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Molecular Docking Studies of *Phoenix dactylifera* L. Against SARS-CoV-2 ACE-2 Receptor

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Abstract

Dates (*Phoenix dactylifera* L.) are one of the most useful plants. According to previous research, those dates contain bioactive compounds with antioxidant, antimicrobial, and anti-inflammatory properties. Furthermore, dates can be used as an antiviral, but the potential of dates as an antiviral, particularly the SARS-CoV-2 antiviral, has received little attention. As a result, the goal of this study was to see if date palm bioactive compounds could be used as SARS-CoV-2 antivirals with molecular docking against the Angiotensin-Converting Enzyme-2 (ACE-2) receptor. The study was carried out using molecular docking methods with Autodock Vina, where 21 chemical compounds found in date palms as ligands were attached to the ACE-2 receptor, and four chemical compounds used as SARS-CoV-2 antiviral medicines, namely chloroquine, favipiravir, plitidepsin, and remdesivir, were used as a control ligand. The results showed that proanthocyanidin B1, B2, and quercetin ligands had the highest interaction and stability with Gibbs free energy values of -9.20 kcal/mol, -9.10 kcal/mol, and -8.20 kcal/mol, respectively. This value is known to be higher than control ligands plitidepsin -9.02 kcal/mol, remdesivir -7.88 kcal/mol, chloroquine -5.65 kcal/mol, and favipiravir -5.38 kcal/mol. As a result, dates can be used as a SARS-CoV-2 antiviral candidate.

Keywords: *ACE-2 receptor, Antiviral, Molecular docking, Phoenix dactylifera*

1 Introduction

The acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes COVID-19 (the coronavirus infectious 2019) is the third highly pathogenic coronavirus to infect people [1]. A significant number of pneumonia cases in Wuhan City, Hubei Province, China, were connected to the COVID-19 pandemic [2].

A variety of medications and vaccinations have been researched and improved to combat SARS-CoV-2. As a result of this research, secondary metabolites isolated from plants and used as the basis for therapeutic materials were discovered to have antiviral potential against the coronavirus family [3]. One of the plants used as medicine is the date palm (*Phoenix dactilyfera* L.), one of the oldest plants to flourish in the Middle East and North Africa [4]. The chemical compounds found in *Phoenix dactylifera* include phytoestrogens, flavonoids, phenolic acids, tocotrienols, phytosterols, tocopherols, tannins, and carotenes. These compounds are responsible for *Phoenix dactylifera*'s medicinal properties, which include anti-hyperglycemic, anticancer, anti-hypertensive, anti-hyperlipidemic, antimicrobial, antioxidant, anti-inflammatory, neuroprotective fertility-enhancing, gastroprotective, immunoprotective, and hepatoprotective activities [4]. According to other research, *Phoenix dactylifera* may have the potential as a dengue antiviral based on molecular docking predictions [5].

Molecular docking is a technique for analyzing powerful chemical compounds in plants using computer tools. Molecular docking has a significant impact on medication discovery due to its speed and potential outcomes. Docking studies predict phytochemical affinities for binding to target proteins or enzymes. [5]. By joining the viral and host membranes and attaching to angiotensin-converting enzyme 2, SARS-CoV-2 spreads to the host (ACE-2) [6]. The fundamental function of the renin-angiotensin system, which is to control blood pressure, fluid, and electrolyte

balance, is carried out by ACE-2. An previous investigation showed that the expression of ACE-2 membrane and plasma level decreased and the pulmonary wound increased after acquiring SARS-CoV-2 [7]. Molecular docking research could be used to develop effective anti-SARS-CoV-2 medicines against ACE-2 because of their important roles. Five active metabolites from Indonesian terrestrial plants and marine organisms have previously been shown to inhibit the SARS-CoV-2 ACE-2 receptor. Furthermore, Moroccan medicinal plants such as *Phoenix dactylifera* can be candidates for SARS-CoV-2 antiviral because its secondary metabolites can inhibit the protein S, 3CLpro, and PLpro of SARS-CoV-2 [8,9].

In the current study, we used secondary metabolites found in *Phoenix dactylifera* to identify suitable SARS-COV-2 common inhibitors using in-silico repurposing. In order to do this, binding energy was calculated against ACE-2, a target of the SARS-CoV-2 receptor, using molecular docking.

2 Method

2.1 Ligand Preparation

Pubmed and Google Scholar papers related to secondary metabolites in *Phoenix dactylifera* were chosen. In this study, ligands in the form of active compounds for the treatment of SARS-CoV-2 were made from 21 naturally occurring chemicals from *Phoenix dactylifera* and a number of control compounds (**Table 1**). The method of ligand preparation refers to Syahputra *et al.*, 2021 [8].

2.2 Receptor Preparation

The ACE-2 receptor was used as the target enzyme in this study. It is bound to 2-acetamido-2-deoxy-beta-D-glucopyranose (NAG ligand), Zn, and Cl ions (PDB ID: 1R42). The method of receptor preparation refers to Syahputra *et al.*, 2021 [8].

2.3 Molecular Docking

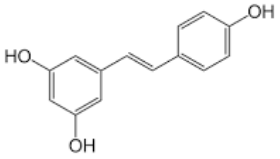
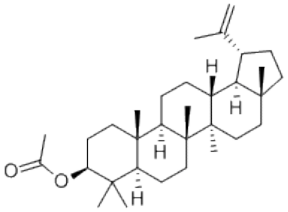
A protein-compound docking investigation was carried out using the molecular docking software AutoDock Vina 4.2. One of the metrics used to identify the ligand docking region at the receptor is the grid box. Ligands and receptors organized using the *PDBQT file format were copied into the Vina folder, and the vina configuration file was typed into notepad and saved as 'conf.txt'. The Vina program was then executed via the command prompt. The output (notepad format) contained the results, which were then analyzed. All other vina parameters were left at their default settings. Virtual screening can benefit from molecular docking, which produces binding affinity energy (ΔG). A lower ΔG value indicates the ligand with the highest potential. Using Discovery Studio, the molecular docking of ligands and receptors was viewed [9].

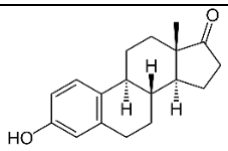
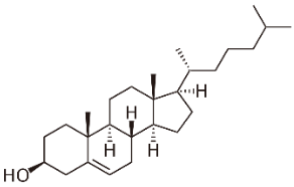
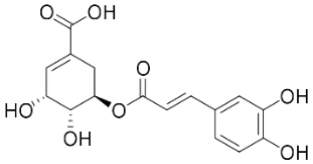
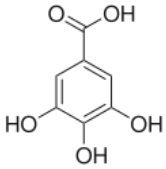
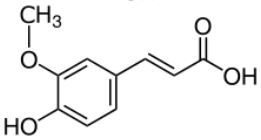
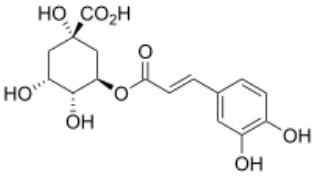
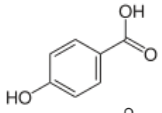
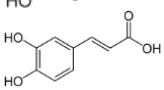
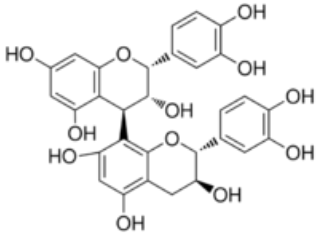
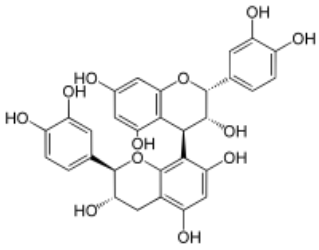
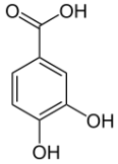
3 Result and Discussion

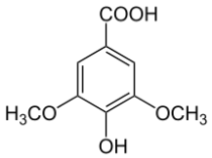
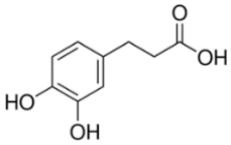
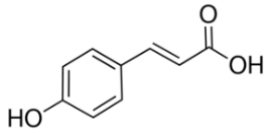
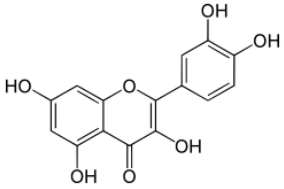
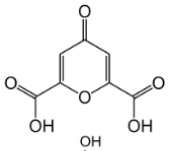
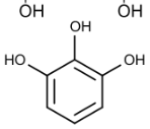
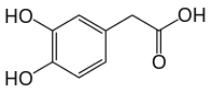
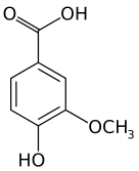
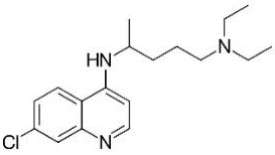
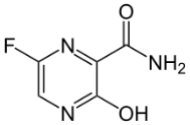
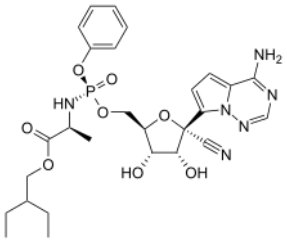
The *Phoenix dactylifera* active ingredients used in this investigation may have medicinal uses. The numerous kinds of chemicals, including steroids, lipids, terpenes, and phenols, that have been identified from diverse reference sources are listed in **Table 1**.

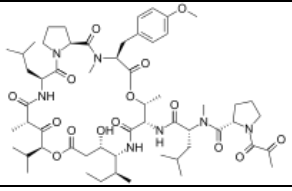
A thorough literature review was used to determine the value of *Phoenix dactylifera* in this study. The majority of research findings on these plants can improve health and prevent disease. Several studies have confirmed that *Phoenix dactylifera* produces a variety of secondary metabolism-derived compounds with antiviral activity. *Phoenix dactylifera* has anti-hyperglycemic, anticancer, anti-hypertensive, anti-hyperlipidemic, antimicrobial, antioxidant, anti-inflammatory, neuroprotective fertility-enhancing, gastroprotective, immunoprotective, and hepatoprotective properties, as well as antiviral properties [4,5].

Table 1. The active compounds of *Phoenix dactylifera* and control compound

Compound	Chemical Structure	Type	Ref.
Resveratrol		Polyphenol	[10]
Lupeol Acetate		Terpene	[10]

Compound	Chemical Structure	Type	Ref.
Estrone		Steroid	[10]
Cholesterol		Sterol	[10,11]
5-O-Caffeoylshikimic Acid		Phenolic acid	[11,12]
Gallic Acid		Phenolic acid	[13,14]
Ferulic Acid		Phenolic acid	[11,13–15]
Chlorogenic Acid		Phenolic acid	[13–15]
p-Hidroxybenzoic Acid		Phenolic acid	[13–15]
Caffeic acid		Phenolic acid	[11–13,15]
Proanthocyanidin B1		Polyphenol	[12]
Proanthocyanidin B2		Polyphenol	[12]
Protocatechuic acid		Phenolic acid	[12,13]

Compound	Chemical Structure	Type	Ref.
Syringic acid		Phenolic acid	[13]
Hydrocaffeic acid		Phenolic acid	[12]
p-coumaric acid		Phenolic acid	[11,13–15]
Quercetin		Flavonoid	[12–15]
Chelidonic acid		Phenolic acid	[15]
Pyrogallol		Phenolic	[14]
3,4-Dihydroxybenzoic acid		Phenolic acid	[15]
Vanillic acid		Phenolic acid	[12–15]
Chloroquine (Control)		Quinoline	[16]
Favipiravir (Control)		Pyrazine	[17]
Remdesivir (Control)		Nucleotide analog	[18]

Compound	Chemical Structure	Type	Ref.
Plitidepsin (Control)		Peptide	[19]

Chloroquine, Favipiravir, Plitidepsin, and Remdesivir—all commonly used medications that have been shown effective in treating SARS-CoV-2 were utilized as a point of comparison. Favipiravir, for example, is a verbal medication that was approved in Japan in 2014 for an unused and reemerging influenza pandemic and has demonstrated strong in vitro activity against SARS-CoV-2 [20]. By selectively targeting the protein eEF1A, the Ascidian-derived drug plitidepsin demonstrated exceptionally significant preclinical effectiveness against SARS-CoV-2 [21].

3.1 Structure and Stability of Receptor

Investigations into the stability and structure of PDB ID 1R42's hACE-2 (human angiotensin-converting enzyme) receptors produced a resolution value of 2.2 and a total of 615 amino acids, 98.37% (605/615) of which were found to be in the region of proteins that form structures (**Figure 1**).

A total of 31 -helix structures and six -sheet structures make up the majority of the ACE-2 protein. The ACE-2 receptors interact with metabolite compounds such as proanthocyanidins, dieckol, corilagin, isovitexin, and phlorofucofuroeckol A via several amino acid residues including Asp 350, Ser 409, Lys 441, Gln 442, and Arg 518, according to hydrogen bond analysis [8].

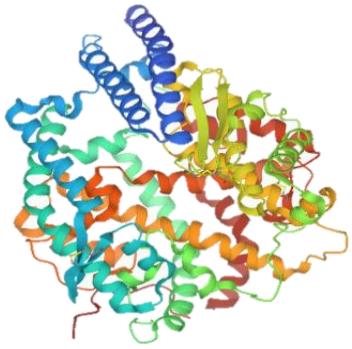


Figure 1. The ACE-2 receptor structure

3.2 Ligand Solubility and Lipinski Analysis

All ligands were optimized in Marvin Sketch 20.12 and their solubility and permeability assessed. The solubility and permeability of the drug candidate can be described by the psychochemical characteristics of the ligand structure. Five Lipinski rules have been reported to predict ligand solubility and permeability, namely: 1) There cannot be more than five hydrogen bond donors in the ligand, 2) There must be no more than ten hydrogen bond acceptors in the ligand, 3) The molecular weight of the ligand should not exceed 500 Da, 4) The log P value of the ligand should not be less than five, and 5) The ligand must have a polar surface area (PSA) of less than 140 and 10-30 rotational bonds [22]. In this study, four parameters were used, as shown in **Table 2**: molecular weight (MW), log P, donor H, and acceptor H.

Table 2. Characteristics of Ligand Based on Lipinski Analysis

Ligand	MW (Da)	Log P	Donor H	Acceptor H	Lipinski
3,4-Dihydroxyphenylacetic acid	168.15	0.72	3	4	Yes
5-O-Caffeoylshikimic acid	336.29	0.16	5	8	Yes
Caffeic acid	180.16	1.2	3	4	Yes
Chelidonic acid	184.10	0.04	2	6	Yes
Chlorogenic Acid	354.31	-0.65	6	9	Yes
Cholesterol	386.65	7.39	1	1	Yes
Estrone	270.37	3.82	1	2	Yes
Ferulic Acid	194.18	1.50	2	4	Yes
Gallic acid	170.12	0.50	4	5	Yes
Hydrocaffeic acid	182.17	1.12	3	4	Yes
Lupeol Acetate	468.75	8.6	0	2	Yes
p-coumaric acid	164.16	1.49	2	3	Yes

Ligand	MW (Da)	Log P	Donor H	Acceptor H	Lipinski
p-Hydroxybenzoic acid	138.12	1.09	2	3	Yes
Proanthocyanidin B1	578.52	3	10	12	No
Proanthocyanidin B2	578.52	3	10	12	No
Protocatechuic acid	154.12	0.8	3	4	Yes
Pyrogallol	126.11	0.8	3	3	Yes
Quercetin	302.24	1.99	5	7	Yes
Resveratrol	228.24	2.97	3	3	Yes
Syringic acid	198.17	1.11	2	5	Yes
Vanillic acid	168.15	1.1	2	4	Yes
Chloroquine	319.87	4.88	1	2	Yes
Favipiravir	157.10	-0.29	2	4	Yes
Plitidepsin	1110.34	3.39	4	15	No
Remdesivir	602.58	3.28	4	12	No

The molecular weight of the ligands as SARS-CoV-2 antiviral candidates ranged between 120 and 1200 Da, with the smallest being 126.11 Da and the largest being 1110.34 Da, according to the psychochemical analysis. Because they are more stable, compounds with a molecular weight of less than 500 Da will be easier to develop as drug candidates. The log P values ranged between -0.7 and 8, the number of hydrogen bond donors between 0 and 10, and the number of hydrogen bond acceptors between 1 and 15. So, based on Lipinski's rule analysis, four ligands did not meet Lipinski's rule: proanthocyanidin B1, proanthocyanidin B2, Plitidepsin, and Remdesivir. Although plitidepsin and remdesivir have been used to treat COVID-19, both have been shown to violate Lipinski's rule. According to previous research, proanthocyanidins, plitidepsin, and remdesivir do not fall under Lipinski's rule [8].

3.3 Toxicity of Ligands

The goal of the ligand toxicity analysis using protox II is to determine the ligand's level of toxicity. The LD50 (Lethal Dose), which is measured in milligrams per kilogram of body weight, represents the degree of toxicity. The dose at which half of test participants pass away upon exposure to the substance is known as the mean lethal dose (LD50). The Globally Harmonized System (GHS), which separates substances into six groups with various degrees of toxicity, defines toxicity class. The six toxicity categories are Class I, which is very lethal if swallowed (LD50 5 mg/kg), Class II, which is fatal if swallowed (5 mg/kg LD50 50 mg/kg), Class III, which is toxic if swallowed (50 mg/kg LD50 300 mg/kg), Class IV, which is harmful if swallowed (300 mg/kg LD50 2000 mg/kg), Class V, which is possibly harmful if swallowed (2000 mg/kg < LD50 ≤ 5000 mg/kg), and Class VI, which is non-toxic (LD50 > 5000 mg/kg) [23].

In this study, it was found that the toxicity level of each ligand was in classes 3, 4, and 5, namely toxic, harmful, and possibly harmful if ingested (**Table 3**). Based on the results of the study, the highest LD50 value was owned by the ligands Lupeol Acetate, Estrone, and Chlorogenic acid which was categorized as possibly harmful if swallowed, while the one with the lowest LD50 was Chelidonic acid which was toxic if swallowed, Plitidepsin as a control ligand was also categorized as toxic if swallowed.

Table 3. Toxicity of Ligand by Protox II

Ligand	LD50 (mg/kg)	Class	Toxicity Category
3,4-Dihydroxyphenylacetic acid	1400	4	Harmful
5-O-Caffeoylshikimic acid	3800	5	Possibly harmful
Caffeic acid	2980	5	Possibly harmful
Chelidonic acid	100	3	Toxic
Chlorogenic Acid	5000	5	Possibly harmful
Cholesterol	890	4	Harmful
Estrone	5000	5	Possibly harmful
Ferulic Acid	1772	4	Harmful
Gallic acid	2000	4	Harmful
Hydrocaffeic acid	2000	4	Harmful

Ligand	LD50 (mg/kg)	Class	Toxicity Category
Lupeol Acetate	5000	5	Possibly harmful
p-coumaric acid	2850	5	Possibly harmful
p-Hydroxybenzoic acid	2200	5	Possibly harmful
Proanthocyanidin B1	2500	5	Possibly harmful
Proanthocyanidin B2	2500	5	Possibly harmful
Protocatechuic acid	2000	4	Harmful
Pyrogallol	300	3	Toxic
Quercetin	159	3	Toxic
Resveratrol	1560	4	Harmful
Syringic acid	1700	4	Harmful
Vanillic acid	2000	4	Harmful
Chloroquine	750	4	Harmful
Favipiravir	1717	4	Harmful
Plitidepsin	200	3	Toxic
Remdesivir	1000	4	Harmful

3.4 Analysis of Binding Affinity Energy

The more negative the resulting value from the molecular docking simulation, according to the binding affinity energy analysis, the more stable the bond between the ligand and the receptor.As a result, in **Table 4**, both ligands and controls with negative energy values for the ACE-2 receptor will be discussed.

Table 4. Gibbs Free Energy Value (kcal/mol) from Molecular Docking Simulation

Ligand	ΔG (kcal/mol)	Ligand	ΔG (kcal/mol)
Proanthocyanidin B1	-9.20	Protocatechuic acid	-6.27
Proanthocyanidin B2	-9.10	p-coumaric acid	-6.22
Plitidepsin (control)	-9.02	3,4-Dihydroxyphenylacetic acid	-5.98
Lupeol acetate	-8.22	Hydrocaffeic acid	-5.90
Quercetin	-8.20	Chelidonic acid	-5.90
Remdesivir (control)	-7.88	Gallic Acid	-5.87
Cholesterol	-7.80	Chloroquine (control)	-5.65
Estrone	-7.78	4-Hidroxy Benzoic Acid	-5.53
5-O-Caffeoylshikimic Acid	-7.57	Syringic acid	-5.43
Chlorogenic Acid	-7.32	Favipiravir (control)	-5.38
Resveratrol	-6.73	Vanillic acid	-5.37
Caffeic acid	-6.67	Pyrogallol	-5.28
Ferulic Acid	-6.43		

The energy required to form a bond between the ligand and the receptor is defined as the binding energy affinity (Gibbs free energy). The lower the required energy, the more stable the receptor-ligand complex [24]. Based on the analysis of the ligand-receptor interaction, it is possible to conclude that several bonds, including hydrogen, van der Waals, and hydrophobic bonds, form between the two. The number of interactions between the ligand and the receptor, such as hydrogen bonds and hydrophobic interactions, will influence activity. In other words, the quantity of hydrogen bonds created during protein-ligand interactions affects how stable a complex structure is, and the complexity of a structure is directly correlated with the number of hydrogen bonds formed [25]. Hydrogen bonds and hydrophobic bonds affect the stability of the bond between the ligand and its target in protein-ligand interactions. If enough hydrogen bonds are combined with hydrophobic interactions, the two molecules will form quite strong bonds [26].

Proanthocyanidin B1 and B2, lupeol acetate, and quercetin are the ligands with the best four Gibbs free energy values (ΔG), whereas remdesivir and ptilidepsin were employed as controls (popular medications) for comparison. Hydrogen bonding analysis revealed that the ACE-2 receptor interacts with metabolites containing Asp350, Asp206, Lys562, Arg514, Ser47, Trp566, Glu564, Gln102, Glu208, Ser43, Asn210, Thr434, Ser44, and Gln98 (**Table 5**). Asn394 had the longest hydrogen bond with a

length of 3.07 Å and Asp350 had the shortest with a length of 1.86 Å.

Table 5. Receptor and ligand interactions based on hydrogen bond analysis

Ligand	Hydrogen bond (Å)	Ligand	Hydrogen bond (Å)
Proanthocyanidin B1	**Asp350** (1.86)	Protocatechuic acid	**Thr434** (2.42)
Proanthocyanidin B2	**Asp206** (2.68), (2.81), **Lys562** (2.08), **Arg514** (2.34)	p-coumaric acid	Ala348 (2.02), **Ser47** (2.40), **Ser43** (2.39) (2.10)
Ptilidepsin (control)	**Ser47** (2.66), **Lys562** (2.90), **Arg514** (2.14)	3,4-Dihydroxyphenylacetic acid	**Trp566** (2.52), **Glu564** (2.20), **Asn210** (2.50) (1.99), **Glu208** (2.99)
Lupeol Acetate	-	Hydrocaffeic acid	**Asp350** (2.57) (1.98), **Ser44** (2.56), Phe40 (2.59)
Quercetin	**Trp566** (2.46), **Glu564** (2.27), **Gln102** (2.66), **Glu208** (2.45)	Chelidonic acid	**Asp350** (2.73), **Ser44** (2.87), **Ser47** (2.37)
Remdesivir (control)	Tyr196 (2.85) (2.20), Gln101 (2.32)	Gallic Acid	His540 (2.83)
Cholesterol	Glu145 (2.47)	Chloroquine (control)	His401 (3.03), Asp382 (3.02)
Estrone	-	4-Hidroxy Benzoic Acid	**Thr434** (2.64)
5-O-Caffeoylshikimic Acid	**Asp350** (2.84), Asn394 (3.07), **Ser43** (2.89), Arg393 (2.34), **Ser47** (2.41)	Syringic acid	-
Chlorogenic Acid	Ala99 (2.77), **Asn210** (2.58), **Gln102** (2.21), (2.43)	Favipiravir (control)	**Gln98** (2.98), **Trp566** (2.38), **Lys562** (2.58) (2.82), **Glu564** (2.73)
Resveratrol	**Asn210** (2.06)	Vanillic acid	**Gln98** (2.71), **Asn210** (1.95)
Caffeic acid	Asn437 (2.31)	Pyrogallol	**Trp566** (2.47), **Asp206** (2.00), **Glu564** (2.63), (2.17)
Ferulic Acid	**Asp206** (2.59), **Asn210** (2.53), (1.95)		

Based on the analyzes that have been carried out, it was concluded that the compounds proanthocyanidin B1, B2, and quercetin were the most potent compounds as candidates for SARS-CoV-2 antiviral based on their interaction with ACE-2. Lupeol acetate, which is a terpene group, cannot be used as an antiviral candidate for SARS-CoV-2 because it does not interact with amino acid residues at the ACE-2 receptor through hydrogen bonds. Proanthocyanidin B1, B2, and quercetin are included in the phenolic compounds, all these compounds are found in palm plants such as dates (*Phoenix dactylifera*) [10,12–15,27].

Based on previous in silico research that proanthocyanidin is a compound found in Indonesian marine and land organisms that can be used as a candidate for SARS-CoV-2 antiviral [8]. Quercetin can inhibit SARS-CoV-2 protein targets PLpro and 3CLpro with docking binding energies of -4.62 and -6.25 kcal/mol, respectively, and it has pharmacological activity such as anti-inflammatory, anti-atopic, pro-metabolic, and antiviral [28]. **Figure 2** depicts the interaction, conformation, and orientation of proanthocyanidin B1 and ptilidepsin (control).

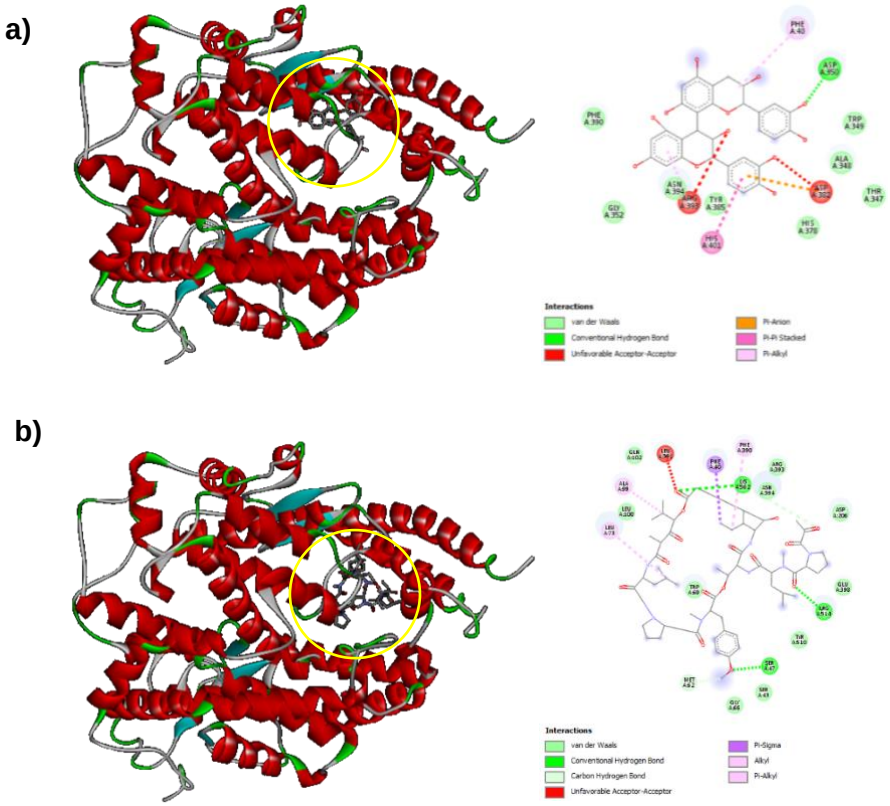


Figure 2. The conformation and interaction of hydrogen bonds between ligands and receptors with a distance < 5 Å. a) ACE-2-proanthocyanidin B1; b) ACE-2-plitidepsin.

4 Conclusion

ACE-2 inhibition is critical in the treatment of COVID-19 because it prevents SARS-CoV-2 spike protein-mediated cell fusion. Proanthocyanidin B1, B2, and quercetin have the lowest docking scores and thus the most binding interactions with the ACE-2 protein. Overall, we conclude that the three phytochemicals proanthocyanidin B1, B2, and quercetin from the date plant (*Phoenix dactylifera*) have the desired properties to be a potent SARS-CoV-2 inhibitor. As a result, additional research involving in-vitro and in-vivo studies on these molecules is warranted.

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