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Research Article

# Study Natural Compound of *Eleutherine americana* as a SaR-CoV-2 Therapeutic Agent : In Silico Approach

Mokhamat Ariefin*, Rizki Rachmad Saputra

Department of Chemistry, University of Palangka Raya

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* Email Author Corresponding :
mokhamatariefin@mipa.upr.ac.id

**ABSTRACT**

Sar-CoV-2 (COVID-19) has rapidly spread globally where it has killed thousands of individuals and infecting almost 1,016,395 others. Numerous people have died as a result of what the World Health Organization (WHO) has deemed a top worldwide health issue, which has also had severe detrimental social and economic impacts. Some Eleutherin americana are said to possess antiviral effects. Children's colds and nasal congestion can be treated with eleutherin americana. Naphthalene, anthraquinone, and naphthoquinone are the three main chemical families that have been identified from E. americana. Eleutherol, isoeleutherol, and eleutherin were the compounds that were identified from E. Americana. Drug-receptor interactions are simulated using computational techniques toward 14 compounds isolated from E. americana. The docking method has been validated by redocking the N3 molecule as a native ligand to the Mpro of Sar-CoV-2 (PDB ID: 7BQY) as a receptor protein. The smaller the RMSD value 0.651 Å, the better the pose obtained through the docking process. Compound **12** has a more negative binding energy are showed -8.6 kcal mol-1, regarding hydrogen bond interaction toward Thr26, His41, Leu141, Asn142, Gly143, Ser144, His163. The stability of the association between the ligand and receptor increases with decreasing binding energy value (ΔG). On the other hand, Compounds **11** and **2** are depicted -8.2 kcal mol-1 and -8.1 kcal mol-1 respectively which is close to **N3** -8.3 kcal mol-1. Undergoing hydrogen bond interaction between **11** with Gly143,Thr26, Leu141, Glu166, Ser144, Cys145, His163, and less hydrogen bond interaction **2** toward Arg188 and Asn 142. Those results resembling the hydroxy group have the best interaction with 7BQY. According to fulfilled data from three candidates **2, 11, 12**, it can be expected that compounds with many hydroxy groups are within the realm of possibility as an antiviral agent for Sar-CoV-2 through inhibiting replication of this virus.

Keyword: E.americana, molecular docking, Sar-CoV-2

## 1. Introduction

Numerous major human diseases, such as issues with global health, are brought on by viral infections. It might be challenging to treat viral infections. Drug-resistant mutants that carry antivirals can be created by ongoing evolution. The development of vaccines and medications has advanced significantly in recent years[1]. Numerous viruses still lack viable vaccinations or antiviral medications. It is highly advised to find new, highly effective antiviral medicines [2], [3]. The fast spread of SARS-CoV-2 (COVID-19) from Wuhan, China, to other parts of the world, where it has killed thousands and infected nearly 1,016,395 people, poses a serious threat to public health, especially comorbidities [4]. Some people's dry coughs result in severe symptoms like pneumonia and fever, while high body temperatures cause severe symptoms including acute respiratory arrest and pneumonia. Similar to SARS-CoV-1, which the World Health Organization has

categorized as a global health emergency, COVID-19 has claimed many lives and had major social and economic repercussions that are believed to have been harmful [5], [6].

Antimicrobial and antiviral drugs' empirical sources historically have included natural compounds. To cure all forms of bacterial and viral diseases, people have employed decoctions of natural materials. Skin diseases brought on by bacteria, viruses, fungus, and herbal plants have all been treated using poultices and topical medications [7]–[9]. Viruses work by preventing their replication and/or infectivity [7]. It has been claimed that some Eleutherin americana contain antiviral properties. Eleutherin americana Merr., a member of the Iridaceae family, has also been referred to as E. bulbosa (Miller) Urb. This plant reaches 600–2000 meters above sea level and thrives in sulfurous environments [10]. Tropical America is where Eleutherine Americana Merr. discovered her origins. From that time on, the plant has been widely grown in South Africa, Thailand, and Hainan Island in South China. Traditionally used as a carminative, E. americana helps treat children's colds and nasal congestion when mixed with galangal. Some Dayak tribe members used the bulb as a treatment for diabetes, breast cancer, stroke, hypertension [11].

In Hainan Island, China, *Eleutherine Americana* MERR (Iridaceae) is widely grown as a traditional medicine to cure cardiac diseases. Several compounds, including elecanacin, isoleutherol, eleutherol, eleutherin, isoeleutherin, hongconin, and four anthraquinone derivatives, were isolated from the bulb of *E. Americana*, which was gathered on the Indonesian island of Java[12]. Naphthalene, anthraquinone, and naphtoquinone are the three main families of chemicals that have been identified from E. Americana. This plant was also found to contain kadsuric acid, stigmasterol, and stigmasterol-3-O-D-glucopyranoside. Hongconin, eleutherol, isoeleutherol, and eleutherin were the chemicals isolated from E. Americana. Additionally, erythrolaccin and the other plant parts that were separated were intriguing; (-)-3-[2-(acetyloxypropyl)] 3,4-dihydro-1,3-dimethyl-1-H-naphthol (2,3) pyran-5,10,dione; 9-methoxy-1, 3-dimethyl-1H-naphtho [2, 3-c] pyran-5, 10-dione; 1,2-hydroxy-8-methoxy-3-methylantraquinone;4,8-dihydroxy-3,4-dimethoxy-1-methyl-anthraquinone-2-carboxylic acid methyl ester; and 9, hydroxy-8-methoxy-1-methyl-1, 3-dihydronap, 1,2-hydroxy-8-methoxy-3-methylantraquinone; 9-hydroxy-8-methoxy-1- methyl-1, 3-dihydronaphtho [2, 3-c] furan-4-O-β-D-glucopyranoside; 1, 2-dihydroxy-8-methoxy-3-methyl-anthra-9, 10-quinone[11]. With IC50 values of 8.5 g/mL and 100 g/mL, respectively, isoeleutherine and isoeleutherol inhibited HIV replication and therefore had the potential to be turned into antiviral drugs. The structural eleucidation of elecanacin and isoleutherol, as well as the inhibitory effects of the other molecule against human topoisomerase II (TOPO II) and the HIV virus as an antiviral agent, are the topics of this communication [12].

It is believed that the field of bioinformatics has the potential methods used to find new drug lead structures and the potential of the natural product as a lead new drug. In the previous study, some researchers have already investigated some natural products as a drug. Kang group's investigated some of the available drugs, such as antibacterial, and antibiotics, for inhibitors of Mpro of SARS-CoV-2 by molecular docking. The results were doxycycline and minocycline was selected as potent inhibitor against SARS-CoV-2 Mpro[13]. Other groups also try to investigate natural product and their derivative as an inhibitor of SARS-CoV-2 Mpro. Sahlan groups evaluated the potency of the Sumatra propolis compound produced by *Tetragonula sapiens* as an inhibitors of ACE-2[14]. ACE-2 is the first gate of infection of SARS-CoV-19[15]. Muchtaridi group also conducted a docking simulation of alpha mangostin and its derivative as a Mpro SARS-CoV-2 inhibitor. The results of their study are the derivative of mangostin is more reactive and potent than alpha-mangostin[16]. Therefore, based on the previous study, some natural product has potency as antiviral drug but the study of many natural products in Indonesian herbal is still not identified. *Eleutherine Americana* is one of the herbal medicine from Indonesia. The study of their natural product against SARS-CoV-2has not been done yet. This paper's key contribution is to use molecular docking research to determine how well the active compound from the natural product *Eleutherine Americana* is an antiviral agent to inhibit the SARS-CoV-2Mpro.

## 2. Materials and Methods

### *2.1. Hardware and software*

A laptop with processor Intel® Core™ i5-7200U, CPU @2.50 GHz, and 8 Gb RAM. The software: The Autodock Vina and Autodock Tools 1.5.6 programs (The Scripps Institute, USA) to conduct molecular docking simulation. Pymol was used to see the binding pocket of the receptors. To interpret 2D interaction, LigPlus was used. Pre-ADMET 2.0 program used to predict absorption, distribution, and toxicity profile. BIOVIA Discovery Studio (downloaded from https://discover.3ds.com) to prepare receptor and binding site of the receptor.

### *2.2. Macromolecules preparation*

The 3D structure of Mpro of Sar-CoV-2 was downloaded from Protein Data Bank (PDB) (https://www.rcsb.org/) with PDB ID 7BQY. This protein is already bound with the native ligand (N3 inhibitor molecule) and has a good resolution (1.70

Å)[14]. The preparation was carried out by removing native ligand structure and water molecules from the macromolecule, adding polar hydrogen atoms, and calculating Kollman charges using AutoDockTool-1.5.6.

*2.3. Protein Binding Site Identification*

The prepared macromolecules were then evaluated and identified the location of their binding sites using BIOVIA Discovery. The binding site is the location of the native ligand and the most responsible site for biological activity. All the amino acids in the binding site radius were used for ligand-protein molecular docking.

*2.4. Ligand Preparation*

The ligand used in this experiment were natural compounds isolated from bawang dayak (E.americana) obtained from PubChem. All ligands were prepared by calculating the Gasteiger charge using AutoDockTools-1.5.6. Structural preparation aims to optimize compounds as a ligand in docking simulation.

*2.5. Molecular Docking Simulation*

Molecular docking was carried out using a specific method of docking by targeting the binding site of Mpro SARS-CoV-2. Molecular docking is done with AutoDock Tools 1.5.6 and AutoDock Vina software [17], [18]. The preparation of ligand and macromolecule (protein) is done using AutoDock Tool 1.5.6. The molecular docking simulation was done using AutoDock Vina. The grid size and central coordinate are adjusted to the position of the N3 ligand as the native ligand. The grid size used is with the center coordinates X = 10.398, Y = -1.254, and Z = 22.353. In this study, the exhaustiveness is set at 64 with num modes = 10 to increase the molecular bonding accuracy.

The simulation begins by redocking the N3 ligand with 7BQY protein. The docking process is said to be valid if the N3 ligand can re-occupy its initial position with an RMSD value of less than 2 Å. After the validation process, the docking process is continued by using ligands from the E.americana extract. The simulation results were obtained in the form of binding energy and binding area. The binding area was analyzed using LigPlus software to analyze hydrogen bonding and other hydrophobic interactions.

## 3. Result and Discussion

*3.1. Molecular docking validation*

In this experiment, the docking method has been validated by redocking the N3 molecule as a native ligand to the 7BQY as a receptor protein. The measured value is in the form of root mean square deviation (RMSD) which indicates the deviation from the binding pose obtained by redocking with the binding pose from the crystal structure. The smaller the RMSD value, the better the pose obtained through the docking process. A good RMSD shows the value ≤ 2 Å[19] . The RMSD value obtained from this experiment is 0.651 Å which is obtained through the PyMOL program.

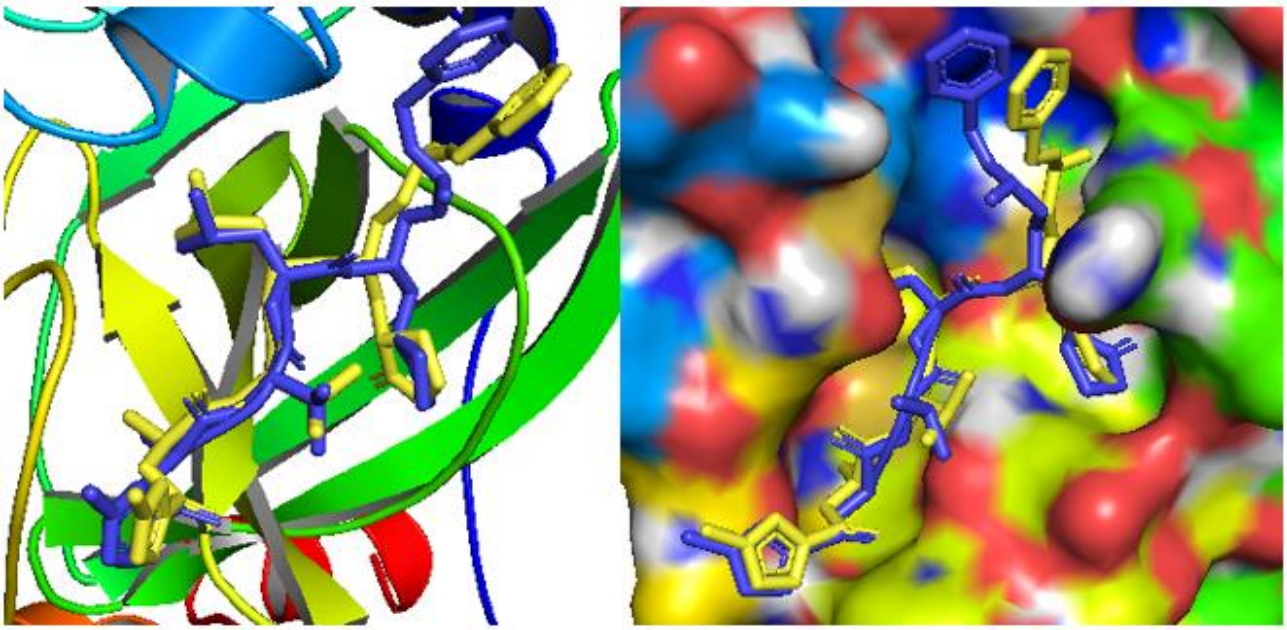
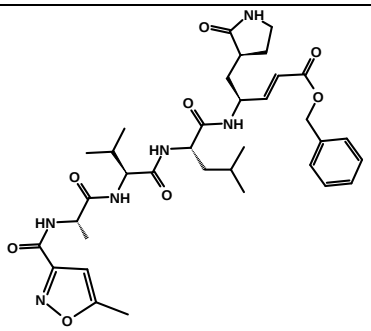
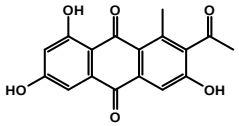
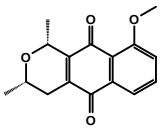
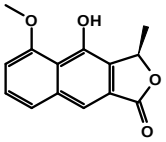
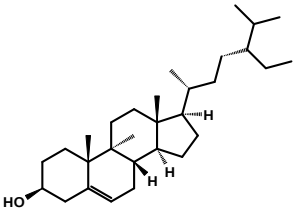
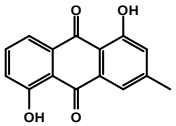
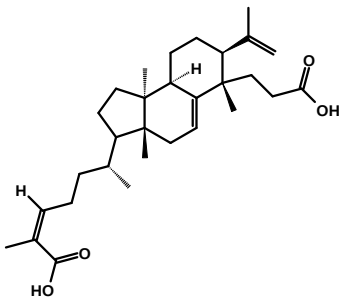
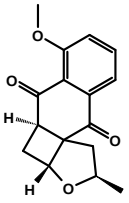
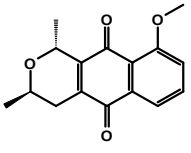
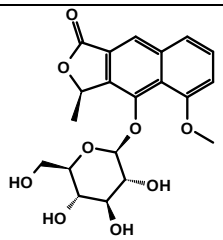
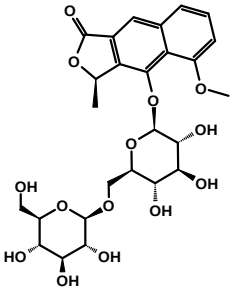
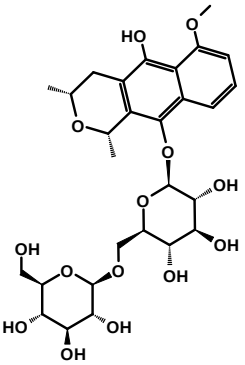
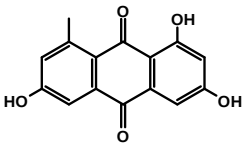
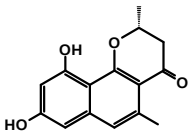
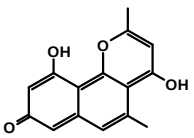


**Figure 1.** 3D visualisation of re-docking result. Yellow is origin pose of N3 inhibitor and blue is re-docking result.

**Table 1**. Natural compound isolated from *E.americana*

| Compound | Name | Structure |
|---|---|---|
| 1 | N3 (native ligand) |  |
| 2 | 2-acetyl-3,6,8-trihidroxy-1-methyl-anthraquinone (PubChem CID: 12742404) |  |
| 3 | Eleutherine (+) (PubChem CID : 10166) |  |
| 4 | Eleutherol (PubChem CID : 120697) |  |
| 5 | Beta sitosterol (PubChem CID : 222284) |  |
| 6 | 1,5-dihidroxy-3-methylanthraquinone (PubChem CID : 5316800) |  |
| 7 | Kadsuric acid (PubChem CID : 5384417) |  |
| 8 | Elecanacin (PubChem CID : 5491405) |  |
| 9 | Isoeleutherine (PubChem CID: 10445924) |  |

| Compound | Name | Structure |
|---|---|---|
| 10 | Eleuthoside A (PubChem CID: 101709341) |  |
| 11 | Eleuthoside B (PubChem CID: 95224384) |  |
| 12 | Eleuthoside C (PubChem CID: 10722258) |  |
| 13 | 1,3,6-trihidroxy-8-methyl-anthraquinone (PubChem CID: 12309204) |  |
| 14 | Dihydroeleutherinol (PubChem CID: 102473740) |  |
| 15 | Eleutherinol (PubChem CID: 136623083) |  |

*3.2. Molecular docking simulation*

The results of molecular docking of 14 compounds contained in *E.americana* have been carried out on $M_{pro}$ COVID-19 with the PDB ID 7BQY. The result of molecular docking is binding energy (ΔG) which indicates the level of stability of the interaction between the ligand and the receptor. The more negative the binding energy value, the more stable the interaction between the ligand and the receptor. More stable interactions between ligand-receptors lead to better activity. In addition, another parameter used is the type of interaction between the ligand and the receptor.

Based on the results of redocking inhibitor N3, the binding energy value obtained was 8.3 kcal mol-1. Compound **12** has a more negative binding energy (-8.6 kcal mol-1) than N3, which indicates that this compound has a more stable interaction than N3 concerning the receptor. In addition, three compounds have binding energies close to the value of N3 such as compounds **11** and **2** (-8.2 kcal mol-1 and -8.1 kcal mol-1). These results indicate that compounds with the hyrodroxy group have the best interaction with 7BQY.

**Table 2.** Ranked binding energy and binding interaction of *E.americana* extract

| Compound | Binding energy (kcal mol$^{-1}$) | Binding site | |
|---|---|---|---|
| | | Hydrogen bonding | Hydrophobic interaction |
| **1 (Native ligand)** | -8.3 | Phe140, Ser144, His163, Glu166, Gln189, Thr190 | Pro148, Ala191, Leu167, His164, Met49, Met165, Gly143, Thr24, Thr25, Leu141, Asn142, Cys145 |
| **12** | -8.6 | Thr26, His41, Leu141, Asn142, Gly143, Ser144, His163 | Met49, Cys145, Met165, Glu166, Leu167, Pro168, Gln189, Thr190 |
| **11** | -8.2 | Thr26, Leu141, Gly143, Ser144, Cys145, His163, Glu166 | Thr25, Leu27, Met49, Phe140, Asn142, His164, Met165, Gln189 |
| **2** | -8.1 | Arg188, Asn142 | His41, Leu141, Cys145, His164, Met 165, Glu166, Asp187,Gln189 |
| **13** | -7.8 | Asn142, Arg188 | His41, Leu141, Cys145, His164, Met165, Glu166, Asp187, Gln189 |
| **10** | -7.6 | Phe140, Asn142, His163, His164, Glu166 | His41, Leu141, Cys145, Met165, Arg188, Gln189. |
| **6** | -7.2 | Glu166 | His41, Tyr54, Asn142, Cys145, His164, Met165, Asp187, Arg188, Gln189 |
| **9** | -7.1 | Glu166 | His41, Leu141, Asn142, Cys145, His164, Met165, Asp187, Arg188, Gln189 |
| **14** | -7.0 | Tyr54, Asp187 | His41, Met49, Met165, Glu166, Arg188, Gln189 |
| **15** | -7.0 | - | His41, Asn142, His164, Met165, Glu166, Asp187, Arg188, Gln189 |
| **3** | -6.9 | His41 | Met49, Asn142, Cys145, His164, Met165, Glu166, Gln189 |
| **4** | -6.6 | Gly143, Glu166 | His41, Met49, Leu141, Asn142, Cys145, His163, His164, Met165, Arg188, Gln189 |
| **5** | -6.6 | - | Thr26, His41, Met49, Phe140, Leu141, Asn142, Gly143, Cys145, His164, Glu166, Gln189 |
| **8** | -6.6 | - | His41, Met49, Phe140, Leu141, Asn142, Cys145, His164 Met165, Glu166, Gln189 |
| **7** | -6.3 | - | His41, Met49, Leu141, Asn142, Gly143, Cys145, His163, Glu166, Arg188,Gln189 |

Interaction analysis is focused on hydrogen bonding interaction. Hydrogen bonds give important influences on the orientation of ligands by a receptor, specific recognition of ligands, and the binding interaction of ligand-receptor [20]. The strength of hydrogen bonding can be divided based on the distance of the interaction. Apart from hydrogen bonds, hydrophobic interaction also has an important influence on binding energy results. Although the hydrophobic interaction is weaker than the hydrogen bond, the hydrophobic existence also indicates that the ligand can proceed with inhibitory activity.

The 2D-illustration of the interaction between Mpro 7BQY and ligand is attached in **figure 2**. According to the figure, inhibitor N3 (redocking) gave hydrogen bond with Phe140, Ser144, His163, Glu166, Gln189, Thr190. However, based on crystallographic data, the inhibitor N3 give hydrogen bonds interaction between Phe140, Gly143, Cys145, His164, Glu166, Gln189, and Thr190 [21]. The similarities of amino acid interaction with N3 might also validate the docking parameter used in this experiment.

In the interaction simulation between nature compound from extract *E.american*, compound **12, 11,** and **2** will be our main discussion because these compounds have higher or close to the binding energy of N3 as a control (native ligand). Compound **12** was able to form a hydrogen bond with Thr26, His41, Leu141, Asn142, Gly143, Ser144, and His163. Compound **12** can not form a hydrogen bond with Phe140, Glu166, Gln189, and Thr190, but Glu166, Gln189, and Thr190

are detected as a hydrophobic interaction. Compound **11** formed hydrogen bond interaction with Thr26, Leu141, Gly143, Ser144, Cys145, His163, and Glu166. Phe140 and Gln189 were detected as a hydrophobic interaction between compound **11** and Mpro. Compound **2** forms a hydrogen bond with Arg188 and Asn 142. The interaction of compounds **12** and **11** is slightly different from the N3 ligand. However, compounds **12** and **11** can bind with an important catalytic dyad of Mpro of SARS-CoV-2, His41, and Cys145[22]. Compound **12** can interact with His41 through hydrogen bond interaction and Cys145 through hydrophobic interaction. Compound **12** also has higher binding similarity (available in **table 3**), so it has higher potency as an inhibitor of Mpro SARS-CoV-2. Compound **11** also has a slightly different interaction with native ligands, so it may have a slightly different inhibition mechanism than Mpro. Moreover, compound **11** also can interact with His41 through hydrogen bonds and has the same binding similarity as compound **12**, so it may have potency as a drug. Compound **2** has lower binding similarity (available in **table 3)** with N3 inhibitor than compounds **11** and **12**. However, this compound can interact with the catalytic dyad of Mpro through hydrophobic interaction. The difference in interaction may affect the binding energy of compound **2** and Mpro. On other hand, it also gives different inhibition mechanisms of compound **2** and Mpro[23].

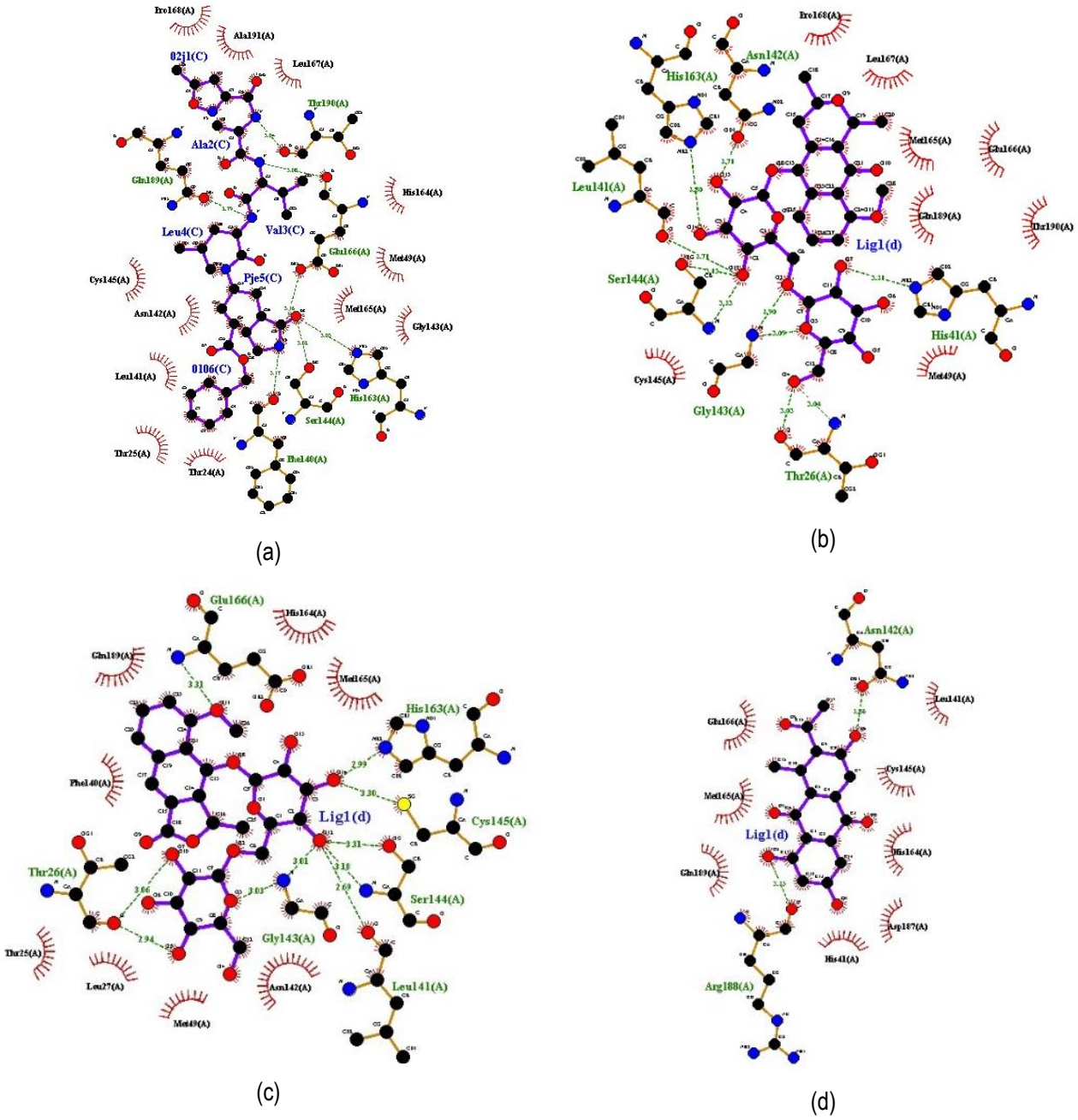



**Figure 2**. 2D-ilustration between 7BQY and ligand. (a) Native ligand (b) compound 12, (c) compound 11, and (c) compound 2

**Table 3**. Binding similarities of some compound with N3

| Compound | Hydrogen bond | Hydrophobic bond | Number of interactions | Binding Similarity |
|---|---|---|---|---|
| **1*** **(Native ligand)** | Phe140, Ser144, His163, Glu166, Gln189, Thr190 | Pro148, Ala191, Leu167, His164, Met49, Met165, Gly143, Thr24, Thr25, Leu141, Asn142, Cys145 | 18 | |
| **12** | Thr26, His41, Leu141, Asn142,Gly143, Ser144, His163 | Met49, Cys145, Met165, Glu166, Leu167, Pro168, Gln189, Thr190 | 15 | 67% |
| **11** | Thr26, Leu141, Gly143, Ser144, Cys145, His163, Glu166 | Thr25, Leu27, Met49, Phe140, Asn142, His164, Met165, Gln189 | 15 | 67% |
| **2** | Arg188, Asn142 | His41, Leu141, Cys145, His164, Met 165, Glu166, Asp187,Gln189 | 10 | 33% |

**Native ligand as a control*

$$\boldsymbol{binding\ similarity} = \frac{\boldsymbol{number\ of\ residue\ that\ similar\ with\ native}}{\boldsymbol{total\ interaction\ in\ native\ ligand}} \times \mathbf{100}\%$$

## 4. Conclusion

In this study, docking simulations were conducted on 14 compounds from extract *E.americana* that has antiviral activities. The result shows, compound **12** has more negative binding energy than N3 as a native ligand and some of them have close binding energy than N3. Compound **11** and **2** have close binding energy than native ligand. A compound with many hydroxy groups showed good interaction between ligands and receptors. Furthermore, compounds with good energy binding and good similarities binding interaction may have a good ability to pretend spread of COVID-19 through inhibit the replication of this virus.

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