through treatments like fillings, root canals, and tooth extractions, as well as antibiotic drugs like amoxicillin. However, excessive use can lead to resistance, resulting in less effective treatment, increased patient morbidity and mortality, and higher health costs (Khasanah *et al*., 2019).

To overcome this problem, scientists are looking for medicinal materials that have low side effects, namely herbal plants. There is a study that states that one of the plants that can potentially be an herbal medicine for antibacterial is Saga herbaceous plant (*A. precatorius*) (Andayani *et al*., 2013). Empirically, the Saga herbaceous plant (*A. precatorius*) is used as an alternative medicine to help treat thrush in the Banten area according to Yusransyah and Izati (2014), cough in the Tasikmalaya area, sore throat in the Karawang area according to Widianto *et al*. (2019), while according to Andayani *et al*. (2013), Saga leaves (*A. precatorius*) can treat canker sores, tonsil cough medicine, and the seeds can treat diabetes and chronic nephritis. It turns out that the Saga plant (*A. precatorius*) has ingredients, including phenols, tannins, flavonoids, alkaloids, terpenoids, and saponins. All such compounds have antibacterial activity (Widianto *et al.*, 2019).

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Research by Andayani *et al.* (2012) stated that the methanol extract of Saga leaves (*A. precatorius*) has antibacterial activity against *S. mutans*, with the smallest resistance zone diameter seen at a concentration of 10%, which is 7 mm, and the largest is seen at a concentration of 100% which is 17.3 mm. And there are also other researchers who state that Saga leaf ethanol extract (*Abrus precatorius*) can inhibit S. *mutans* with the smallest inhibitory zone at a concentration of 1%, which is 6.06 mm, while the largest at a concentration of 10% is 18.02 mm (Nisak *et al.*, 2021). Several structures of compounds that were successfully isolated from *A. precatorius* (Xiao *et al.*, 2017; Okoro *et al.*, 2021) can be seen in Figure 1.

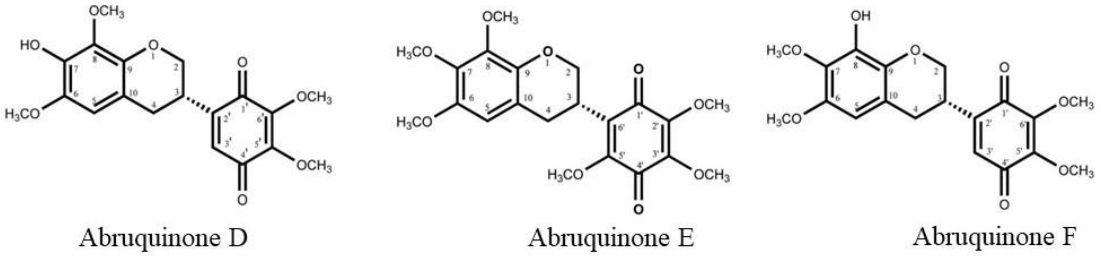


Figure 1. Sample of the structures.

With the potential of Saga herbaceous plants against antibacterials, it is necessary to research more specific Saga herbaceous plants against the antibacterial *S. mutans*. *In silico* test is a research method that uses database technology to develop further research. The *in silico* method can see the interaction between ligands and receptors, know the pharmacokinetic properties, and get results faster (Makatita *et al.*, 2020). Based on the background, this study aims to find candidates for medicinal materials from Saga herbaceous plant compounds as antibacterial *S. mutans* through *in silico* study.

RESEARCH METHODS

The tools used are computer hardware and software. The hardware used is a computer with Intel Core TM i5-6400 PC specifications @3.90GHz (4CPUs), *Nvidia Geforce* GTX 970 *Gigabyte OC Edition* GPU, 8GB DDR4 RAM, and Laptop (ACER) DESKTOP-17KCTT8 Intel® *Core* ™ i5-2450M CPU @2.50GHz; 4GB RAM; *system type* 64-bit; *Operating system*: *Windows 10 Pro*. The software used *Chemdraw Ultra* 8.0, Marvin Sketch 5.2.5.1, *AutoDock Tools 1.5.6, Molegro Molecular Viewer, PyRx 0.9.8, AMBER 16,* and *BIOVIA Dyscovery Studio 2017*. Web server programs such as KNApSAcK, PreADMET, PDBsum, RCSB PDB, and Lipinski's Rule of Five were used.

The ingredients used in this study were 29 compounds of Saga herbaceous plants (*A. precatorius*) obtained from KNApSAcK (http://www.knapsackfamily.com/KNApSAcK/). The receptor used is an antibacterial receptor (*deoxycytidylate deaminase*) with the code PDB ID: 2HVW (Hou *et al.*, 2008) downloaded from the *Protein Data Bank* (PDB) in the https://www.rcsb.org/ website in the form of .pdb format. With the comparison drug used, namely amoxicillin.

Receptor Preparation and Validation

The receptors used are downloaded from the *Web Protein Data Bank*. The receptors are validated in PDBsum, which can provide details of the receptor structure, schematic diagrams of molecules in each structure, and their interaction with ligands. Receptors are said to be good when the residual plot contained in most favored regions (A, B, L) is more than 90% and disallowed regions [X, X] is less than 0.8% (Ruswanto *et al.*, 2018; Mardianingrum *et al.*, 2021b).

Docking Validation

The parameter used for this docking validation is the Root Mean Square Deviation (RMSD) value. The docking method uses natural ligands with the AutodockTools 1.5.6 program and it is said to be valid if the RMSD value obtained is ≤ 2 Å (Zubair *et al.*, 2020).

Ligand Preparation

Compounds downloaded or drawn using ChemDraw Ultra 8.0 were copied and pasted in Marvin Sketch 5.2 software by protonation at pH 7.4 ligands and saved with format *.mrv. Then, the search results for ligand confirmation were saved with the *.mol2 format (Ruswanto, 2015).

Toxicity and Pharmacokinetic Screening

In this study, ADME predictions were carried out on Saga herbaceous plant compounds (*A. precatorius*). The structure of the compound was converted into a mole file (*.mol) and then submitted to the *PreADMET website*, which automatically calculates predictive absorption for Caco-2, HIA (*Human Intestinal Absorption*), and bound plasma binding (PPB) cells. Toxicity tests were carried out on compounds of the Saga herbaceous (*A. precatorius*) in search of Ames and carcinogenicity tests of compounds (Mardianingrum *et al*., 2021a; Ruswanto *et al*., 2020)

Screening Ligand-Based Drug Likeness

Drug Scans were used to observe the nature of their similarity with existing drugs (*Drug Likeness*) performed using the rule of *good medicine* (*Lipinski's rule of five*) and oral bioavailability of ligands. A compound was classified to have properties similar to drugs if it meets two or more conditions with the observed parameters, namely molecular weight <500 g/mol, lipofility <5, hydrogen bond donor <5, hydrogen bond acceptor <10, and molar refractory between 40 – 130 (Ruswanto *et al.*, 2015).

Molecular Docking

The molecular process of docking was carried out using the PyRx program (Dallakyan *et al*., 2015; Pawar *and* Rohane, 2021; Yuliana *et al*., 2013; Kondapuram *et al*., 2021). Ligands that have been prepared with natural ligands were added into protein macromolecules and then forwarded. The Gridbox data was adjusted during the docking validation step, and the AutoGrid was run until it finished. The resulting binding energies were then selected and ordered.

Molecular Dynamics Simulation

Simulation of molecular dynamics of docking complex of protease enzymes with ligands was carried out using the AMBER 16 MD program through several stages, namely: file preparation, minimization, heating, equilibration, production, and analysis of molecular dynamics simulation results with RMSD (Root Mean Square *Deviation*), RMSF (*Root Mean Square Fluctuation*) parameters and changes in interaction distance. The latter was visualized using *the* Discovery Studio Visualizer (Zubair *et al*., 2020; Mardianingrum *et al*., 2022).

RESULTS AND DISCUSSION

Receptor Analysis and Preparation

The receptors used are 2HVW (ligand code: DDN), and the obtained receptors have a resolution value of 1.67 Å, which is considered good because they meet the requirements of the most favored regions parameter with a value of 91.2% and a disallowed region parameter of 0.0%. Therefore, the 2HVW receptor can be used as a target protein for molecular docking to antibacterial activity, as seen in Figure 2.

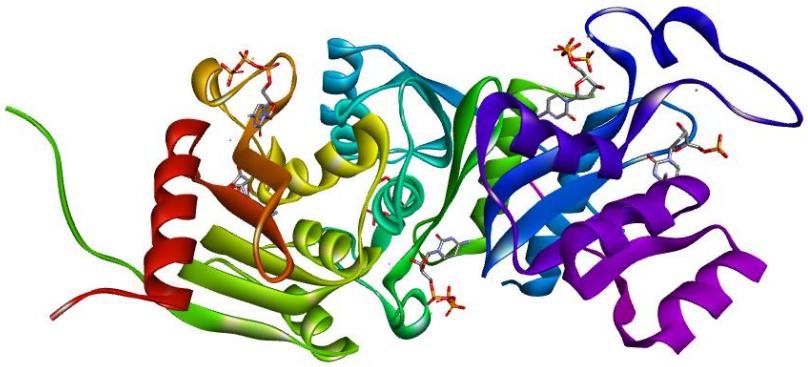
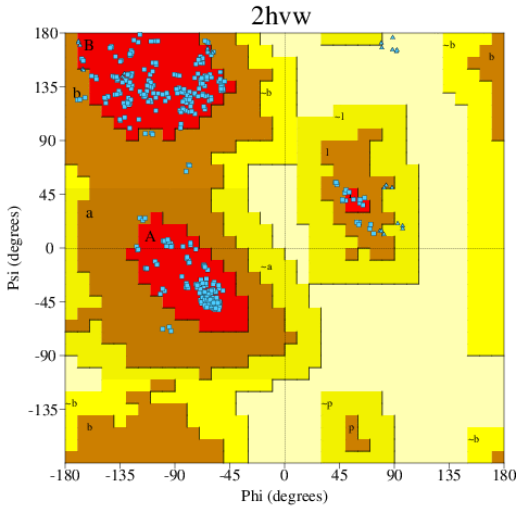


Figure 2. The active site of the 2HVW protein with the natural ligand.

The active site of the 2HVW receptor with the number of amino acids contained in receptor 148 whose target protein interacts with 12 amino acid residues, namely Ala72, Arg26, Arg121, Asn45, Cys24, Cys66, Cys99, Glu73, His65, His71, Thr69, Tyr120 forming hydrogen bonds, as well as hydrophobic bonds with 4 residues, namely Ala27, Cys102, Pro98 and Val29. The results of Ramachandran plot statistics and the active site of the 2HVW receptor can be seen in Figure 3.



		No. of residues	%-tage
Most favoured regions	[A,B,L]	362	91.2%
Additional allowed regions	[a,b,l,p]	35	8.8%
Generously allowed regions	[~a,~b,~l,~p]	0	0.0%
Disallowed regions	[XX]	0	0.0%
Non-glycine and non-proline residues		397	100.0%

Figure 3. Ramachandran plot statistics of 2HVW receptors [Source: PDBsum Database].

Receptor Validation

Docking validation was carried out with *Gridbox* measurements, namely x = 11.76; y = 15.995; z = 51.721, then continued with *docking* analysis using *AutoDockTools* generated an RMSD value of 0.336 Å with a binding energy value of -12.20 kcal/mol. The 2HVW receptor obtains an RMSD value that matches its requirements, which is below 2 Å (< 2Å), with a relatively small amount of energy. The validation results of the docking method can be seen in Figure 4.

Figure 4. Initial conformation 2HVW receptor overlay form (gray) and after simulated redocking validation (yellow) [Source: Visualization of Discovery Studio Visualizer].

Based on the visualization results, it can be seen that the interaction of the 2HVW receptor is the presence of hydrogen bonds with amino acid residues Ala72, Asn45, Cys66, Cys99, Glu73, and Tyr120 (Figure 5). The hydrogen bonds formed are predicted to have a stable interaction with natural ligand bonds inside the most complex 2HVW receptors. Based on these results, it can be stated that the validation of this molecular docking method meets the validation requirements and can be used for the next stage of *in silico* testing.

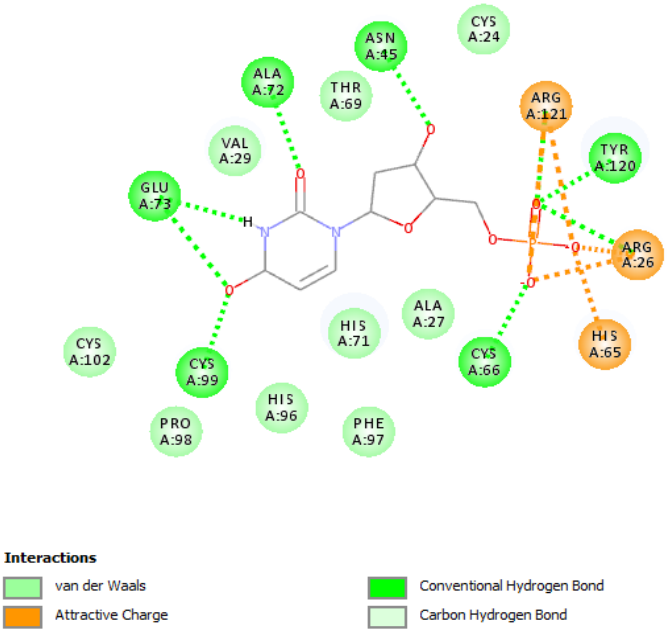


Figure 5. Visualization of natural ligand interactions after validation (*re-docking*) of 2HVW receptors [Source: Visualization of Discovery Studio Visualizer].

Toxicity and Pharmacokinetic Screening Results

Toxicity and ADME testing were carried out using PreADMET, which aims to predict the processes of absorption, distribution, metabolism, excretion, and toxicity in the human body *in silico*. Toxicity testing is the ability of chemicals to cause damage as toxins. Drugs have a therapeutic effect and side effects or toxins, so it is necessary to predict toxicity to recognize the potential of toxins from drugs as a consideration in their use. The parameters analyzed are mutagenic and carcinogenic. Pharmacokinetics is used to predict ADME in Saga herbaceous plant compounds, with parameters including Caco-2 (*Human colon adenocarcinoma*) to determine the ability to penetrate cell membranes, HIA (*Human Intestinal Absorption*) to predict absorption in the small intestine, bound PPB (*Protein Plasma Binding*) and the ability to penetrate the brain to predict distribution in the body (Kartasasmita *et al*., 2015). The results of toxicity and pharmacokinetics screening tests can be seen in Table 1.

The results of toxicity and pharmacokinetics screening analysis (Table 1) of 29 compounds in Saga herbaceous (*A. precatorius*) that meet the requirements there are 6 test compounds, namely Abruquinone C, Abruquinone B, Abruquinone D, Abruquinone E, Abruquinone F, and Abruquinon G. In this study, six compounds were selected to proceed to the molecular docking stage because these six compounds met the selection parameters of pharmacokinetics and toxicity. Based on the criteria on toxicity and pharmacokinetic prediction, a compound would ideally be Non-mutagenic, Non-carcinogenic in both mice and rats, have medium to high Caco-2 (Human *colon adenocarcinoma*) permeability, have medium to good HIA, and have weak PPB (though this depends on the intended therapeutic use and desired pharmacokinetic profile).

Ligand-Based Drug Likeness Screening Results

A screening of Lipinski's Rule of Five predictions was performed on the 6 test compounds. Drug likeness refers to the oral administration of drugs related to the process of absorption and distribution of drugs. The physicochemical properties of the compounds are indispensable for analyzing the similar properties of compounds with oral drugs and estimating the pharmacokinetic processes of medicinal compounds in the body. The results of the drug scan can be seen in Table 2. The analysis based on Table 2 indicates that all six selected compounds have met Lipinski's rules; thus, it can be stated that the test compounds can be used orally. However, the analysis shows that the comparing drug of amoxicillin is still better than the test compounds.

Table 1. Results of screening toxicity and pharmacokinetic studies.

Compound Name	Toxicity			Pharmacokinetic Predictions		
	ames_test	Carsino Mouse	Carsino Rat	Caco-2	HIA	PPB
Amoxicillin (Comparison drug)	Mutagen	+	-	0.35[a]	62.93[b]	23.35[b]
Luteolin	Mutagen	-	+	4.54[b]	79.42[c]	99.71[a]
Isoorientin	Mutagen	-	-	4.10[b]	14.98[a]	63.45[b]
L-Abrien	Mutagen	-	-	2.06[a]	85.19[c]	41.64[b]
Trigonelline	Mutagen	-	-	20.99[b]	94.69[c]	4.66[b]
Hypaphorine	Mutagen	-	-	17.90[b]	90.97[c]	26.78[b]
Gallic acid	Mutagen	-	+	13.85[b]	53.69[b]	65.38[b]
Abrusoside A	Non Mutagen	+	+	20.14[b]	78.91[c]	90.65[a]
Glycyrrhetinic acid glycoside	NonMutagen	+	+	20.74[b]	83.42[c]	91.83[a]
Stigmasterol	Non Mutagen	+	+	52.33[b]	100[c]	100[a]
All-trans-squalene	Mutagen	+	+	23.40[b]	100[c]	100[a]
Abrectorin	Mutagen	+	+	8.373[b]	93.37[c]	87.56[b]
Swertisin 8-methyl ether	Non Mutagen	+	-	10.51[b]	45.65[b]	50.50[b]
Abrusin	Non Mutagen	+	+	7.32[b]	45.65[b]	50.44[b]
Delphinidin 3-sambubioside	Non Mutagen	-	-	9.10[b]	3.97[a]	21.50[b]
Abruquinone	Non Mutagen	+	-	8.41[b]	1.80[a]	74.52[b]
Abruquinone A	Mutagen	-	-	36[b]	98.18[c]	71.29[b]
Abruquinone C	Non Mutagen	-	-	13.3[b]	93.86[c]	67.61[b]
Abruquinone B	Non Mutagen	-	-	43.04[b]	97.58[c]	65.25[b]
3-[(4-O-beta-D-Galactopyranosyl-beta-D-xylopyranosyl) oxy]-2-(4-hydroxy-3,5-dimethoxyphenyl)-7-methoxy-4H-1-benzopyran-4-one	Non Mutagen	-	-	8.97[b]	15.89[a]	36.11[b]
Precatorin III	Non Mutagen	-	-	8.26[b]	13.71[a]	37.90[b]
Precatorin II	Non Mutagen	-	-	10.44[b]	11.56[a]	35.62[b]
5,7-Dihydroxy-4',6-dimethoxyisoflavone 7-O-beta-D-galactopyranoside	Non Mutagen	+	-	9.77[b]	61.32[b]	55.37[b]
Abruquinone D	Non Mutagen	-	-	14.63[b]	93.86[c]	67.02[b]
Abruquinone E	Non Mutagen	-	-	49.37[b]	96.72[c]	50.86[b]
Abruquinone F	Non Mutagen	-	-	13.29[b]	93.86[c]	66.40[b]
Abrussaponin I	Non Mutagen	+	-	20.79[b]	11.96[a]	80.40[b]
Abrussaponin II	Non Mutagen	+	-	20.02[b]	0.45[a]	48.73[b]
Abruquinone G	Non Mutagen	-	-	10.69[b]	86.91[c]	77.12[b]
Kaikasaponin III methyl ester	Non Mutagen	+	-	20.75[b]	19.94[a]	77.83[b]

Description: Caco-2 (<4 Low [a]; 4 – 70 Medium [b]; >70 High[c])
HIA (0% – 20% Bad[a]; 20% – 70 % Medium [b]; 70 – 100 % Good [c])
PPB (>90% Strongly Bound [a]; <90 % Weakly Bound [b])

Table 2. Drug scan test results according to *Lipinski's Rule of Five*.

Compound Name	Lipinski's Rule of Five				
	Molecular Weight	Log P (Lipofility)	Hydrogen Bonding Donor	Hydrogen Bond Acceptor	Refractory Molar
	<500 g/mol	<5	<5	<10	40 – 130
Amoxicillin (Comparison drug)	365	0.02	5	8	90.69
Abruquinone C	376	1.54	1	8	93.04
Abruquinone B	390	1.84	0	8	97.92
Abruquinone D	376	1.54	1	8	93.04
Abruquinone E	420	1.82	0	9	103.88
Abruquinone F	376	1.54	1	8	93.04
Abruquinone G	408	2.35	3	9	102.16

Molecular Docking

Molecular docking simulations on Saga herbaceous plant compounds as test ligands were performed on the 2HVW receptor (ligand code: DDN). The Gridbox parameters performed are the same as at the redocking validation stage. The reason for configuring the Gridbox is to guide the test ligands; thus, they interact specifically within the designated region of the receptor. The outcome of the docking process yields information on binding affinity (ΔG), inhibition constant (Ki), and the presence of hydrogen bonding.

Based on the data in Table 3, it can be seen that compounds that have small binding affinity values are Abruquinone D and Abruquinone F, which have values comparable to amoxicillin (a comparison drug) and native ligand with the binding affinity of -6.43; -7,08; -7.69; -8.56 kcal/mol, respectively. These results confirm that the native ligand, amoxicillin, Abruquinone D, and Abruquinone F, are predicted to form stable interactions with the bacteria S. mutans. This analysis suggests their potential as effective antibacterial drugs.

Table 3. Results of docking of test ligand molecules with 2HVW receptor.

Compound Name	2HVW	
	Binding Affinity (kcal/mol)	Ki (μM)
Amoxicillin (Comparison drug)	-7.69	2.3
Native ligand	-8.56	0.531
Abruquinone C	133.37	-
Abruquinon B	195.37	-
Abruquinone D	-6.43	38.67
Abruquinone E	-2.2	24220
Abruquinone F	-7.08	12.64
Abruquinone G	2.64	-

The bonds that can be observed from the results of molecular docking are hydrogen and Van Der Waals bonds. These bonds greatly affect the stability of the conformation formed between the ligand and the receptor. The improvement evidence of molecular interaction can be found in Table 4, and its visualization is available in Figure 5. The results of the interaction of molecular enhancers can be seen in Table 4 and Figure 6. Based on this visualization, one can observe the amino acid residues that form hydrogen bonds between the comparison compounds and the two selected test compounds. Specifically, these interactions occur at the active sites of Ala72 (Ala106) and Glu73 (Glu106), which are known to be located in helix-4. It is predicted that these interactions are stable, suggesting that the test compounds may exhibit similar biological activity to the comparison compounds (comparison drugs). This is because they bind to the same amino acid residues. More hydrogen bonds between compounds and amino acid residues indicate a more stable and favorable interaction, as previously noted (Muchtaridi *et al.*, 2014).

Table 4. Interaction of molecular docking results.

Compound Name	Hydrogen Bonding	Hydrophobic Bonding
Amoxicillin (Comparison drug)	Ala72, Arg26, Asn45, Cys66, Glu73, Thr69	Ala27, His65, Ile67, Ile100, Tyr120, Pro98
Abruquinone D	Ala72, Glu73, Phe97	Arg121, Asn45, Cys99, His65, His96, Ile67, Thr69, Tyr120, Pro98
Abruquinone F	Ala72, Arg121, Cys66, Glu73, His65, Phe97	Arg26, Asn45, Cys99, Ile67, His96, Thr69, Tyr120, Pro98

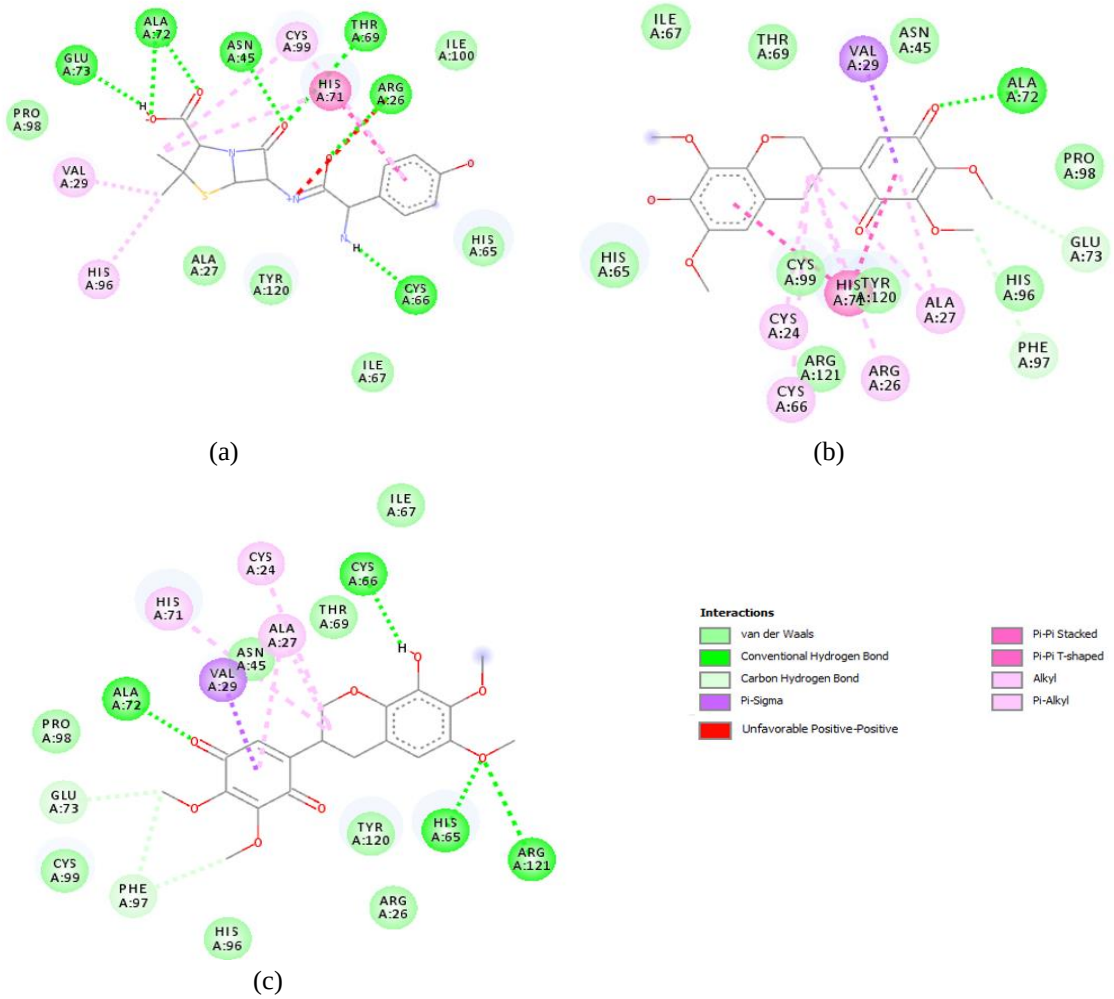


Figure 6. The 2D visualization of the interaction of 2HVW receptor bonds with (a) Amoxicillin, (b) Abruquinone D, and (c) Abruquinone F.

Molecular Dynamics Simulation

The RMSD result is depicted in Figure 7. The RMSD of the Abruquinone D (ligand 23) against the receptor showed a stability range at a time of 4 – 20 ns, with an RMSD value of ± 3Å. The Abruquinone F (ligand 25) against the receptor showed a stability range at a time of 2 – 4 ns with a value of RMSD ± 2 Å would be less stable. Meanwhile, amoxicillin (a comparison drug) against receptors showed a stability range at a time of 4 – 5 ns with an RMSD value of ± 3.5 Å. However, the RMSD of native ligand is extremely erratic from start to end. This shows that Abruquinone D is predicted to have a stable interaction with the 2HVW receptor if it was compared with others. From these results, it can be predicted that Abruquinone derivative compounds have the potential as antibacterial, which is in accordance with the results of other studies (Okoro *et al.*, 2022).

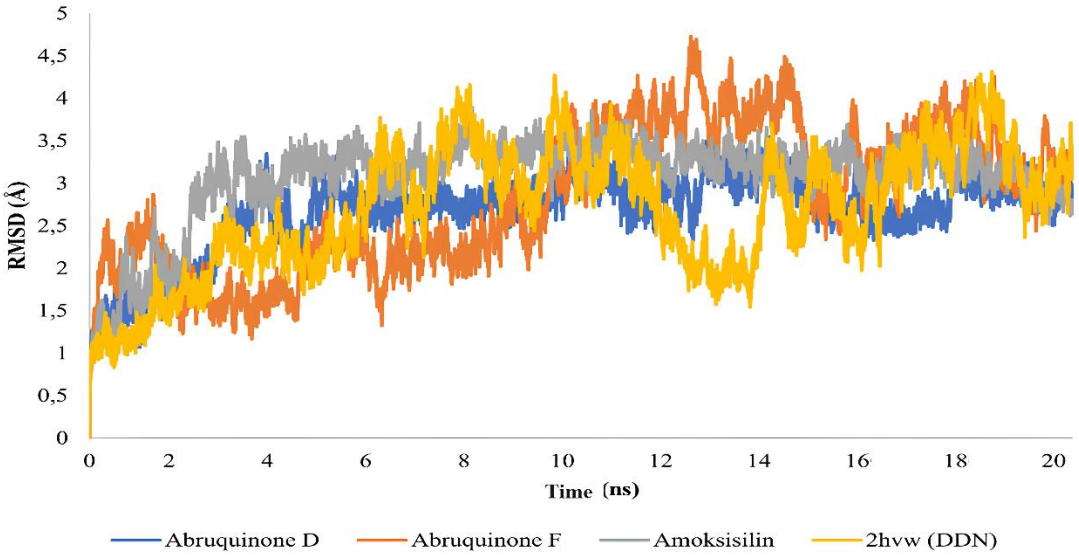


Figure 7. Graph of RMSD values from simulated molecular dynamics of compounds Abruquinone D, Abruquinone F, Amoxicillin and native ligand (DDN).

The analysis (RMSF) shows fluctuations in the amino acid residues that make up the receptors in the simulation process to represent the residue's flexibility (Figure 8.). High residues and fluctuations indicate high flexibility and unstable interactions due to frequent changes in their positions during the simulation. This is consistent with the findings of Mardianingrum *et al*. (2021a), which suggest that residues with low fluctuations play an active role in the binding between ligands and receptors, as they do not exhibit high flexibility.

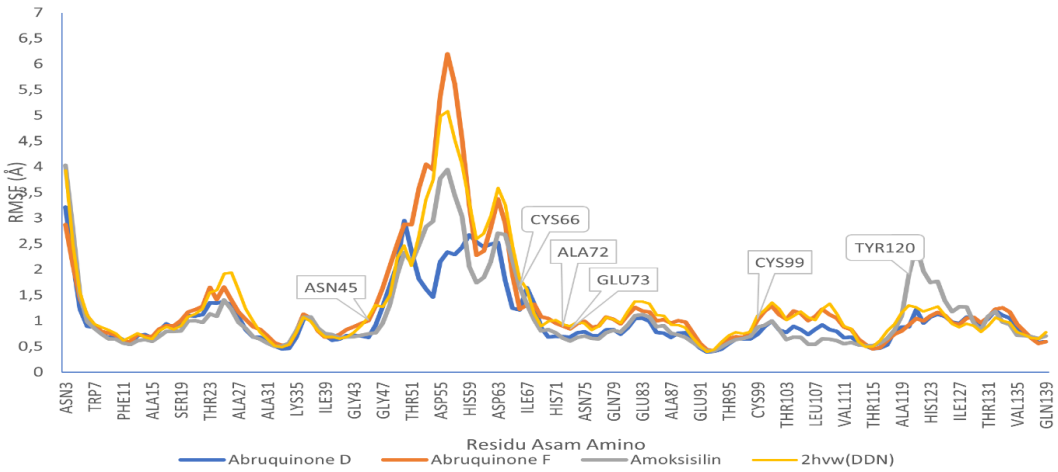


Figure 8. RMSF graph results of molecular dynamics simulation of compounds abruquinone D, abruquinone F, amoxicillin, and native ligand (DDN).

Based on Figure 8, the active site consists of amino acid residues, namely Asn45 (Asn79), Cys66 (Cys100), Ala72(Ala106), Glu73 (Glu107), Cys99 (Cys133) and Tyr120 (Tyr154). Abruquinone F undergoes higher fluctuations than Abruquinone D, native ligand, and amoxicillin if its active site consists of Asn45(Asn79), Ala72 (Ala106), Glu73 (Glu107), and Cys99 (Cys133). Meanwhile, if amino acids Cys66 (Cys100) and Tyr120 (Tyr154) are present in the active site, amoxicillin experiences higher fluctuations than Abruquinone D and Abruquinone F.

Table 5 shows that Abruquinone D complex with receptors has a lower total bond-free energy value (ΔG_{TOTAL}) than amoxicillin and Abruquinone F. The electrostatic energy (EEL) is the energy component with the greatest effect on the system. The total value of bond-free energy (ΔG) in the Abruquinone D system against receptors is lower (-41.3876 kcal/mol) than amoxicillin (-37.2918 kcal/mol), but it was bigger than native ligand (-57.8527). This shows that the level of affinity of Abruquinone D to receptors is better and has more potential as an antibacterial against *S. mutans* bacteria than amoxicillin (a comparison drug), but it was less than native ligand.

Table 5. Calculation of the bonding energy of the amoxicillin, abruquinone D and abruquinone F systems against receptors with the MM-GBSA Method.

Energy Component (kcal/mol)	System			
	Ligand 23 (Abruquinone D)	Ligand 25 (Abruquinone F)	Amoxicillin	2HVW (DDN)
VDWAALS	-45.9499	-33.7635	-42.7188	-25.6893
EEL	-23.2312	-64.0084	-3.48	-256.8363
EGB	33.0641	76.973	13.4859	229.3433
ESURF	-5.2705	-4.0533	-4.5789	-4.6704
ΔG gas (VdW+EEL)	-69.1811	-97.7719	-46.1989	-282.5256
ΔG solv (EGB+ESURF)	27.7935	72.9197	8.9071	224.6729
ΔG total (VdW+EEL+EGB+ESURF)	-41.3876	-24.8521	-37.2918	-57.8527

The shifting position of the selected ligand is observable in snap 1, snap 5, snap 10, snap 15, and snap 20 of each compound (Figure 9, Figure 10, and Figure 11). Figure 9 shows that the position of the ligand in the Abruquinone D compound during the simulation from snap 1 to snap 20 has no significant shift. The position of the ligand is fixed from the beginning to 20 ns.

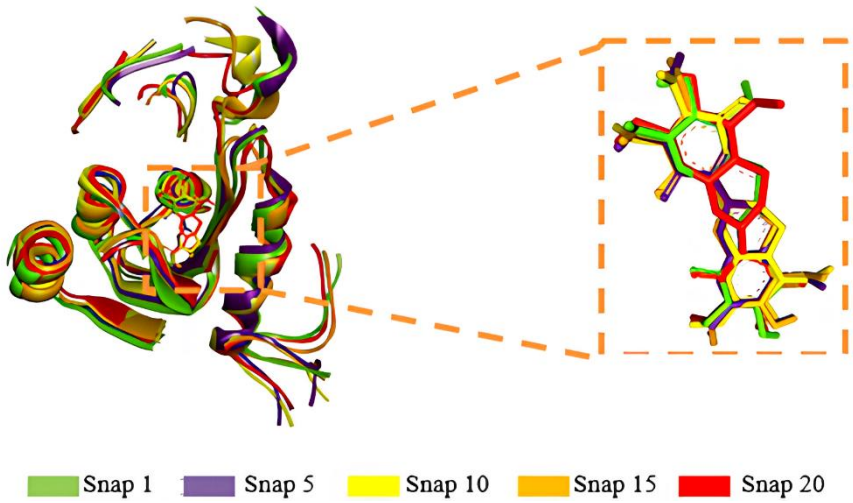


Figure 9. Superimpose results of molecular dynamics simulation of Abruquinone D.

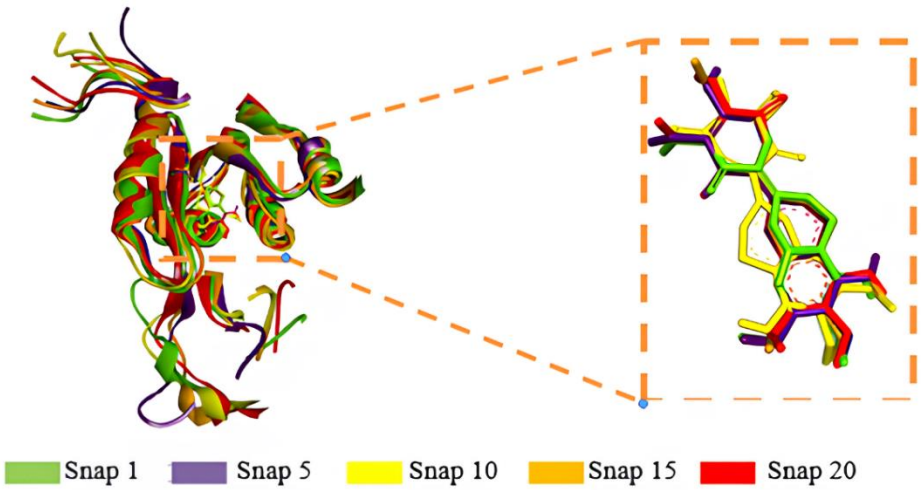


Figure 10. Superimpose simulation results of molecular dynamics compound Abruquinone F.

This amino acid is obtained from the homology modeling results (inset of Figure 9). Homology is the most accurate computational method of predicting the 3D structure of the target protein with a similarity of at least 30% amino acid arrangement to the structure of the molded protein. This modeling can also explore the interaction mechanism between target proteins and ligands on an atomic scale (Saudale, 2020). The MM-GBSA calculation method produces the ligand system's free energy (ΔG) bonding with receptors in molecular dynamics simulations. The smaller the free energy (ΔG), the greater the ability of a compound to interact with receptors.

Based on Figure 10, the position of the ligand in the Abruquinone F compound during 10 ns simulation was released. However, at 15 ns, the position gradually returned and completely returned to the initial position at 20 ns. Figure 11 shows the no-shift position observed in the amoxicillin compound during the simulation. It can be concluded from these results that Abruquinone D and Amoxicillin are in a fixed position. Moreover, the RMSD in Figure 6 shows that Amoxicillin and Abruquinone D can be antibacterial candidates, in which Abruquinone also has a lower RMSD value than amoxicillin.

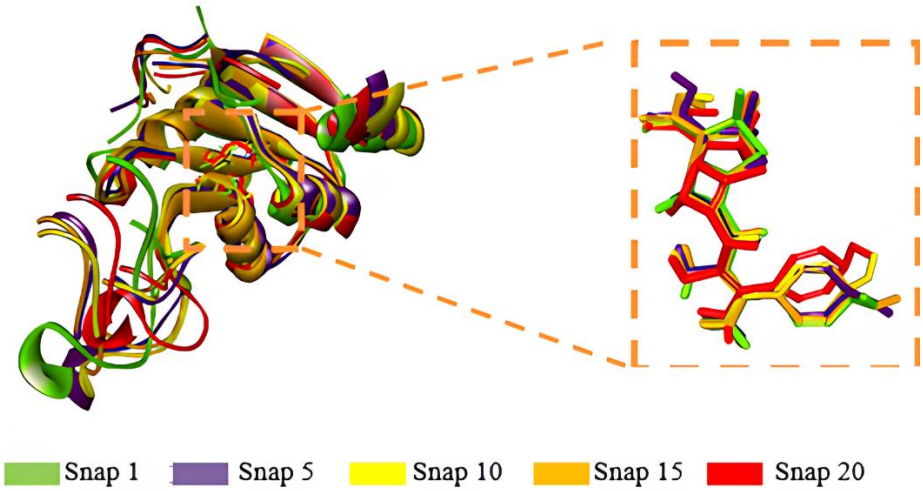


Figure 11. Superimpose simulation results of molecular dynamics of Amoxicillin compounds.

CONCLUSION

The results of the molecular docking and molecular dynamic simulations between the active compound from the Saga herbaceous (*A. precatorius*) and the deoxycytidylate deaminase receptor show that the compound Abruquinone D has a better interaction than Abruquinone F. Therefore, the compound Abruquinone D can potentially be used as an antibiotic against *S. mutans* bacteria.

CONFLICT OF INTEREST

There is no conflict of interest in this article.

AUTHOR CONTRIBUTION

RM: Conceptualization, Methodology; NES: Data Analysis, Manuscript Drafting; SRNE: Manuscript Review; RR: Manuscript Review and Editing.

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