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Research Article

# *In-silico* Studies of Jatropha curcas Bioactive Compounds as Anti SARS-CoV-2

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## Abstract

COVID-19 is a disease caused by Coronavirus a new type Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) which includes a disease outbreak that began at the end of December 2019 marked by a mysterious pneumonia case of unknown etiology, starting in Wuhan, China which until now it is still a concern and has not experienced a termination of the case. Jatropha curcas L. has several secondary metabolites that have antiviral activity which can be a potential antiviral therapy for SARS-CoV-2. The purpose of this study was to determine the compounds contained in the Jatropha plant and the interactions that occur in inhibiting SARS-CoV-2 by molecular docking and molecular dynamic. The results showed that the compounds rhoifolin and stellarin-2 had physicochemical properties with large molecular weights and good pharmacokinetics and toxicity. Results docking score docking was -94.8779 against the 5R7Y receptor and then -108.2190 for stellarin-2 to the 7TLL receptor and had good stability in molecular dynamics compared to native ligands and Molnupiravir for comparison. The interactions formed were 6 hydrogen bonds in rhoifolin and 7 hydrogen bonds in stellarin-2. This shows that rhoifolin and stellarin-2 have potential as anti-SARS-CoV-2 candidates.

**Keywords:** Jatropha; Molecular Docking; Molecular Dynamic; Rhoifolin; SARS-CoV-2; Stellarin-2

## Introduction

The COVID-19 disease outbreak began at the end of December 2019 starting in Wuhan, Hubei Province, China marked by a mysterious pneumonia case of unknown etiology, which is still a concern and has not experienced a termination of cases. COVID-19 is a disease caused by Coronavirus a new type Severe Acute Respiratory Syndrome Coronavirus-2 [18].

Jatropha (*Jatropha curcas* L.) has several complex metabolites that have antiviral activity including flavonoids, alkaloids, phenols, saponins and tannins which can be potential antiviral therapies for SARS-CoV-2 [1]. The activity inhibits the entry of the HIV virus [1,4], has significant antivirus activity against the dengue [22] and has inhibitory activity for the influenza virus [10,15]. There are currently no available drug therapy options for treating COVID-19 [2].

Studies *In silico* that can be carried out are by using molecular docking to predict how the interaction between proteins (receptors) and bioactive compounds (ligands) [21] also includes molecular dynamics to determine the stability of proteins in binding complexes with ligands. Comparative drugs used are Remdesivir, Nirmatrelvir, Molnupiravir and Favipiravir. Uses *In silico* have shown that the use of comparator drugs is a potential inhibitor in the inhibition of viral replication [5]. So far, there has been no research that has conducted research, therefore in this study the authors intend to conduct *in silico* on Jatropha plant compounds against the SARS-CoV-2 receptor.

## Materials and Methods

### Receptors analysis

Analysis Target receptor analysis was carried out by looking at the PDB protein profile on the website (https://www.rscb.org/)

with consideration of the receptors that work in inhibiting SARS-CoV-2 and looking at the stability of the receptor through the results of the Ramachandran Plot [19].

### Receptor preparation

Receptor (protein) preparation using software YASARA is deleting systems that are not needed in the protocol docking as residue, then addition of hydrogen and removal of water molecules.

### Ligand preparation

The structural ligands of the test compounds, comparisons and native ligands were prepared by protonating pH 7,4 and conforming the ligands using MarvinSketch.

### Ligand screening

Screening ligan was carried out using the website (http://www.swissadme.ch/index.php). The criteria for a good drug orally can follow Lipinski's Rule of Five [12].

### Validation of method docking

Repetition docking between the native ligand and the target receptor is carried out in the validation process of the docking by checking the validation of the parameters that will be used for docking the test compound. The results show that it is said to be valid if the result of the RMSD value is ≤2.0Å [17].

### Docking of ligands

Docking was carried out by ligands against receptors using the PLANTS linked by the Co-pendrivelinux-KDE. Docking results in the form of docking scores.

### Results visualization docking

The results of the lowest docking scores were visualized and interpreted to determine the interaction between the ligand-proteins that occurred using MOE software.

### Pharmacokinetic and toxicity prediction

Ligand Toxicity Testing based on pkCSM Online Tool (http://structure.bioc.cam.ac.uk/pkcsm) and admetSAR (http://lmmd.ecust.edu.cn/admetsar2) [16].

### Molecular dynamic

Molecular Dynamic was performed using the Google Colab AMBER system (https://colab.research.google.com/github/pablo-arantes/making-it-rain/blob/main/Protein_ligand .ipynb), the input material namely the best ligand from molecular docking and target protein. The processed results are in the form of interactions between Ligand-Protein, RMSD and RMSF values.

### Synthesis prediction

Prediction of compound synthesis pathway can be done using the website ChemicalAI (https://chemairs.chemicalai.cn/#/) by inserting the compound SMILES code which is then obtained from the prediction of compound synthesis [3].

## Results and Discussion

### Receptors analysis

Receptors were analyzed based on the PDB protein profile based on experimental data, namely organism(s) stating *Severe Acute Respiratory Syndrome Coronavirus 2* and with a resolution value of less than 2Å, the lower the receptor resolution value, the better the receptor stability. The receptors used consisted of PDB ID: 5R7Y, 7JKV, 7TLL and 7VH8. The results in Figure 1. show good stability and can be used as a receptor. This is because all target receptors meet the rules and parameters of the Ramachandaran plot analysis by showing the number of non-glycine residue plots contained in the dissalowed regionsis less than 0.8% [19].

### Receptor preparation

Receptor preparation was carried out on the target receptors 5R7Y, 7JKV, 7TLL and 7VH8 with the aim of producing only native protein without native ligands as well as water molecules or unwanted residues. The removal of a water molecule allows the ligand to fill the space previously occupied by water. The resolution of the crystal structure in the file is not able to predict the presence of hydrogen, so it is added to form hydrogen bonds and can be observed [17].

### Ligan preparation

preparation is carried out using software Marvinsketch. Preparation of ligands (native ligands, test compounds, comparison compounds) is carried out by a geometric optimization process by protonating the ligand at pH 7.4 with the aim of adjusting to the pH conditions of the blood in the body and also by carrying out the conformation. Process of a protonated molecule for the purpose of obtaining low potential energy [19].

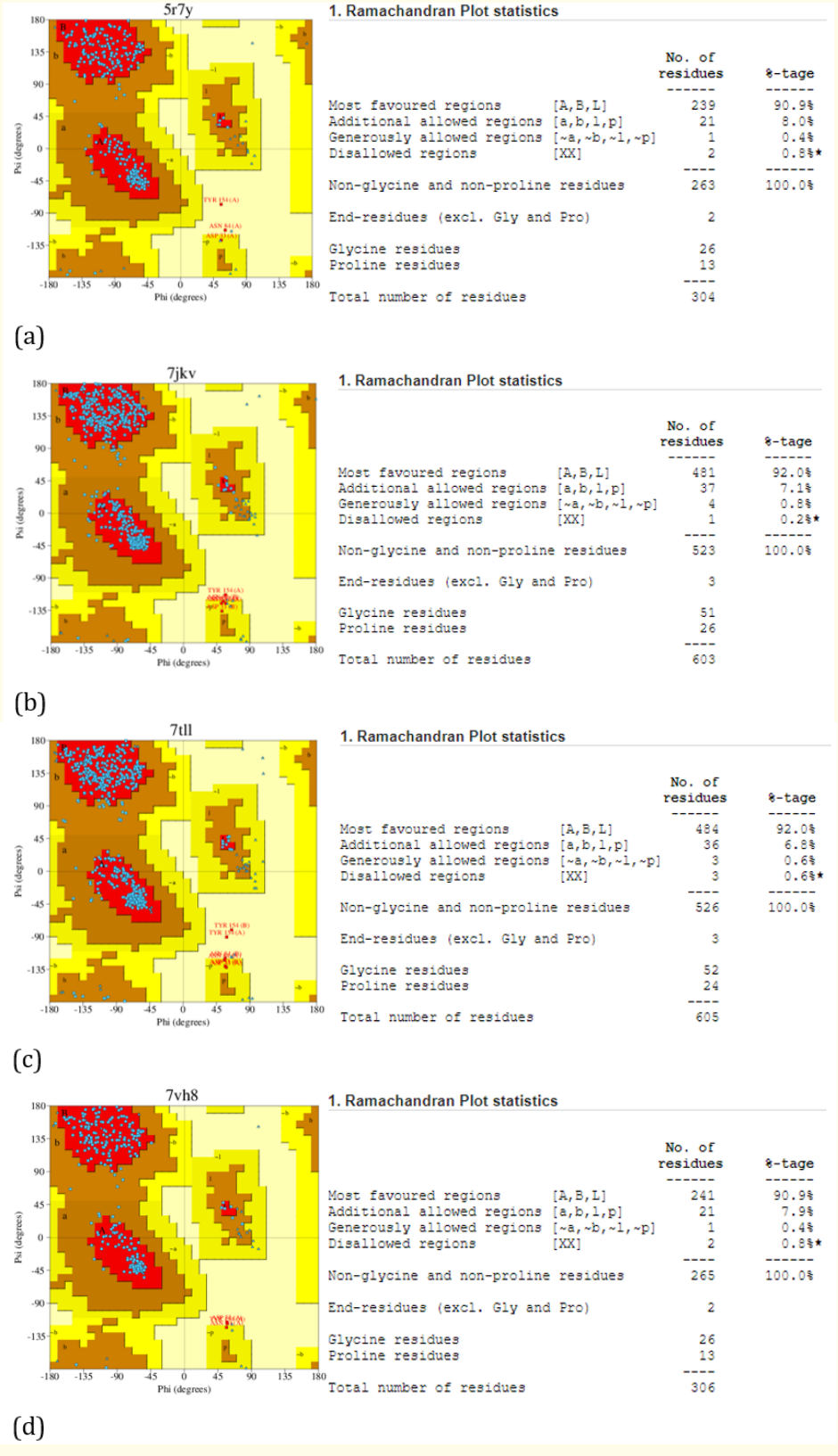



**Figure 1:** Statistics of Ramachandran Plot Receptor Code (a) 5R7Y; (b) 7JKV; (d) 7TLL; (d) 7VH8.

## Ligand Screening

Lipinski's Rule of Five was carried out to determine the criteria for a good drug. The definition of four ranges of physicochemical parameters according to Lipinski's law of five (2004) shows that molecular weight (MW) values <500 g/mol, donor hydrogen bond values (NH) <5, acceptor hydrogen bond values (O and N) <10 and logarithm of partition coefficient water/octanol (Log P) <5) [20]. Prediction results according to Lipinski test compounds are shown in Table 1.

| Compounds | Parameter Lipinski's Rule | | | | Compounds | Parameter Lipinski's Rule | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Molecular Weight (g/mol) | Donor H Bond | Acceptor H Bond | LogP | | Molecular Weight (g/mol) | Donor H Bond | Acceptor H Bond | LogP |
| Remdesivir | 602.58* | 4 | 12* | 2.12* | Gamma Sitosterol | 414.71 | 1 | 1 | 8.02* |
| Nirmatrelvir | 499.53 | 3 | 8 | 1.60 | Isofocusterol | 412.69 | 1 | 1 | 7.94* |
| Molnupiravir | 329.31 | 4 | 8 | -1.65 | Isorhoifolin | 578.52 | 8 | 14 | -1.10* |
| Favipiravir | 157.10 | 2 | 4 | -0.57 | Isovitexin | 432.38 | 7* | 10 | -0.23 |
| 12-deoxyphorbol-13-Phenyl-acetate | 466.57 | 3 | 6 | 2.75 | Jatropham | 113.11 | 2 | 2 | -1.00 |
| 17 alpha-Hydro-pregnolone | 332.48 | 2 | 3 | 3.63 | Jatropholone | 296.40 | 1 | 2 | 4.62 |
| 24-ethylcolesterol | 414.71 | 1 | 1 | 8.02* | Jatrophone | 312.40 | 0 | 3 | 4.07 |
| 2-furankarbok-saldehida | 151.12 | 3 | 5 | -2.02 | Marmesin | 246.26 | 1 | 4 | 1.87 |
| 3,5-dihidroxy-4-metoxybenz-aldehyde | 247.04 | 2 | 4 | 1.68 | Myricetin | 318.24 | 6* | 8 | 1.69 |
| 3,7-Di-O-methyl-quercetin | 330.29 | 3 | 7 | 2.59 | Pachypadol | 344.32 | 2 | 7 | 2.90 |
| 3-O-methylquercetin | 316.26 | 4 | 7 | 2.29 | Peposterol | 454.73 | 0 | 2 | 8.66* |
| 5-[2-(4,5,5-Trimethyl-cyclopent-1-enyl)-ethylidene] pyrimidine-2,4,6(1H,3H,5H)-trione | 262.30 | 2 | 3 | 0.90 | Phenol, 2, 4-bis(1-methyl-1-phenyl) | 302.41 | 1 | 1 | 5.36* |
| 7-keto-beta sitosterol | 428.69 | 1 | 2 | 7.20* | Phytate | 660.04* | 12* | 24* | -3.13 |
| Apigenin | 270.24 | 3 | 5 | 2.58 | Protoctheucuic acid | 154.12 | 3 | 3 | 0.80 |
| Beta Amyrin | 426.72 | 1 | 1 | 8.17* | Pyrogallol | 126.11 | 3 | 3 | 0.80 |
| Beta Sitosterol | 414.71 | 1 | 1 | 8.02* | Rhoifolin | 578.52* | 8* | 14* | -1.09 |
| Campesterol glucoside | 562.82 | 4 | 6 | 3.78 | Rutin | 610.52* | 10* | 16* | -1.69 |
| Cholestenol | 386.65 | 1 | 1 | 7.53* | Stellarin-2 | 624.54* | 11* | 16* | -3.03 |
| Cimifugin | 306.31 | 2 | 6 | 1.22 | Stigmasterol | 41.,69 | 1 | 1 | 7.80* |
| Coniferaldehide | 178.18 | 1 | 3 | 1.50 | Taraxerol | 426.72 | 1 | 1 | 8.17* |
| Curcacycline | 766.98* | 9* | 9* | -3.68 | Tirucallol | 426.72 | 1 | 1 | 8.48* |
| Curcusone | 296.40 | 0 | 2 | 4.20 | Tomentin A | 442.50 | 4 | 7 | 4.21 |
| Daidzein | 254.24 | 2 | 4 | 2.87 | Vicenin-2 | 594.52* | 11* | 15* | -3.04 |
| Delta7-avenosterol | 412.69 | 1 | 1 | 7.94* | Vitexin | 43.,38 | 7* | 10 | -0.23 |
| Delta-selinene | 204.35 | 0 | 0 | 4.87 | | | | | |

**Table 1:** Ligand Screening.

Note: The sign (*) does not meet Lipinski's rules.

## Validasi metode docking

Software YASARA with PLANTS is used to validate the docking by performing between native ligands with target receptors that have previously been redocking. The results of the validation will then be compared between the position of the native ligand and the position of the copy. The parameters used are seen in the results of RMSD <2Å [11]. Based on Figure 2. it can be seen that receptors with RMSD values <2Å consist of receptors with PDB ID 5R7Y, 7JKV, 7TLL and 7VH8 with RMSD values of 1.74Å, 0.71Å, 1.42Å and 1.22Å, respectively. The RMSD results indicate that each receptor is said to be valid. RMSD <2Å indicates the position of the copy ligand (redocking) is not much different from the position of the native ligand which has been tested experimentally by showing a similar position, so that these receptors can be used for the docking.

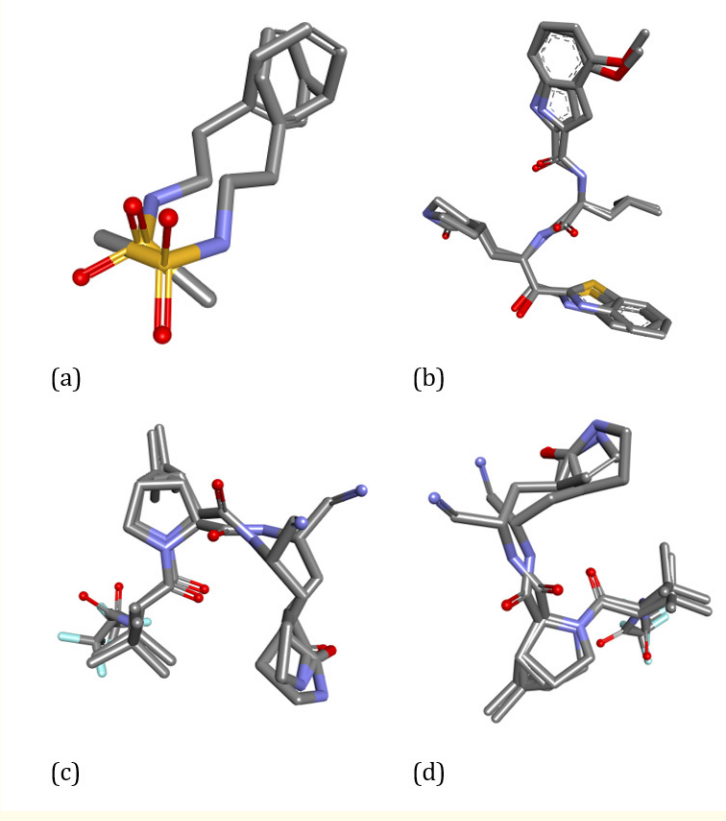



**Figure 2:** Overlap native ligands with ligands copy (redocking) receptors (a) 5R7Y; (b) 7JKV; (c) 7TLL; (d) 7VH8.

## Docking against receptor

Docking of the ligand to this receptor results in docking scores which indicates a measurement of the drug's ability to bind to the receptor and aims to describe the binding affinity of the stability of the complex formed [7]. The results from PLANTS show that lower or lower anchorage scores are considered good, assuming that less energy is required for the compound to bind to its target receptor. Based on Table 2. each compound has docking against the target receptor that has a target on SARS-CoV-2. Score results docking receptors 5R7Y to native ligand N-(2-phenylethyl)-methane-sulfonamide of -64.8688. The results docking compounds contained in Jatropha (*Jatropa curcas* L.) have a docking lower from native ligands as many as 34 compounds. Rhoifolin score docking compared to other test compounds with a result of -94.8779 and a lower yield than the comparison of Favipiravir of -53.3138 and Molnupiravif of -77.5443.

The results docking to the 7JKV receptor in Table 2. have a docking on the native ligand (N-[(2S)-1({(1S,2S)-1-(1,3-benzothiazole-2-yl)-1hydroxy-3[(3)-2-oxopyrrolidin-3yl]propane-2-yl} amino)-4-methyl-1-oxopentan-2-yl] -4-methoxy-1H-indole-2-carboxamide) was -123.4190 with compounds that did not have docking a lower. The test compound that has the docking compared to other test compounds namely Rutin is -101.3570 too lower than

the comparison with Favipiravir with a score of -59.0745, Molnupiravir of -84.6564 and Nirmatrelvir of -93.7499.

Based on Table 2 the results docking of the test compound against the 7TLL target receptor resulted in a docking lower native ligand (1R,2S,5S)-N-{(1E,2S)-1-imino-3-[(3S)-2-oxopyrrolidin-3yl]pro-pan-2-yl}-6,6-dimethyl-3-[3-methyl-N-(trifluoro-acetyl)-Lvalyl]-3-azabicyclo[3.1.0]hexane-2carbo-xamide is -103.2640, on the test compound Stellarin-2 with a value of -108.2190 and lower than the comparison of Favipiravir of -56.8900, Molnupiravir of -84.2485 and Nirmatrelvir of -104.1470.

| No | Compounds (Ligand) | Docking Score Against Receptors | | | |
|---|---|---|---|---|---|
| | | 5R7Y | 7JKV | 7TLL | 7VH8 |
| 1 | Native Ligand | -64.87 | -123.42 | -103.26 | -104.66 |
| 2 | Favipiravir | -53.31 | -59.07 | -56.89 | -56.38 |
| 3 | Molnupiravir | -77.54 | -84.66 | -84.25 | -82.37 |
| 4 | Nirmatrelvir | -95.03 | -93.75 | -104.15 | -107.60 |
| 5 | Remdesivir | -108.54 | -119.08 | -121.46 | -121.48 |
| 6 | 12-deoxyphorbol-13-phenylacetateacetateacetate | -83.00 | -57.26 | -56.20 | -56.96 |
| 7 | 24-ethylcholesterol | -81.64 | -89.80 | -93.40 | -94.55 |
| 8 | 2-furankarboksaldehida | -46.78 | -50.99 | -48.65 | -48.10 |
| 9 | 3, 5-dihydroxy-4-methoxybenzaldehydedehyde | -48.08 | -51.56 | -53.75 | -54.04 |
| 10 | 3,7-Di-O-methylquercetin | -63.20 | -69.77 | -71.83 | -77.90 |
| 11 | 5-[2-(4,5,5-Trimethyl- 1pyrimidine-2,4,6(1H,3H,5H)-trione | -68.85 | -69.93 | -73.68 | -74.92 |
| 12 | 7-keto-beta sitosterol | -81.12 | -95.78 | -88.57 | -89.36 |
| 13 | Apigenin | -68.08 | -79.87 | -76.31 | -76.16 |
| 14 | Avenosterol | -84.83 | -86.43 | -92.31 | -85.84 |
| 15 | Beta Amyrin | -71.55 | -70.68 | -75.44 | -71.38 |
| 16 | Beta Sitosterol | -81.88 | -87.39 | -89.49 | -91.10 |
| 17 | Campesterol glucoside | -89.10 | -93.26 | -99.31 | -96.21 |
| 18 | Cholestenol | -83.10 | 81.89 | -86.11 | -85.43 |
| 19 | Cimifugin | -70.57 | -76.27 | -77.39 | -79.31 |
| 20 | Coniferaldehide | -59.33 | -68.04 | -63.77 | -64.68 |
| 21 | Curcacycline | -70.49 | -87.04 | -86.54 | -92.75 |
| 22 | Curcusone | -66.07 | -68.92 | -74.79 | -73.09 |
| 23 | Daidzein | -63.89 | -74.11 | -71.54 | -72.04 |
| 24 | Delta-Selinene | -59.74 | -70.56 | -66.71 | -64.58 |
| 25 | Gamma Sitosterol | -81.17 | -89.96 | -89.19 | -91.10 |
| 26 | Hydro17 alpha-Hydroxypregnenolone | -64.25 | -75.40 | -79.97 | -79.91 |
| 27 | Isofocusterol | -85.04 | -87.81 | -88.15 | -87.38 |
| 28 | Isorhoifolin | -82.23 | -94.03 | -97.32 | -97.13 |
| 29 | Isovitexin | -78.76 | -87.66 | -90.40 | -93.07 |
| 30 | Jatropham | -51.68 | 54.88 | -54.35 | -54.43 |
| 31 | Jatropholone | -67.58 | -73.53 | -72.16 | -71.29 |
| 32 | Jatrophone | -66.11 | -69.66 | -72.14 | -69.87 |
| 33 | Marmesin | -67.00 | -74.03 | -73.71 | -72.24 |
| 34 | Myricetin | -67.40 | -80.17 | -81.33 | -81.34 |

| | | | | | |
|---|---|---|---|---|---|
| 35 | O-3-O-methylquercetin | -65.57 | -77.17 | -72.14 | -75.84 |
| 36 | Pachypadol | -61.82 | -69.60 | -68.27 | -66.94 |
| 37 | Peposterol | -89.09 | -86.76 | -91.95 | -88.99 |
| 38 | Phenol, 2,4-bis(1-methyl-1-phenyl) | -74.62 | -79.45 | -89.68 | -86.46 |
| 39 | Phytate | -72.45 | -71.07 | -68.82 | -67.63 |
| 40 | Protoctheucuic | -57.40 | -65.02 | -60.75 | -61.79 |
| 41 | Pyrogallol | -58.59 | -58.78 | -57.35 | -59.36 |
| 42 | Rhoifolin | -94.88* | -98.42 | -104.67 | -95.31 |
| 43 | Rutin | -85.94 | -101.36* | -101.89 | -97.38 |
| 44 | Stellarin-2 | -83.00 | -10.26 | -108.22* | -98.05 |
| 45 | Stigmasterol | -82.56 | -88.58 | -87.84 | -89.99 |
| 46 | Taraxerol | -71.41 | -75.21 | -73.77 | -69.17 |
| 47 | Tirucallol | -80.12 | -78.16 | -78.96 | -76.67 |
| 48 | Tomentin A | -93.08 | -95.78 | -100.79 | -98.32* |
| 49 | Vicenin-2 | -85.83 | -97.81 | -101.20 | -85.81 |
| 50 | Vitexin | -86.08 | -90.73 | -94.14 | -94.59 |

**Table 2:** Docking Against Receptor.

Note: The sign (*) of the test compound with the lowest docking score for each receptor.

Scores docking on the test ligands in the target protein 7VH8 in Table 2. are not lower than the native ligand (1R,2S,5S)-N-{(1E,2S)-1-imino-3-[(3S)-2-oxo-pyrrolidin-3-yl]propan-2-yl}-6,6-di-methyl-3[3-methyl-N-(trifluoro-acetyl)-L-valyl]-3-azabicyclo[3.1.0]-hexane-2-carboxamide of -104.6630 in the test compound Tomentin A of -98.3206 and lower than the comparison of Favipiravir -56.3806 and Molnupiravir of -82.3665.

Score docking obtained indicate that there is the ability of the compounds to bind to the target receptor.

The results of the tethering, it can be estimated that the above compounds have the potential as anti-coronavirus.

## Results visualization docking

Results visualization docking was performed to identify significant interactions between ligands and receptor binding sites. Hydrogen bonding is an interaction that is obtained from the results between ligands and proteins, where hydrogen bonds are the main bonds that occur in many biological systems. The hydrogen bonds formed indicate the stability of the protein in the biological system. Visualization was performed on the compound with the docking for each receptor consisting of receptors with PDB ID 5R7Y, 7JKV, 7TLL and 7VH8. Compounds that were visualized consisted of Rhoifolin compounds, Rutin, Stellarin-2, and Tomentin A.

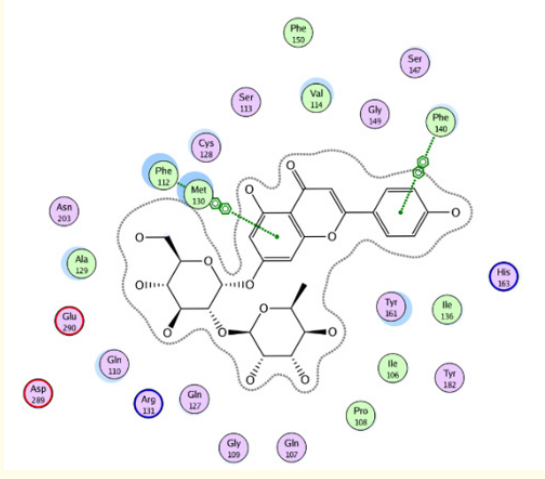



**Figure 3:** 2D Visualization of Rhoifolin Against 5R7Y Receptors.

Based on Table 3 the results of 2D visualization can be seen on receptors 5R7Y on native ligand N-(2-phenylethyl) methanesulfonamide hydrogen bonds to the amino acid Tyr161. The results of Figure 3 show that Rhoifolin with the *docking* to the 5R7Y receptor has hydrogen bonds to the amino acids Phe112 and Phe140.

**Table 4:** Pharmacokinetic and Toxicity Prediction.

| Prediction | | Compounds | | | |
|---|---|---|---|---|---|
| | | Rhoifolin | Rutin | Stellarin-2 | Tomentin A |
| A | Absorption in the intestine (%) | 89.15 | 80.41 | 87.61 | 86.57 |
| | Caco-2 Permeability (Log Ppap in $10^{-6}$ cm/s) | -0.942 | -0.949 | -1.102 | -0.366 |
| | P-glyprotein substrate | Yes | Yes | Yes | Yes |
| | P-glyprotein I Inhibitor | No | No | No | No |
| | P-glyprotein II Inhibitor | No | No | No | No |
| D | VDss (human) (Log L/Kg) | 1.14 | 1.663 | 0.378 | 0.615 |
| | BBB Permeability (Log BB) | -1.702 | -1.889 | -2.147 | -1.388 |
| | CNS Permeability (Log PS) | -4.798 | -5.178 | -5.08 | -2.902 |
| M | CYP2D6 Substrate | No | No | No | No |
| | CYP3A4 Substrate | No | No | No | Yes |
| | CYP1A2 Inhibitor | No | No | No | No |
| | CYP2C19 Inhibitor | No | No | No | Yes |
| | CYP2C9 Inhibitor | No | No | No | No |
| | CYP2D6 Inhibitor | No | No | No | No |
| | CYP3A4 Inhibitor | No | No | No | Yes |
| E | Total Clearence (Log/mg/kg/hari) | -0.005 | -0.369 | -0.266 | -0.045 |
| | Renal OCT2 substrate | No | No | No | No |
| T | LD50 Log (mg/kg BB/hari) | 2.498 | 2.850 | 2.483 | 2.491 |
| | Hepatotoxity | No | No | No | No |
| | Carsinogenic | No | No | No | No |

Note: A= Absorption; D= Distribution; M= Metabolism; E= Excretion

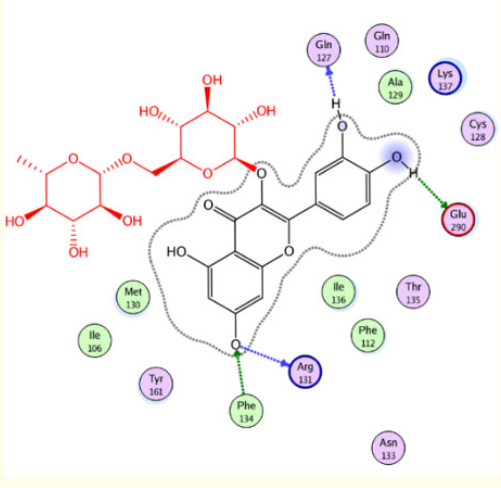



**Figure 4:** 2D Visualization of Rutin Against 7JKV Receptors.

Table 3 shows the results of 2D visualization that can be seen against receptors 7JKV in the native ligand that has hydrogen bonds in the amino acids Cys128 and Phe112. Figure 4 shows Rutin score *docking* to the 7JKV receptor has hydrogen bonds to amino acids Gln127, Glu290, Arg131 and Phe134.

Results Table 3 shows the results of 2D visualization known to receptors 7TLL on native ligands that have hydrogen bonds to the amino acids Tyr126, Val148. Figure 5 shows that Stellarin-2 with the docking for the 7TLL receptor has hydrogen bonding to the amino acid Cys128, Thr135.

Table 3 shows the results of 2D visualization can be seen against receptors 7VH8 in the native ligand that has hydrogen bonds to the amino acids Asn151, Ser113, Gln127, Phe112, Phe150. Figure 6 shows Tomentin A with the docking to the 7TLL receptor having hydrogen bonding to the amino acid Met130.

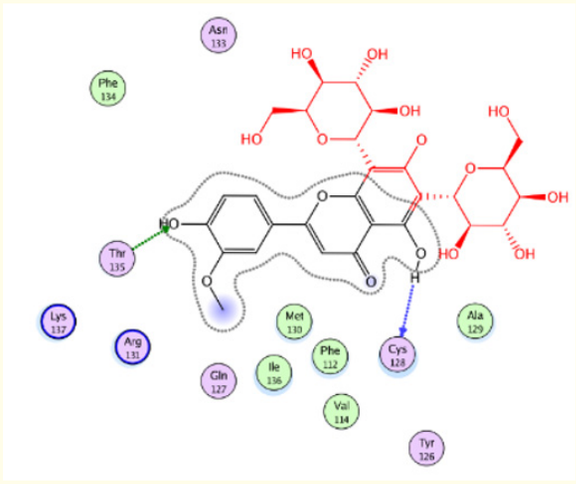



**Figure 5:** 2D Visualization of Stellarin-2 Against 7TLL Receptor.

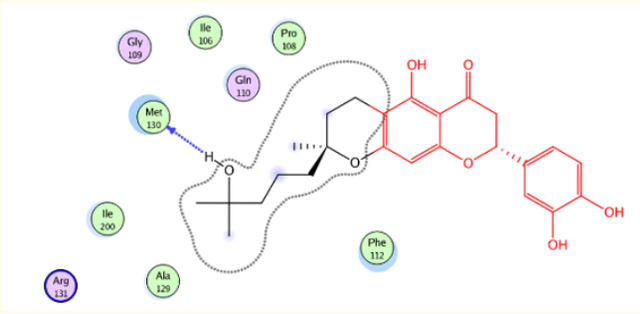



**Figure 6:** 2D Visualization of Tomentin A Against 7VH8 Receptors.

## Pharmacokinetic and toxicity prediction

Absorption, distribution, metabolism, excretion (ADME) and toxicity profiles were performed to evaluate the pharmacokinetic predictions of the compounds with the docking of other compounds at each receptor.

A compound having absorption <30% indicates poor absorption and >80% indicates good absorption, which indicates that the compound has good absorption. Caco2 permeability indicates absorption in the intestine orally, Papp values >8x10 cm/s, or Papp >0,90 indicates high Caco2 permeability. Table 4 shows that the compounds have poor permeability, then the results of the compounds show that they will be absorbed through P-glycoprotein but not absorbed by P-glycoprotein I and II [8].

Compounds with a VDss value >0.45 were declared to have a high and low volume of distribution when the VDss log <-0.15. Table 4. shows only the Stellarin-2 compound, the VDss value shows a low value <0.15. Blood Brain Barrier (BBB) with a log value of >0.3 indicates that the drug can penetrate the brain barrier, while log BB <-1 cannot penetrate the brain barrier, the results in Table 4 show that the compound has a poor ability to penetrate the brain barrier. Central Nervous System (CNS) indicates the ability of a drug to penetrate the central nervous system. Compounds with a LogPS value >-2 were said to be able to penetrate the CNS and a logPS value <-3 were considered unable to penetrate the CNS. The results show Table 4. that all these compounds cannot penetrate the CNS [6].

**Table 4:** Pharmacokinetic and Toxicity Prediction.

| Prediction | | Compounds | | | |
|---|---|---|---|---|---|
| | | **Rhoifolin** | **Rutin** | **Stellarin-2** | **Tomentin A** |
| A | Absorption in the intestine (%) | 89.15 | 80.41 | 87.61 | 86.57 |
| | Caco-2 Permeability (Log Ppap in $10^{-6}$ cm/s) | -0.942 | -0.949 | -1.102 | -0.366 |
| | P-glyprotein substrate | Yes | Yes | Yes | Yes |
| | P-glyprotein I Inhibitor | No | No | No | No |
| | P-glyprotein II Inhibitor | No | No | No | No |
| D | VDss (human) (Log L/Kg) | 1.14 | 1.663 | 0.378 | 0.615 |
| | BBB Permeability (Log BB) | -1.702 | -1.889 | -2.147 | -1.388 |
| | CNS Permeability (Log PS) | -4.798 | -5.178 | -5.08 | -2.902 |
| M | CYP2D6 Substrate | No | No | No | No |
| | CYP3A4 Substrate | No | No | No | Yes |
| | CYP1A2 Inhibitor | No | No | No | No |
| | CYP2C19 Inhibitor | No | No | No | Yes |
| | CYP2C9 Inhibitor | No | No | No | No |
| | CYP2D6 Inhibitor | No | No | No | No |
| | CYP3A4 Inhibitor | No | No | No | Yes |
| E | Total Clearence (Log/mg/kg/hari) | -0.005 | -0.369 | -0.266 | -0.045 |
| | Renal OCT2 substrate | No | No | No | No |
| T | LD50 Log (mg/kg BB/hari) | 2.498 | 2.850 | 2.483 | 2.491 |
| | Hepatotoxity | No | No | No | No |
| | Carsinogenic | No | No | No | No |

Note: A= Absorption; D= Distribution; M= Metabolism; E= Excretion

The metabolic profile in Table 4 shows enzymes that function in metabolizing or detoxifying drugs in the liver with cytochrome P450 (CYP450) enzymes, with the results showing that only Tomentin A compounds are metabolized to CYP314 substrates, CYP2C19 inhibitors and CYP314 inhibitors.

The excretion profile in Table 4 is in the form of Total Clearance related to bioavailability, and functions to reach concentrations in a steady state by determining the dose level [9]. In addition, there is also Organic Cation Transporter 2 (OCT2) which is a transporter in the kidney, where the results obtained are that all compounds do not bind to the OCT2 renal substrate.

The toxicity profile in Table 4 shows that the compounds obtained LD50 with relatively harmless results and also the compounds do not cause liver damage or are carcinogenic.

## Molecular dynamic

Molecular Dynamic (MD) was carried out on candidate test compounds that had previously been subjected to the molecular docking. The molecular docking obtained from the docking lowest native ligands and Molnupiravir were used as comparison ligands. The results of molecular dynamics require analysis of the results, such as the value of Root Main Square Deviation (RMSD), Root Main Square Fluctuation (RMSF) and changes in bond interactions that occur.

RMSD to show that the protein remains in a stable and undenatured state. Figure 7 shows the RMSD graph of the 5R7Y receptor as a whole, the system achieving a generally stable conformation at 1-6 ns. the average RMSD was 2Å for the native ligand 1,8Å for the Rhoifolin ligand and 1,5Å for the Molnupiravir, where the RMSD value <2Å indicates the simulation is said to be stable. An increase in the value of RMSD fluctuations that is too high indicates the presence of denatured proteins resulting from the released protein bonds [13].

During the simulation, there were fluctuations in the amino acid residues that make up the receptor, which were indicated by the RMSF value, so that the RMSF could represent the flexibility of the residue [14]. The amino acid residues in Figure 8 on the 5R7Y receptor have some fluctuations ranging from 0-2Å, high fluctuations in the amino acid residues Asn72, Ala193, Gly278 and Gly302. Rhoifolin showed a low pocket on the residues Glu166, His164, Gln189, Thr24, Gly143, Met165, His41 which indicated that the binding area between Rhoifolin and the 5R7Y receptor was stable.

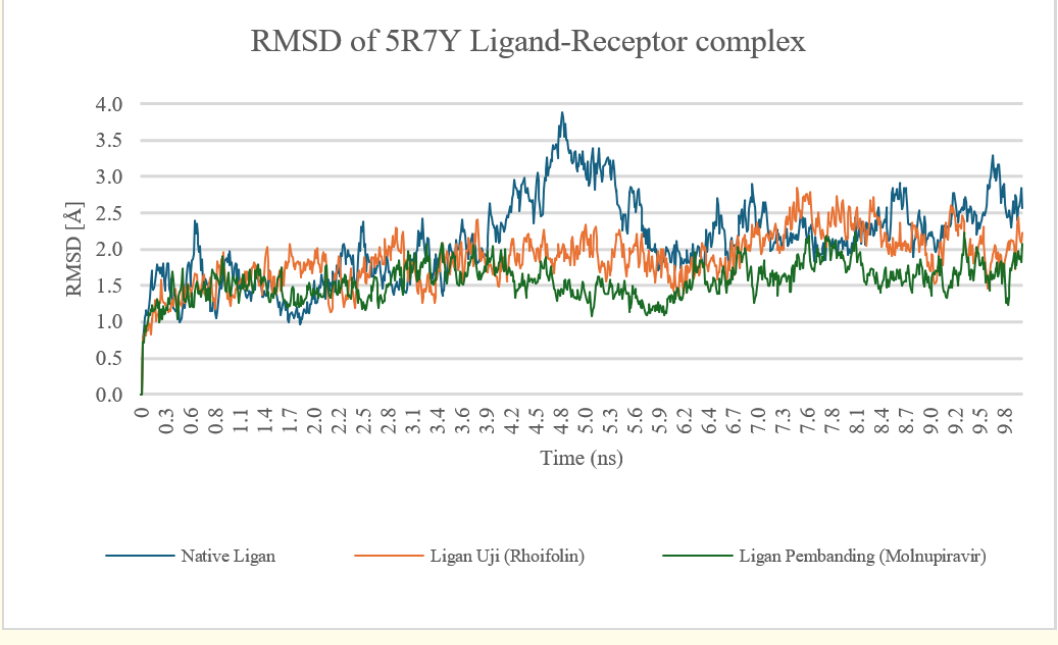



**Figure 7:** Graph of RMSD 5R7Y RMSD ligand-receptor complex.

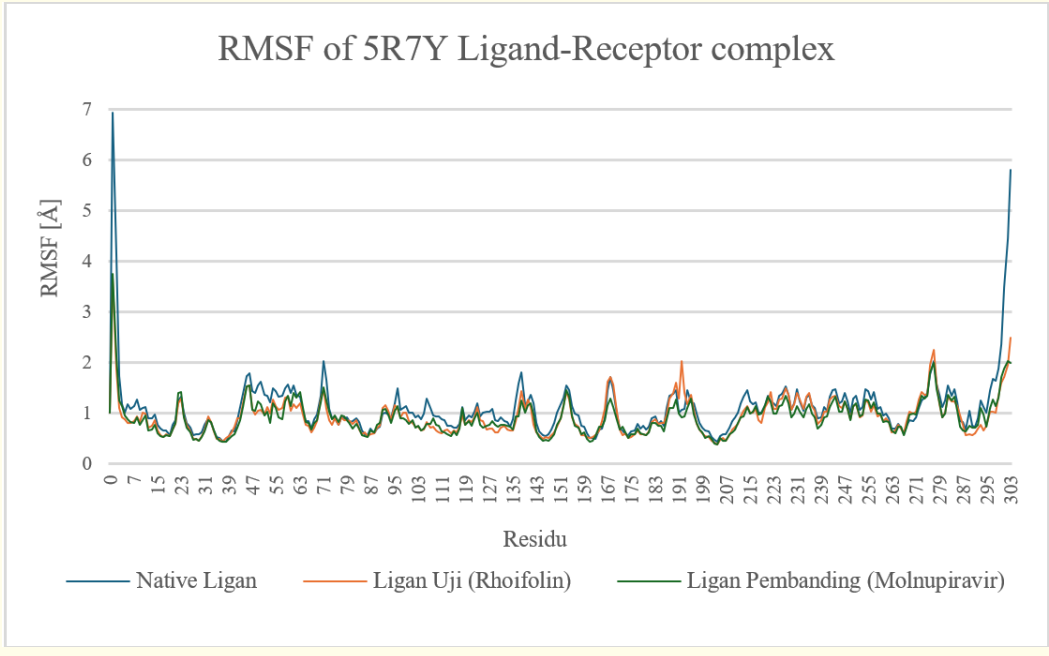



**Figure 8:** Graph of RMSF 5R7Y RMSD ligand-receptor complex.

Figure 9 shows the RMSD value of the complex with the 7JKV receptor as a whole, the system reached a stable condition after reaching a time ranging from 0.25ns. The average fluctuation results showed that the RMSD value for the 7JKV receptor at Rutin was 1.58Å, the native ligand was 1.4Å and molnupiravir as a comparison was 1.57 Å. RMSD value <2Å indicates the molecule is said to be stable. Rutin seen from the results of RMSD showed less stability than the native ligand and the comparison Molnupiravir.

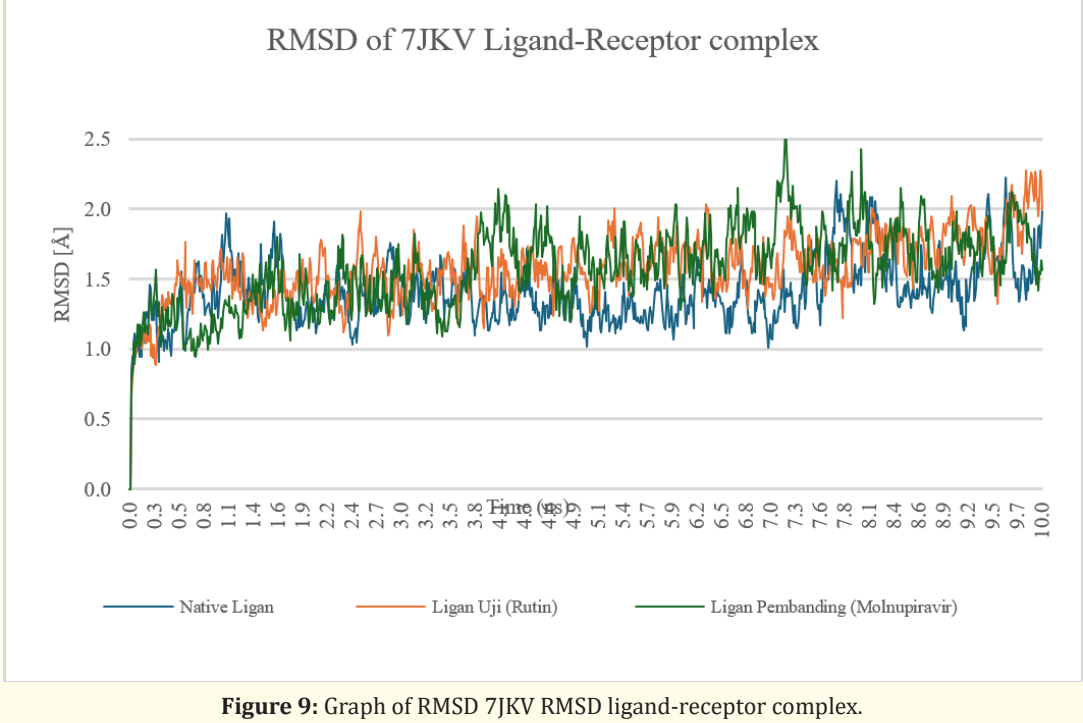



**Figure 9:** Graph of RMSD 7JKV RMSD ligand-receptor complex.

The amino acid residues in Figure 10 which show RMSF values of 0-2.3Å, have high fluctuations in the amino acid residues Asn72, Leu167, Arg279, Asp47 and Gly195. Then there was also pocket of rutin against the 7JKV receptor, which occurred at the amino acid residues Gln189, His163, Leu27, Gly143, Met49, Arg188, Ser144, His164 and Thr25. This indicates that the binding area between rutin and the 7JKV receptor is stable.

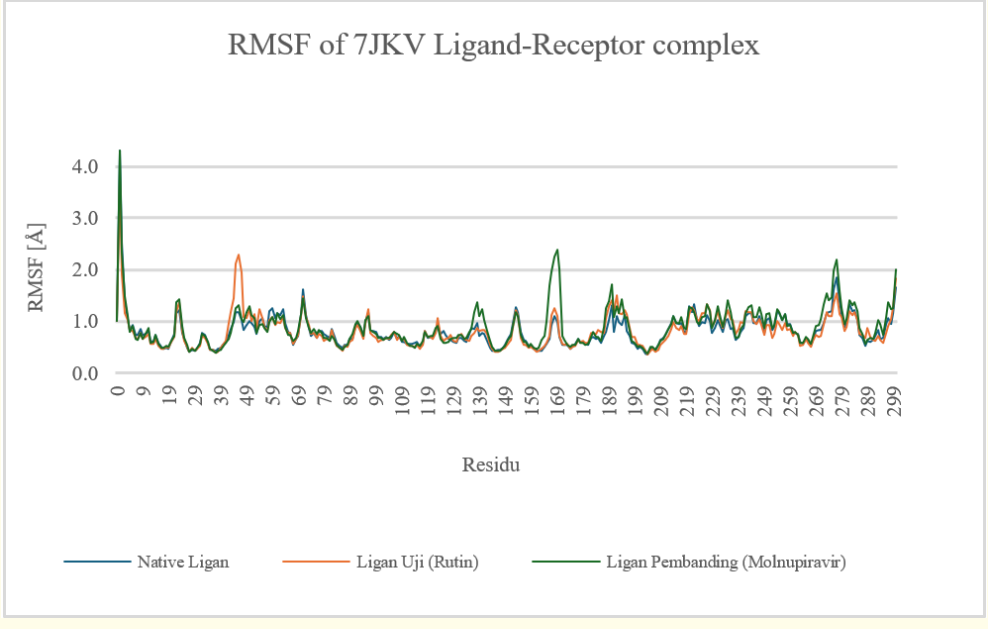



**Figure 10:** Graph of RMSF 7JKV RMSD ligand-receptor complex.

In Figure 11 shows the overall RMSD value, the system reached a stable condition after reaching a time of about 2 ns. Stellarin-2 has an average RMSD value of 1.5Å during the simulation, 1.8Å for native ligand and 1.3Å for molnupiravir. The results show that where the RMSD value is <2Å, the molecule is said to be stable.

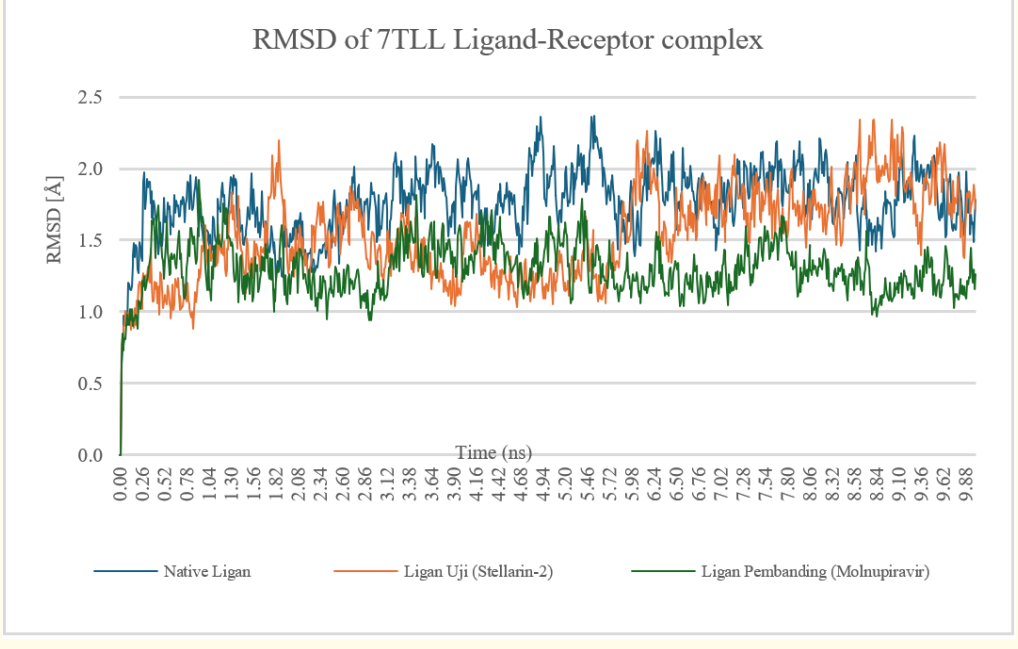



**Figure 11:** Graph of RMSD 7TLL RMSD ligand-receptor complex.

Figure 12 shows a graph of RMSF values for the ligand-receptor complex 7TLL with fluctuation stability at 0-2Å having some high fluctuations in the amino acid residues Thr25, Asn72, Ala193, Asp155, Gly170 and Arg279. Then, pockets occurred in the stellarin-2 compound shown at the amino acid residues Arg188, Thr190, Gln189, Gln192, Phe140, Ala191, Pro168, His163, Ser144 and Cys145. This indicates that the binding site between stellarin-2 and the 7TLL receptor is stable.

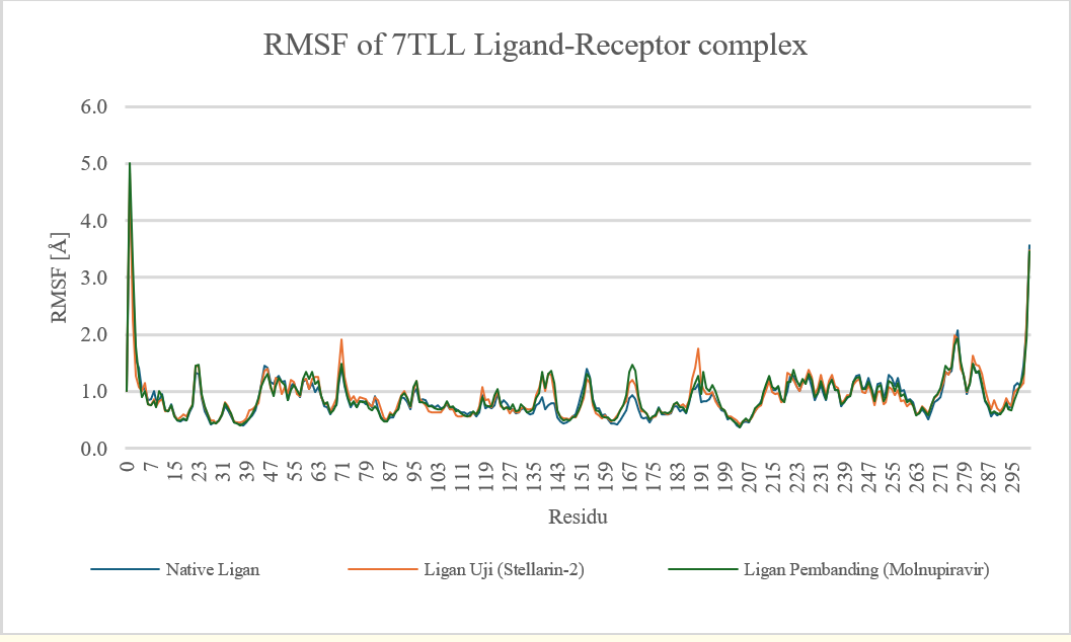



**Figure 12:** Graph of RMSF 7TLL RMSD ligand-receptor complex.

In Figure 13 shows the overall RMSD value, the system reaches a stable condition after reaching a time ranging from 1.8-5ns. The average RMSD value obtained in tomentin A during the simulation was 1.7Å, the native ligand was 1.5Å and molnupiravir was 2Å, where the RMSD value <2Å indicates the molecule is said to be stable.

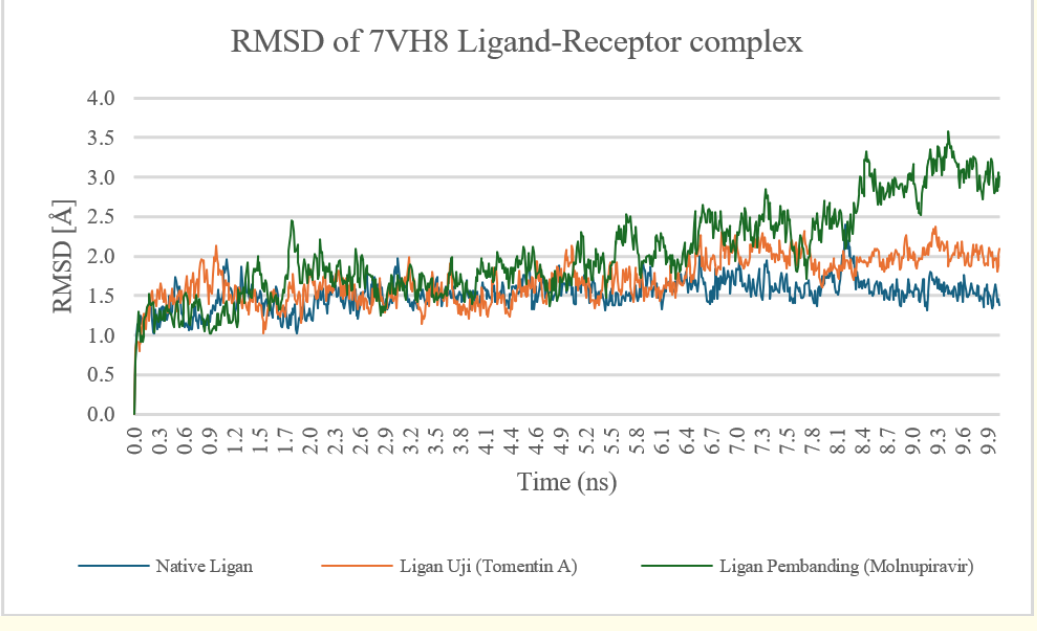



**Figure 13:** Graph of RMSD 7VH8 RMSD ligand-receptor complex.

**Table 5:** Results of 2D Visualization Compound Bonds Between Molecular Docking and Molecular Dynamic.

| No | Compounds | Molecular Docking | | Molecular Dynamic | |
|---|---|---|---|---|---|
| | | Hydrogen Bond | Non-Hydrogen Bond | Hydrogen Bond | Non-Hydrogen Bond |
| 1 | Rhoifolin | Phe112, Phe140 | Met130, Ala129, Val114, Phe150, Ile136, Ile106, Pro108, Asn203, Glu290, Gln110, Asp289, Arg131, Gln127, Gly109, Gln107, Tyr161, Tyr182, His163, Ser147, Gly149, Ser113, Cys128 | Glu166, His164, Gln189, Thr24, Gly143, Asn142 | Met162, His41, Met49, Arg188, Ser46, Thr25, Thr26, Phe140, Ser144, Cys145 |
| 2 | Rutin | Gln127, Glu290, Arg131, Phe134 | Met130, Ile106, Ile136, Phe112, Ala129, Tyr161, Asn133, Thr135, Gln110, Lys137 | Gln189, His163, Leu141, Gly143, Ser144, Thr26 | Leu27, Met49, Arg188, Thr190, Glu168, His41, Met165, Asn142, His164, Thr25, Cys145 |
| 3 | Stellarin-2 | Cys128, Thr135 | Ala129, Met130, Phe112, Ile136, Phe134, Lys137, Arg131, Gln127, Asn133 | Arg188, Thr190, Glu166, Phe140, His163, Leu141, Ser144 | Met165, Gln189, Gln192, Ala191, Leu167, Pro168, His164, Asn142, Gly143, Cys145 |
| 4 | Tomentin A | Met130 | Ile106, Pro108, Phe112, Ala129, Ile200, Gly109, Gln110, Arg131 | Gln192, Thr190, Arg188, Gln189, Thr26 | Asp187, Met49, Asn142, Gly143, Leu27, Met165, His164, Glu166 |

Figure 14 shows a graph of RMSF values at the 7VH8 receptor with fluctuations ranging from 0-2Å, having some high fluctuations in the amino acid residues Gly23, Ser46, Asn72, Gly170, Gly278. Then some showed a pocket on tomentin A on amino acid residues Gln192, Asp187, Arg188, Gly143, Thr26, Leu27, His41 and Glu166. This indicates that the binding area between tomentin and the 7VH8 receptor is stable.

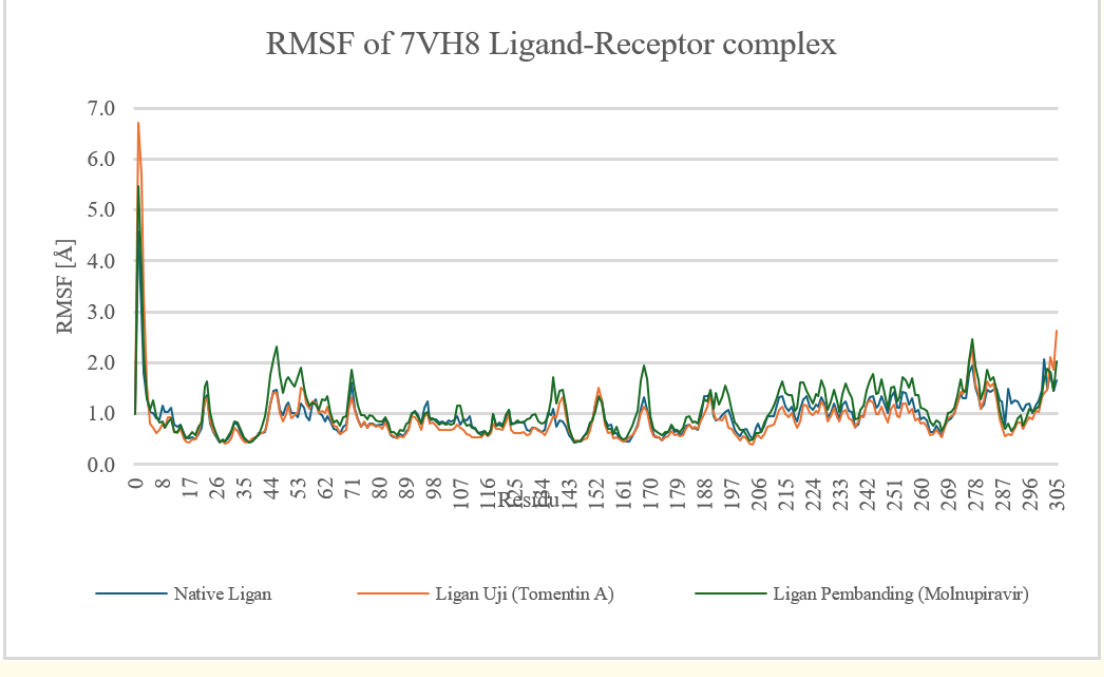



**Figure 14:** Graph of RMSF 7VH8 RMSD ligand-receptor complex.

The results in Table 5 show a change in the type of interaction between the molecular docking results and the molecular dynamic. Rhoifolin results in molecular docking there are 2 hydrogen bonds in the amino acids Phe112 and Phe14, while the molecular dynamic show there are 6 hydrogen bonds in the amino acids Glu166, His164, Gln189, Thr24, Gly143 and Asn142.

The results are in Table 5 rutin in molecular docking are 4 hydrogen bonds in the amino acids Gln127, Glu290, Arg131 and Phe134, while the molecular dynamic show that there are 6 hydrogen bonds in the amino acids Gln189, His163, Leu141, Gly143, Ser144 and Thr26.

The results in Table 5. show stellarin-2 in molecular docking there are 2 hydrogen bonds in the amino acids Cys128 and Thr135, while the molecular dynamic show there are 7 hydrogen bonds in the amino acids Arg188, Thr190, Glu166, Phe140, His163, Leu141 and Ser144.

The results in Table 5 tomentin A shows that in the molecular docking there are hydrogen bonds in the amino acid Met130, while the molecular dynamics show that there are 5 hydrogen bonds in the amino acids Gln192, Thr190, Arg188, Gln189, Thr26.

This shows that there is a change in hydrogen bonds which are strong and important bonds in biological systems, which can show the stability of a protein in binding. It can be concluded that the more stable bond is after molecular dynamics with the result that the addition of hydrogen bonds increases.

## Synthesis prediction

Prediction of the synthesis pathway is carried out on the compound by inserting the SMILES code for the compounds rhoifolin and stellarin-2 which is then obtained from the prediction of the compound [3]. The manufacture of a compound from a parent structure to obtain better results, whether related or not related to the active substance, is the goal of compound synthesis.

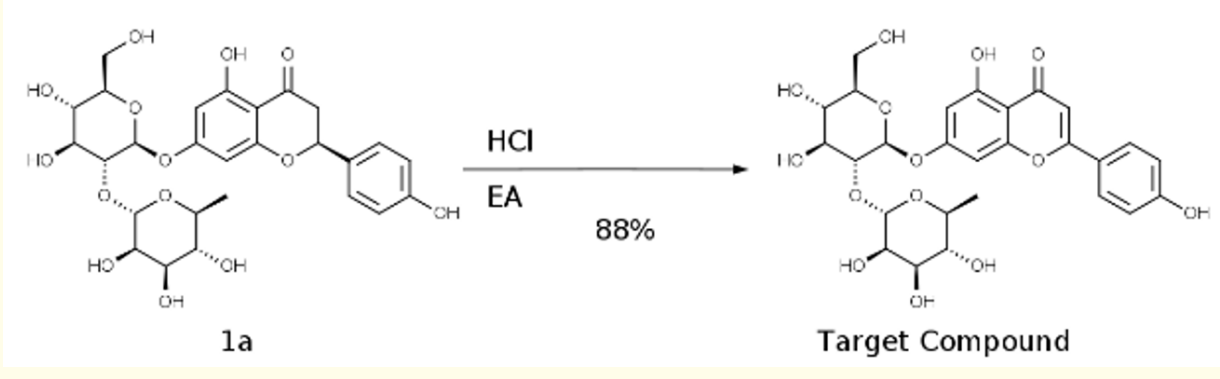
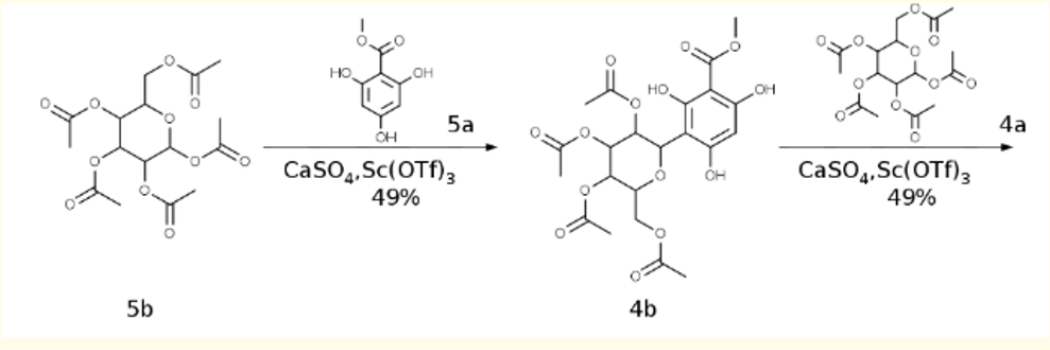



**Figure 15:** Prediction of the Synthesis Pathway for Rhoifolin Compound.



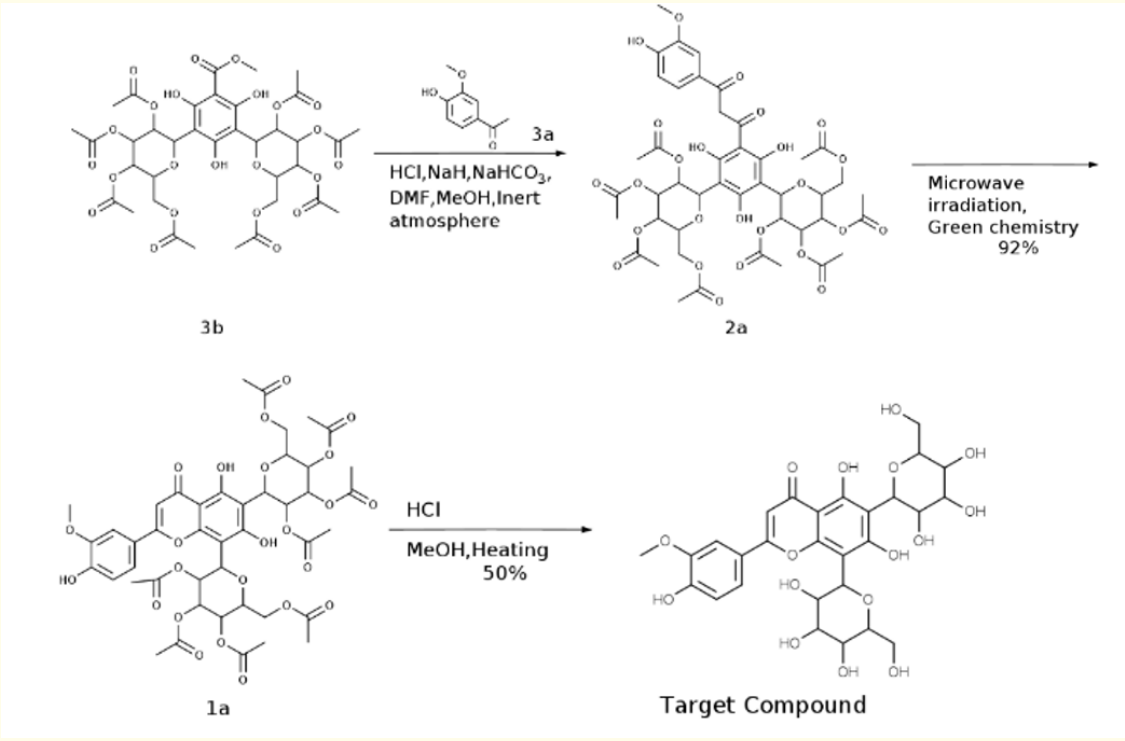



**Figure 16:** Prediction of the Synthesis Pathway for Stellarin-2 Compound.

Prediction of the synthesis pathway of rhoifolin compounds is shown in Figure 15. with the results obtained 88% success rate of the reaction template with a number of experiments, the level of similarity with rhoifolin compounds is 100%. Prediction of the synthesis pathway for stellarin-2 is shown in Figure 16. with 50% yield and the similarity level with stellarin-2 is 94%, prediction of the stellarin-2 synthesis pathway has 5 steps.

## Conclusion

Based on the results of the study, 45 compounds contained in *Jatropha curcas* (*Jatropha curcas* L.) obtained molecular compounds having the docking at the 5R7Y, 7JKV, 7TLL and 7VH8 receptors. These compounds are Rhoifolin with a score of -94.8779 against the 5R7Y receptor, Rutin against the 7JKV receptor with a score of -101,3570, Stellarin-2 with a score of -108.2190 against the 7TLL receptor and Tomentin A with a score of -98.3206 against the 7VH8 receptor. Physicochemical properties having large molecular weight and good ADMET. The results of molecular dynamics at each receptor were Rhoifolin with RMSD ±1.8Å and RMSF with fluctuation stability 0-2Å at the 5R7Y receptor, Rutin with RMSD ±1.58Å and RMSF fluctuation stability ranging from 0-2.3Å at the 7JKV receptor, Stellarin -2 with RMSD ±1.5Å and RMSF fluctuation stability 0-2Å at 7TLL receptors and Tomentin A with RMSD ±1.7Å and RMSF fluctuation stability 0-2Å at 7VH8 receptors.

So, it can be concluded that the results of molecular docking and molecular dynamics have lower docking than native ligands and Molnupiravir at the 5R7Y receptor with the interaction that occurs there are 6 hydrogen bonds in the Rhoifolin compound as well as the Stellarin-2 compound at the 7TLL receptor with 7 hydrogen bonds. This shows that the compounds rhoifolin and stellarin-2 are potential candidates for inhibiting SARS-CoV-2.

## Conflict of Interest

There is no conflict of interest in this research.

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