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Original article

The potential active compounds of *Jatropha multifida Linn.* as an anti-COVID-19 mouthwash: In silico study

Muhammad Chair Effendi[1], Aisyah Fitri Qurrata 'Ayun[2], Annisa Putri[2], Dhiky Dwi Kurniawan[3], Dinda Aprilla Salsabila[2], Fahrunisa Tunjung Malihahsisna[2]
[1]Department of Pediatric Dentistry, Faculty of Dentistry, Universitas Brawijaya, Malang, Indonesia
[2]Undergraduate Program in Dentistry, Faculty of Dentistry, Universitas Brawijaya, Malang, Indonesia
[3]Undergraduate Program in Pharmacy, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia

ABSTRACT

Background: *Povidone-iodine 1% mouthwash is one of the products recommended for preventing and controlling COVID-19 infection in dental procedures. Jatropha multifida Linn. has the same antiseptic effect as povidone-iodine.* ***Purpose:*** *The objective is to determine the effectiveness and interaction effect of secondary metabolites from the latex of Jatropha multifida Linn. and povidone-iodine against the main protease (MPro) SARS-CoV-2 and the SARS-CoV-2 spike protein - ACE2 receptors.* ***Methods:*** *The in silico test was used in this study and carried out using the Molegro Virtual Docker software for molecular docking and BIOVIA Discovery Studio and PyMOL for visualization.* ***Results:*** *The results show that secondary metabolite compounds contained in the latex of Jatropha multifida Linn. have a better effectiveness potential in relation to MPro SARS-CoV-2 and SARS-CoV-2 spike protein - ACE2 receptors than povidone-iodine.* ***Conclusion:*** *The latex of Jatropha multifida Linn. shows potential as a preventive and curative therapy for COVID-19 in the in silico study.*

Keywords: *COVID-19; in silico; Jatropha multifida Linn.; mouthwash; povidone-iodine*
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Correspondence: Muhammad Chair Effendi, Department of Pediatric Dentistry, Faculty of Dentistry, Universitas Brawijaya. Jl. Veteran, Malang, 65145, Indonesia. E-mail: chair.fk@ub.ac.id

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as a pandemic causing a new coronavirus illness (COVID-19) by the World Health Organization in 2019. According to a phylogenetic study, SARS-CoV-2 may have evolved from the zoonotic cycle and unexpectedly unfolded through human-to-human transmission. The infectious respiratory droplets released by a sick person when coughing or sneezing can spread to healthy people who come within six feet of the sick person. Complete virus particles from SARS-CoV-2 need the presence of four structural proteins: spike, envelope, membrane, and nucleocapsid.[1] Coronaviruses have a helical nucleocapsid that encloses the viral RNA and is surrounded by the viral surface protein spike, membrane, and envelope originating from the host membrane.[2]

Recent studies have claimed that the SARS-CoV-2 spike glycoprotein (the S glycoprotein) and the ACE2 receptor interact with the same kinetic and thermodynamic properties toward the ACE2 receptor.[3] The S protein from the coronavirus envelope is used as a target when making antibodies in vaccine production because this protein is a pathway whereby viruses can enter host cells. The surface of the S protein may mediate the interaction with the cell surface receptor ACE2. The S protein comprises two functional subunits responsible for binding to the host cell receptor (an S1 subunit including the receptor-binding domain/RBD) or for the fusion of the viral and cellular membranes (an S2 subunit).[3] The function of subunit S1 is to bind to receptors on host cells. The function of the S2 subunit is to fuse the viral and host cell membranes.[4] The viral RNA is encased in a nucleocapsid composed of the M and E proteins connected to a lipid bilayer coming from the host cell membrane.

Protein S from the coronavirus envelope is used as a target when making antibodies in vaccine production because this protein is a pathway whereby viruses can enter

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host cells.[5] The surface of the S protein may mediate the interaction with the cell surface receptor ACE2. The viral RNA is encased in a nucleocapsid composed of the M and E proteins connected to a lipid bilayer produced from the host cell membrane.[6]

A possible entry site for SARS-CoV-2 is via the mouth and throat. Various oral mucosal tissues, including the tongue and the floor of the mouth, have the SARS-CoV-2 ACE2 cellular entry receptors.[7,8] Povidone-iodine, the main ingredient in Betadine® mouthwash, has attracted great interest because of its ability to inactivate coronavirus. Povidone-iodine, as stated by Hassandarvish et al.,[9] has been demonstrated to be 99.99% effective against the SARS-CoV-2 virus within 15 seconds. Based on these findings, Anderson et al.[10] have concluded that povidone-iodine, because of its quick viral action and wide antibiotic range, has a significant role in preventing SARS-CoV-2 infections. However, using 1% povidone-iodine mouthwash can potentially cause thyroid dysfunction and aspiration pneumonitis as side effects. There are also reported cases of anaphylaxis, contact dermatitis, and edema after exposure. Ingestion of the mouthwash in high concentrations or quantities may lead to acute kidney injury, liver toxicity, or both.[11,12] Anti-SARS-CoV-2 mouthwash may function by blocking the virus's ability to replicate by interfering with the viral envelope and nucleic acid, altering the structure of the glycoprotein, reducing the charge on the glycoprotein, and preventing the virus from attaching to glycosaminoglycans on the cell surface. The results of the current study suggest that a mouthwash made from the latex of *Jatropha multifida Linn.* can potentially inhibit the S protein binding to the ACE2 receptor.[13]

Several pharmacological investigations have been conducted on *Jatropha multifida Linn.* to ascertain its characteristics. The leaves, latex, and fruits of this plant are used to treat wound and skin infections, ulcers, oral thrush, and fever. Roots and stems containing diterpenoids have the anticancer, antimicrobial, antimalarial, cytotoxic, antitumor, insecticidal, and molluscidal activities of *Jatropha multifida Linn*.[14] The active substances contained in the latex of *Jatropha multifida Linn.* include flavonoids, tannins, phenols, and alkaloids.[15] In addition, other chemical compounds are known to exist in this plant's latex, such as quercetin,[16] acacetin, apigenin, proanthocyanidins,[17] multifidone, multidione, multifolone,[15] multifidanol, and multifidenol.[18]

Another previous study found that *Jatropha multifida Linn.* has an antiseptic effect with the same potential as povidone-iodine.[19] *Jatropha multifida Linn.* plants are also used as herbal drugs in the development of new anti-influenza drugs.[20] Based on the statement above, researchers are interested in conducting an in silico test to determine the potential effects of the secondary metabolites of *Jatropha multifida Linn.* and povidone-iodine against the main protease (MPro) SARS-CoV-2 and the SARS-CoV-2 spike protein - ACE2 receptors. This is one of the efforts being made to find an antiviral mouthwash for the prevention and treatment of the COVID-19 virus.

MATERIALS AND METHODS

This research uses the following tools and materials: hardware in the form of a personal laptop HP Intel® Core 5 Gen 8th, Radeon graphics, Molegro Virtual Docker 5 licensed, BIOVIA Discovery Studio ver 21.1.1, PyMOL, Microsoft Office Excel 2013 software, the secondary metabolites of *Jatropha multifida Linn.* and povidone-iodine ligands that were downloaded from the PubChem database, as well as the MPro SARS-CoV-2 and the SARS-CoV-2 S protein - ACE2 receptors downloaded from the Protein Data Bank database. In this study, an in silico test was conducted, and ligands were used from secondary metabolites of *Jatropha multifida*, including the structure of compounds iodin_CID_807, acacetin_CID_5280442, apigenin_CID_5280443, proanthocyanidin_CID_108065, quercetin_CID_2280343, multidione_CID_101477139, multifidanol_CID_57390908, multifidenol_CID_57399656, multifidone_CID_25181402, dan multifolone_CID_ 102025875. In addition, the control ligand povidone-iodine_CID 6917 was used.

All ligands were downloaded from the PubChem compound database of the National Center for Biotechnology Information. The MPro SARS-CoV-2 and the SARS-CoV-2 S protein - ACE2 receptors were used; these were downloaded from the Protein Data Bank database as receptors. Preparation was then carried out using the Discovery Studio version 21.1.1 and Molegro Virtual Docker 5 software. The compound identified as *Jatropha multifida Linn.* interacted with the MPro SARS-CoV-2 protein in the cavity volume 125.95; surface 410.88 with X -12.66 A; Y -28.86 A; and Z -1.05A and with the SARS-CoV-2 S protein - ACE2 receptors in cavity X 28.12; Y -44.46; Z 38.45; volume 210,944 A3, surface 721.92 A2 and radius 15. The docking Moldock Score Grid parameters were 0.30 A; Maximum RMSD 2; number running 10, binding pose structure 5.

The molecular docking process was carried out using Molegro Virtual Docker 5 software, while the ligands and proteins were prepared and the results visualized using BIOVIA Discovery Studio 21.1.1 and PyMOL. Docking calculation results were displayed in notepad format, and the highest affinity in the form of bond energy (ðG) determined the value of the docking conformation. The docking results of the ligand and MPro SARS-CoV-2 protein was achieved using Molegro software to see the affinity of the ligand and analyzed with BIOVIA Discovery Studio 21.1.1 software. The results of the docking between the compound SARS-CoV-2 S protein - ACE2 receptors superimposed with PyMOL software and analyzed with Discovery Studio 21.1.1 to analyze the active site of the compound binding to the target protein, identify the binding residue or the active site of the protein and potential activity

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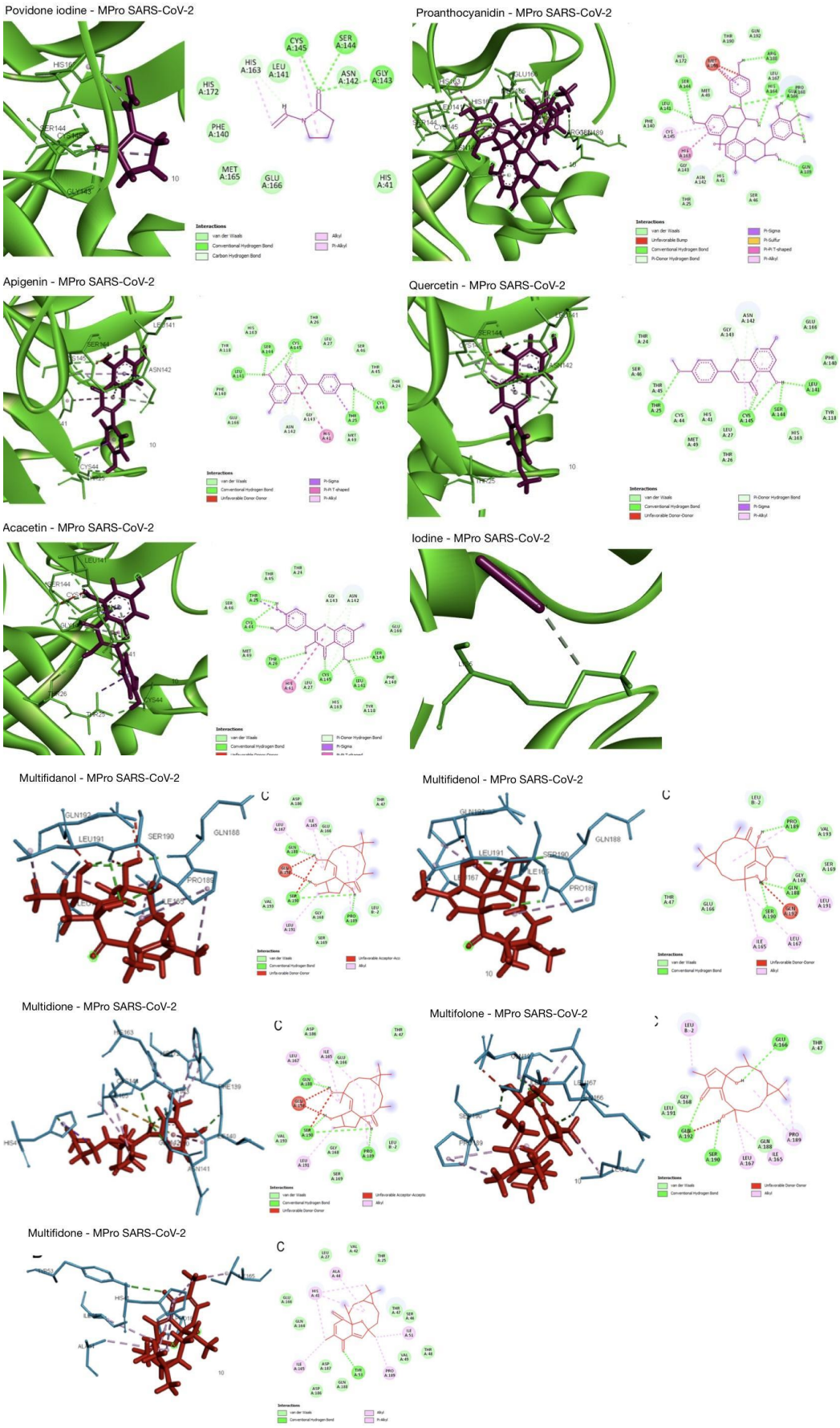

Figure 1. 3D and 2D docking models between *Jatropha multifida Linn.* and povidone-iodine ligands toward MPro SARS-CoV-2.

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of the *Jatropha multifida Linn.* compound as an antiviral by inhibiting the interaction between ACE2 receptors and the spike protein.

RESULTS

The povidone-iodine ligand with MPro SARS-CoV-2 binds to the active sites of GLY143, SER144, CYS145, and HIS163 with a binding affinity of -159.2 kJ/mol. Iodine binds to the active site of the MPro SARS-CoV-2, which is different from the control and other *Jatropha multifida Linn.* compounds, namely LYS5 with hydrogen bonds. It has a binding affinity of -161.9 kJ/mol. Acacetin binds to the MPro protein at the amino acid residues THR25, CYS145, LEU141, SER144, ASN142, ASN142, GLY143, and ASN142, with a binding affinity of -254.9 kJ/mol. Proanthocyanidin shows the lowest binding affinity out of all the compounds (-363 kJ/mol) and shows active sites, namely GLU166, HIS164, GLN189, LEU141, SER144, GLU166, ARG188, ASN142, MET165, HIS163, CYS145, MET165 with MPro SARS-CoV-2 Apigenin - MPro SARS-CoV-2 binds at residues CYS145, LEU141, SER144, THR25, CYS44, ASN142, GLY143, HIS41, with a binding affinity of -246,9 kJ.mol. The active sites of quercetin with MPro SARS-CoV-2 are CYS145, THR26, LEU141, SER144, CYS44, THR25, ASN142, GLY143, HIS41, which have a binding affinity of -270.4 kJ/mol. The multifidone compound binds to the active site residues TYR53, ALA44, ILE51, PRO189, ILE165, and HIS41, with a binding affinity of -242.54 kJ/mol. Multifidanol shows active site residues against MPro SARS-CoV-2, including GLN188, PRO189, SER190, ILE165, LEU167, LEU191, and GLN192, with a binding affinity of -291.03 kJ/mol. Multifidenol binds to the MPro SARS-CoV-2 protein at the active sites GLN188, PRO189, SER190, ILE165, LEU167, LEU191, and GLN192, with a binding affinity of -308 kJ/mol. The multidione compound binds to the amino acid residues HIS41, GLY142, ALA143, CYS144, PHE139, ILE140, ASN141, ILE165, PHE139, HIS163, HIS172 and has a binding affinity of -327.39 kJ/mol. Multifolone binds to the MPro SARS-CoV-2 at GLN192, SER190, GLU166, PRO189, ILE165, LEU167, and LEU-2, with a binding affinity of -302.45 kJ/mol (Figures 1 and 2).

The povidone-iodine - S glycoprotein-ACE2 has the active sites LYS353, GLY496, ARG403, TYR453, TYR495, PHE497, and TYR505, with a binding affinity of -175.268 kJ/mol. The proanthocyanidin complex - S glycoprotein-ACE2 shows active sites, namely ARG403, GLN409, LYS417, TYR505, GLU37, ASP30, GLN388, ALA387, GLU406, TYR453, GLY416, GLU37, HIS34, ILE418, PRO389, and ASN33, with a binding affinity of -356.3242 kJ/mol. The acacetin - S glycoprotein-ACE2 has the active sites ASN33, ARG393, TYR505, ARG403, GLU37, TYR453, HIS34, and TYR495, with a binding affinity of -271.613 kJ/mol. The quercetin complex - S glycoprotein-ACE2 has the active sites ASN33, ARG393, ARG403, GLU37, TYR505, ASP30, TYR453, HIS34, and PRO389, with a binding affinity of -264.185 kJ/mol. The apigenin - S glycoprotein-ACE2 complex has the active sites ASN33, ARG393, TYR505, GLU37, TYR 453, and HIS34, with a binding affinity of -250.062 kJ/mol. The multifidanol compound binds to the S glycoprotein-ACE2 protein at the active sites ARG403, TYR505, GLU37, TYR505, PRO389, and HIS34, with a binding affinity of -276 kJ/mol. Multifidenol binds to the S glycoprotein-ACE2 protein at amino acid residues ARG403, TYR505, GLU37, PRO389, and HIS34, with a binding affinity of -291.25 kJ/mol. The multidione complex - S glycoprotein-ACE2 has the active sites ARG403, GLN409, TYR505, GLU406, HIS34, and ARG403, with a binding affinity of -288.8 kJ/mol. Multifolone with S glycoprotein-ACE2 has the

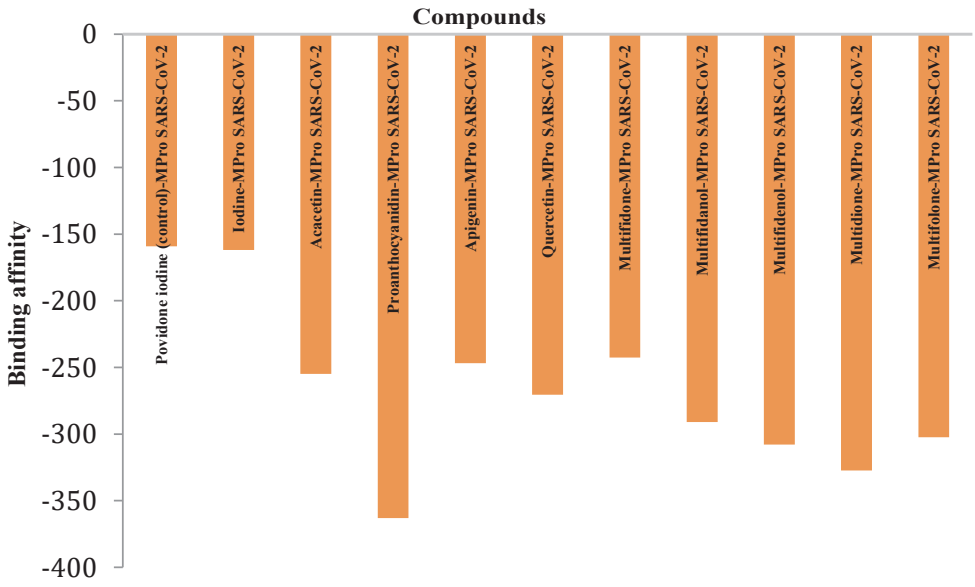

Figure 2. Binding affinity between *Jatropha multifida Linn.* and povidone-iodine ligands toward MPro SARS-CoV-2.

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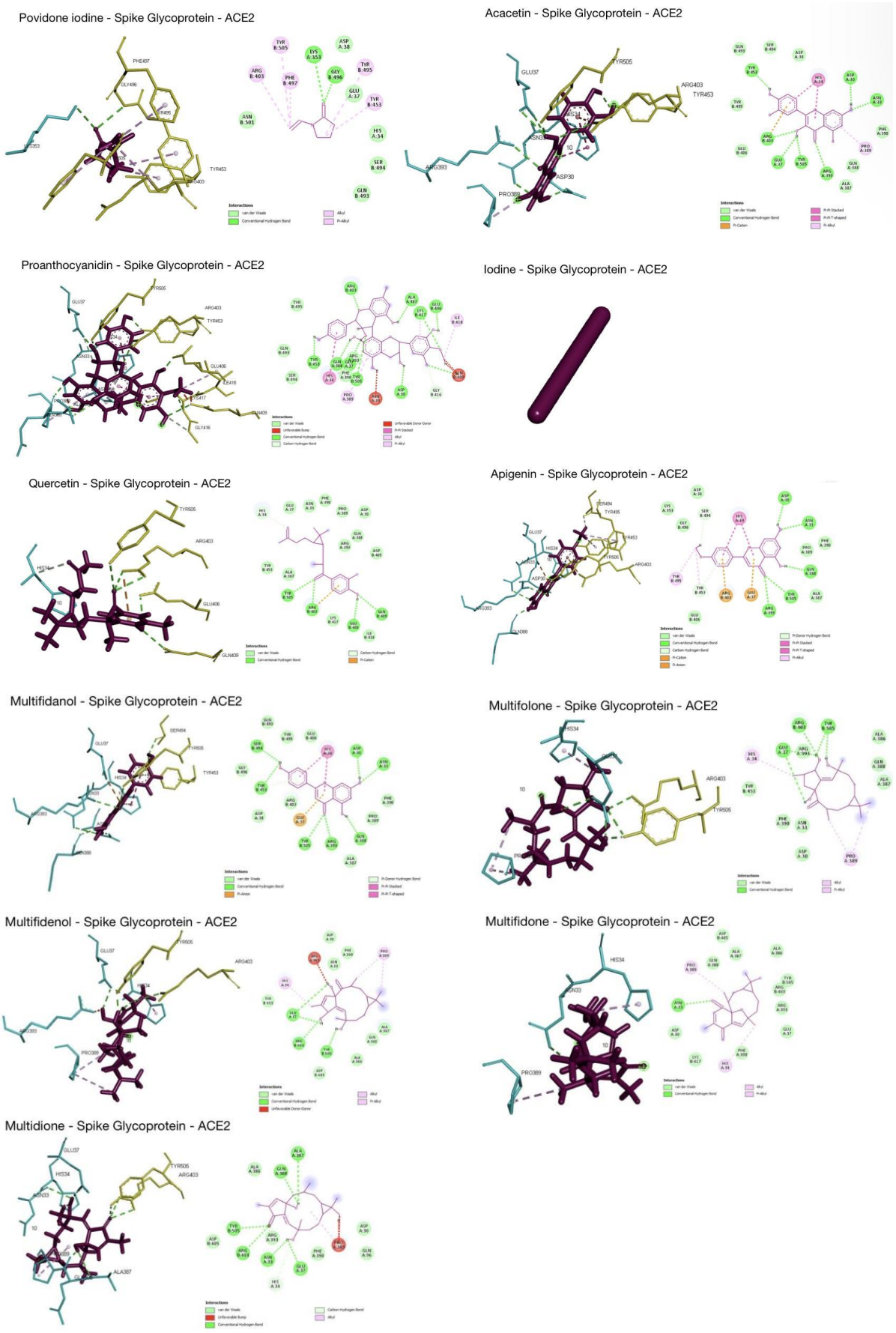

Figure 3. 3D and 2D docking models of *Jatropha multifida Linn.* and povidone-iodine ligands toward spike glycoprotein-ACE2.

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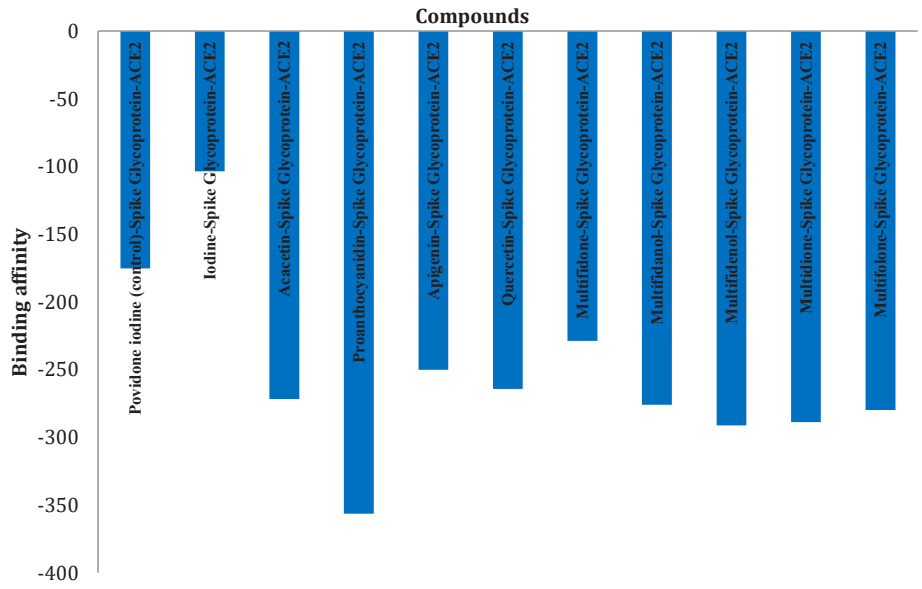

Figure 4. Binding affinity between *Jatropha multifida Linn.* and povidone-iodine ligands toward spike glycoprotein-ACE2.

active sites ARG403, TYR505, ASN33, GLU37, ALA387, GLN388, HIS34, and PRO389, with a binding affinity of -279.8 kJ/mol. The multifidone - S glycoprotein-ACE2 has the active sites ASN33, PRO389, and HIS34, with a binding affinity of -228.768 kJ/mol (Figures 3 and 4).

DISCUSSION

Infection with COVID-19 is hypothesized to begin with the spike (S) protein of SARS-CoV-2 interacting with the angiotensin-converting enzyme 2 (ACE2) receptor in human cells.[21] SARS-CoV-2 has been demonstrated to bind to human ACE2 in in vitro studies. Coronaviruses use an extracellular, transmembrane S glycoprotein that is a homotrimer to gain entrance to host cells.[4]

Compounds bound between the ACE2 receptor and the SARS-CoV-2 S protein showed the same potency as povidone-iodine, including acacetin, apigenin, proanthocyanidin, quercetin, multidione, multifidanol, multifidenol, and multifolone. The molecule has a strong binding affinity for the SARS-CoV-2 S protein residue and the ACE2 receptor through hydrophobic interactions, hydrogen bonds, and van der Waals forces. However, the two compounds of *Jatropha multifida*, iodine and multifidone, were unlikely to inhibit the interaction between the SARS-CoV-2 S protein and the ACE2 receptors. Iodine compounds showed no interaction with the target proteins, multifidon compounds showed interactions with ACE2 receptors only, and interactions with ACE2 were still bound to the SARS-CoV-2 S protein.

The MPro SARS-CoV-2 showed results where acacetin, apigenin, quercetin, proanthocyanidin, multifidone, multifolone, multidione, multifidenol, and multifidanol were identified as binding amino acid residues to the same MPro SARS-CoV-2 protein as povidone-iodine (i.e., SER144 and CYS145). This indicates that the nine compounds may have the same potential as povidone-iodine to inhibit the MPro SARS-CoV-2 . Interestingly, all the ligands, except iodine, bound to the MPro protein in the catalytic site region (i.e., the HIS41 and CYS145 residues), which indicates that these nine compounds can reduce protease activity against SARS-CoV-2.

MPro is an enzyme that is essential for processing polyproteins translated from RNA.[22] The primary function of MPro is to release functional polypeptides from polyproteins through a proteolytic method.[23] Decreased MPro activity could potentially inhibit further SARS-CoV-2 infections. Proanthocyanidins showed the lowest bond energy of all the compounds, with hydrogen bonding, hydrophobicity and unfavorable interactions. Quercetin, acacetin, and apigenin, which are flavonoid groups, also bind to the MPro SARS-CoV-2 protein lower than povidone-iodine did as a control. In addition, multifidone, multifolone, multidione, multifidenol, and multifidanol also showed lower binding energies than povidone-iodine as a control. Likewise, iodine showed a lower bond energy than povidone-iodine as a control. The lower the bond energy between the ligand and protein, the stronger the ligand or compound binds.[24]

This result is consistent with previous research suggesting that quercetin may affect SARS-CoV-2 by interacting with 3CLPro, PLpro, and the S protein.[25] Apigenin 7-glucoside-4'-p-coumarate exhibits various antiviral activities both in vivo and in vitro; that is, it inhibits MPro SARS-CoV-2 ,[26] against enterovirus 71 (EV71), human immunodeficiency virus (HIV), and adenovirus. Apigenin can inhibit foot and mouth disease virus (FMDV) infection replication.[4] Numerous studies with tannins as the main component show good effects on the replication of different viruses, namely enveloped viruses (influenza A/H3N2 and A/H5N3 viruses, vesicular stomatitis virus, and

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herpes simplex virus type 1/HSV-1) and non-enveloped viruses (poliovirus, coxsackievirus, and adenovirus).[27] The content of terpenoids (multidione, multifidone, multifolone, multifidanol, and multifidenol) is useful due to its anticancer, antitumor, antileshmanial, antimalarial, antimicrobial, cytotoxic, insecticide, and molluscidal activities, which have been described previously.[28,29]

The binding affinity describes the strength/affinity of the bond resulting from the receptor–ligand interaction in the form of low energy in the formation of the receptor drug complex. This indicates the stability of the interaction (binding) of the ligand with the receptor at the binding site. The lower the binding affinity between the ligand and protein, the stronger the ligand or compound binds, meaning it has the potential to inhibit SARS-CoV-2. All the tested latex of the *Jatropha multifida Linn.* compounds had a lower binding affinity than povidone-iodine, except for the iodine compounds contained in *Jatropha multifida Linn*.

Overall, the latex of *Jatropha multifida Linn*. has the potential to be used as a mouthwash in preventive and curative therapy for COVID-19. The limitations of this study are that neither in vivo nor in vitro toxicity tests and clinical trials were carried out. In the future, this research will add a toxicity test for all the latex of *Jatropha multifida Linn*. compounds. It will do this virtually, using ProTox-II to obtain compound toxicity data. This research's long-term plan can then continue either in vitro or in vivo.

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