

In silico Identification of Antiviral Polyphenols from *Phoenix dactylifera* Targeting SARS-CoV-2 Main Protease

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Abstract: COVID-19, caused by SARS-CoV-2, depends on its main protease (Mpro) for viral replication. This study evaluated the potential of polyphenolic compounds from *Phoenix dactylifera* as Mpro inhibitors using molecular docking, molecular dynamics (MD) simulations, and ADMET profiling. Three ligands - flavoxanthin, violaxanthin, and neoxanthin, demonstrated the strongest binding affinities to Mpro, although still lower than tipranavir. MD simulations indicated that all three ligands maintained stable interactions with Mpro, while PCA revealed no major structural deviations in the complex. ADMET screening identified 18 compounds with acceptable pharmacokinetic properties. Overall, the top three ligands exhibited favorable binding energies and stability, supporting their potential as Mpro inhibitors. Further *in vitro* and *in vivo* validation is needed to support this hypothesis.

Keywords: SARS-CoV-2; antiviral; molecular dynamics; phoenix dactylifera; YASARA; COVID-19.

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1. Introduction

Coronavirus Disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), remains a major global contributor to both morbidity and mortality. The virus was first identified in December 2019 in Wuhan, Hubei Province, China [1–6]. With viruses resistant to vaccines and uneven access to healthcare, finding quick

and effective treatments and prevention measures for COVID-19 is more urgent than ever before. This crisis has prompted scientists and governments to intensify their efforts to develop treatments and prevent the spread of this disease quickly and effectively [7]. SARS-CoV-2 is still closely related to SARS-CoV and has many similarities with SARS-CoV [8]. Research on the functions and crystal structures of target receptors is essential for the development of antiviral drugs. The main protease (Mpro) plays an essential role in viral replication and is a potential target for developing new SARS inhibitors. Mpro, also known as protease 3CL, is believed to be required for the cleavage of polyproteins pp1a and pp1ab. Mpro exists as a homodimer, and many coronaviruses have high sequence homology with the three-dimensional structure and amino acid sequence of this enzyme. *In silico* studies have reported that hesperidin inhibits both the main protease and RNA polymerase of SARS-CoV-2. The researchers employed a combined approach of molecular docking and dynamic simulation, incorporating several evaluative parameters such as Root-Mean-Square Deviation (RMSD), Root-Mean-Square Fluctuation (RMSF), Radius of Gyration (Rg), Solvent-Accessible Surface Area (SASA), and the total number of hydrogen bonds [9]. Another report indicated that once SARS-CoV-2 attaches to caveolae and enters the intracellular endosome, cathepsin L emerges as the primary protease. According to the proposed pathway, the host cell receptor is an enzyme known as angiotensin-converting enzyme 2 (ACE2), which binds to the viral spike (S) protein and subsequently triggers proteolysis of the S1 subunit on the viral surface [10]. Therefore, the main protease (Mpro) is a promising molecular target for drug development. [4,5,7,11–25].

Since ancient times, medicinal plants have been widely used to treat various diseases in humans, one of which is the date (*Phoenix dactylifera*), which is known to have several potential health benefits [26]. The date palm has played an important role as a food source in supporting food security across the Middle East and North Africa (MENA) region [27]. Dates are highly nutritious because they contain bioactive compounds, such as polyphenols, anthocyanins, and carotenoids. They also contain vitamins, minerals, sugars, and fibers [28–30]. Plant-derived polyphenols are well known for their antioxidant properties, cholesterol-lowering effects, and other health benefits, including cancer chemoprevention, diabetes prevention, and cardiovascular disease prevention [31–35].

In the absence of early antiviral interventions, numerous studies have explored medicinal plants because of their diverse phytochemicals with established antiviral, anti-inflammatory, and immunomodulatory properties. Several species, including *Curcuma longa*, *Zingiber officinale*, and *Allium cepa*, and various essential oils have been evaluated for their potential to mitigate viral pathogenesis. *Phoenix dactylifera* (date palm), widely used in traditional medicine and rich in polyphenols, has demonstrated multiple biological activities and clinical benefits in COVID-19 patients. However, despite the increasing interest in natural antiviral agents, no previous study has specifically investigated the interaction of *P. dactylifera* polyphenols with the SARS-CoV-2 main protease (Mpro), a critical enzyme for viral replication. This knowledge gap highlights the novelty of the present study, which evaluated the binding affinity, dynamic stability, and pharmacokinetic profiles of *P. dactylifera* polyphenols as potential Mpro inhibitors through molecular docking, molecular dynamics simulations, and ADMET analysis [36].

In this study, the SARS-CoV-2 main protease (Mpro) structure with the PDB ID 6Y2E was selected as the model system. The choice of 6Y2E over other available structures, such as 6LU7, was based on two considerations. First, 6Y2E is considered more representative for docking simulations because it contains a naturally bound, noncovalent inhibitor and lacks

covalent modification of the catalytic residue Cys145, in contrast to 6LU7, which is complexed with an irreversible inhibitor. Second, comparative studies have shown a low correlation between ligand-binding poses and affinities obtained from 6LU7 and 6Y2E ($R^2 = 0.236$), indicating that docking outcomes are highly dependent on the selected protein structure [44]. Therefore, the use of 6Y2E is expected to yield interaction simulations that are more physiologically relevant [36–45]. This study aimed to investigate the inhibitory potential of date-derived polyphenolic compounds against Mpro using an integrated docking and molecular dynamics approach, complemented by ADMET and principal component analyses. [38, 46–53]. The workflow of this study is illustrated in Figure 1.

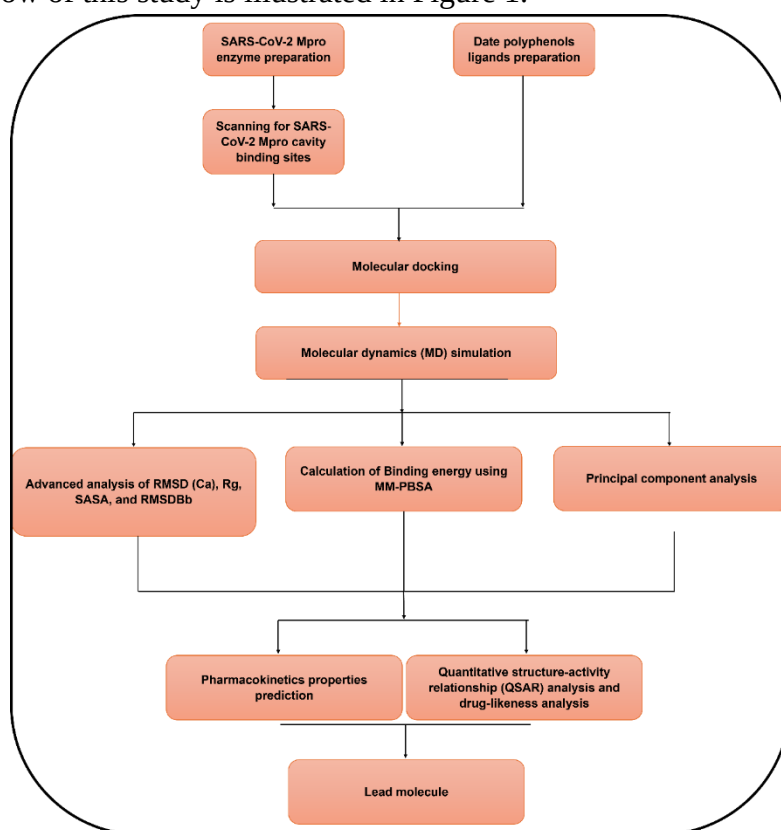


Figure 1. Schematic diagram depicting the workflow adopted to carry out this study.

2. Materials and Methods

2.1. Materials.

The materials used in this study were the Mpro structure of the SARS-CoV virus, which was downloaded from the Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB) (<https://www.rcsb.org/>) with PDB ID code “6Y2E”. All test ligands were downloaded from PubChem.

2.2. Tools.

The equipment used in this study was an HP 250 G5 Notebook PC with Windows 10 Professional 64-bit operating system, Intel ® Core i3-6006U processor specifications, and Intel Core i7-8750H CPU equipped with 32 GB of RAM and a 64-bit Windows 11 operating system, and 4.00 GB RAM. The software used to conduct the research was YASARA structure (Bioinformatics 30,2981–2982 version 19.9.17, the Netherlands), Discovery Studio by Dassault

Systems BIOVIA (Dassault Systems. Version: 24.1), and FactoMineR and factoextra packages on R-Studio (Version 4.4.2).

2.3. Date polyphenol ligands preparation.

To investigate the potential of polyphenol compounds of the date to act as inhibitors of SARS-CoV-2, we obtained a list of these compounds from Yasin *et al.* [54]. To obtain the three-dimensional structures of the compounds, we used the PubChem database (<https://pubchem.ncbi.nlm.nih.gov/>). The following is a list of 21 compounds downloaded for three-dimensional structures using PubChem, flavoxanthin (PubChem CID: 5281238), violaxanthin (PubChem CID: 448438), lutein (PubChem CID: 5281243), neoxanthin (PubChem CID: 5282217), beta-carotene (PubChem CID: 5280489), procyanidin (PubChem CID: 107876), luteolin (PubChem CID: 5280445), quercetin (PubChem CID: 5280343), apigenin (PubChem CID: 5280443), lycopene (PubChem CID: 446925), lignans (PubChem CID: 443013), epicatechin (PubChem CID: 72276), caffeic (PubChem CID: 689043), ferulic-acid (PubChem CID: 445858), o-Coumaric (PubChem CID: 637540), p-Coumaric (PubChem CID: 637542), 4-Hydroxybenzoic (PubChem CID: 135), protocatechuic (PubChem CID: 72), vanillic (PubChem CID: 8468), gallic acid (PubChem CID: 370), and syringic acid (PubChem CID: 10742), while the controls used were ritonavir (PubChem CID: 39622) [55], tipranavir (PubChem CID: 54682461), and raltegravir (PubChem CID: 54671008) [1]. The three-dimensional structures of the ligands downloaded in (. sdf) format were prepared using the YASARA structure. Each ligand was prepared by adding hydrogen atoms, setting the force field to Amber03, and performing energy minimization. The prepared ligands were stored in. sdf format, with a filename ending in “_ligand.sdf” to indicate that they were ready to bind to the receptor. This file format is compatible with the YASARA Structure algorithm, allowing the execution of molecular docking commands.

2.4. SARS-CoV-2 Mpro enzyme preparation.

In this study, the specific target was the SARS-CoV-2 main protease (Mpro). The target enzyme was obtained from the RCSB PDB (<https://www.rcsb.org/>) using the PDB ID “6Y2E”. The enzyme has a resolution of 1.75 Å, as determined by crystallization results [56]. The enzyme was downloaded in PDB format for enzyme preparation using YASARA structure software. The preparation procedure involved adding missing hydrogen atoms and removing water molecules from the crystal structure. The amber03 force field was employed to minimize the energy of the enzyme, and the prepared enzyme was saved in PDB format for use in molecular docking simulation [57–59].

2.5. Scanning for SARS-CoV-2 Mpro cavity binding sites.

We used the CavityPlus open server (<http://www.pkumdl.cn/cavityplus>) to find amino acid residues that have the potential to help bind to the target protein of SARS-CoV-2 Mpro, so the results were used to detect potential binding sites on the protein surface [60,61].

2.6. Molecular docking.

We optimized both the ligand and target receptor through preparations that included the removal of water molecules, addition of polar hydrogen atoms, setting of the amber03 force field, and energy minimization. Molecular docking was carried out using the YASARA

structure software with the dock_run.mcr macro file. The number of runs was increased from 25 to 50 by modifying the "runs" file section. In this study, we used the VINA method available in YASARA structure [62,63] and set the force field to amber03. The simulation cell was defined to encompass the entire receptor surface, with the grid box dimensions set to 76.14 Å × 76.14 Å × 76.14 Å. These dimensions were selected to cover the predicted binding site regions identified using CavityPlus. Therefore, grid box validation was not required in this study. The protein target was set as rigid, whereas the ligands were set as flexible in the simulation. The settings for the molecular docking simulation in YASARA structure were kept constant, except for those mentioned above [58,63–65]. The identification and analysis of Mpro-ligand interactions were performed using the Discovery Studio Visualizer software [58].

2.7. Molecular dynamics (MD) simulation.

MD simulation was carried out using the YASARA structure protocol for the three best compounds to study the stability performance of protein-ligand complexes that aim to inhibit target proteins. In the MD simulation, several sets of settings needed to be adjusted, including the AMBER14 force field, the physiological standard pH value (7.4), and the counter ion (Na⁺ or Cl⁻) at a concentration of 0.9% to maintain a neutral state of the system. The simulation was performed at a constant pressure and temperature, and the molecular complex was simulated for 20 ns with frame capture every 100 ps to analyze the trajectory with various parameter evaluations. The macro script we customized earlier (md_run.mcr), available in the YASARA structure folder, was used to run the MD simulation. The simulation was run at 298K and with a time step of 1.25 f and a cut-off of 8 [66–70]. Finally, simulation snapshots were calculated for the bond-free energy using the BoundaryFast approach with the YASARA structure. The bond energy was calculated using the BoundaryFast approach [71].

2.8. Principal component analysis (PCA).

After completing the MD, we processed several variables, such as energy and trajectory, using principal component analysis (PCA). The MD trajectory data were initially scaled due to the different variables, then normalized before PCA analysis was carried out using the FactoMineR and factoextra packages in RStudio. The data we processed resulted from trajectories and thermodynamic changes over 20 ns [72,73]. In this study, PCA was applied to examine collective motion patterns in protein dynamics. PCA is a widely used multivariate exploratory technique for dimensionality reduction that transforms the original data matrix into a set of new, uncorrelated variables, known as principal components (PCs), which are ranked according to their contributions to the total variance of the dataset. This approach is particularly useful for data classification and pattern recognition in biomolecular conformational ensembles. From a statistical reliability perspective, interpretation of PCA results is commonly supported by inspection of scree plots and cumulative variance contributions of the selected principal components, where components accounting for the majority of the variance (typically >70–80%) are considered to represent the essential dynamics of the system [74,75].

2.9. Pharmacokinetics properties prediction.

To predict the pharmacokinetic properties, including absorption, distribution, metabolism, excretion, and toxicity (ADMET), of the date polyphenols and controls used in

this study, we utilized the pkCSM tool, a web-based tool available at <https://biosig.lab.uq.edu.au/pkcsm/prediction> [76–78]. The selection of this tool was based on extensive published validation, in which its predictive models—such as those for lipophilicity (iLOGP), intestinal permeability, and cytochrome P450 inhibition—have been benchmarked against large experimental datasets, demonstrating strong statistical performance and relevance to drug design. The prediction workflow followed established procedures: compound structures in SDF format were converted to SMILES, processed by the server to add hydrogen atoms, and used to generate 3D conformations, which were subsequently employed to compute physicochemical, pharmacokinetic, and drug-likeness parameters computationally [79].

2.10. Quantitative structure-activity relationship (QSAR) analysis and drug-likeness analysis.

The data on polyphenol compounds obtained from the literature study and PubChem were then analyzed to determine whether they are orally bioavailable or not using the SCFBIO webserver (<http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp>) [80,81]. The compounds were then submitted in .sdf format, and the parameters used for the Lipinski rule of five are molecular mass <500 Da, high lipophilicity (LogP) <5, hydrogen bond donors (HBD) <5, hydrogen bond acceptors (HBA) <10, and molar refractivity (MR) 40–130. A quantitative structure-activity relationship (QSAR) was predicted by submitting the compounds' SMILES into the PASS web server (<http://way2drug.com/PassOnline/>). This was done to predict the antiviral properties [80–83].

3. Results and Discussion

Rational drug design is an emerging field that aims to accelerate the drug development process by targeting specific proteins essential for the virus life cycle [68,84,85]. In this study, we used several *In silico* approaches to find drug candidates that target specific proteins essential for the virus life cycle, with the goal of speeding up the drug development process. The target receptor we chose was SARS-CoV-2 Mpro, and the ligands were date polyphenols.

Dates are the most popular fruit in the MENA region. Different varieties of dates are available in the market, and the global demand for dates is increasing every year. The global date production and consumption levels have been steadily growing [86]. The global date production grew by 41% overall, while the global consumption of table dates amounted to approximately 974 thousand metric tons in 2020, up from 875 thousand metric tons in 2019 [86,87]. This fruit contains so many classes of bioactive components that are of considerable benefit to human health. The amount of production and consumption of date fruit is related to the global COVID-19 pandemic caused by SARS-CoV-2, prompting us to analyze its potential in efforts to inhibit SARS-CoV-2.

The role of dates has been widely studied, including preventing microbial growth and biofilm formation, anti-radical, antifungal, antibacterial, anti-hyperglycaemic, nephroprotective, neuroprotective, anticancer, fertility-enhancing, anti-hyperlipidemic, anti-inflammatory, antioxidant, and anti-proliferative properties [28–30,88,89]. In addition, the fact that polyphenols themselves have various benefits is good because polyphenols are natural plant secondary metabolites and show extraordinary multipotential abilities to help control and modulate ROS, metal toxicity, inflammation, apoptosis, signal transduction, ion channels, and neurotransmitters [32].

3.1. Protein-druggable cavities.

First, we predicted the protein surface to evaluate and identify protein cavities that could bind with drug candidates. The analysis results with CavityPlus show that 12 cavities were detected by the system (Table 1). However, we only used Cavity number 2 because it has a drug score of -143 and medium druggability properties (Figure 2). The results of the analysis of amino acid residues from CavityPlus are presented in Table 2.

Table 1. Cavity analysis results.

PDB ID	Cavity no.	Predicted maximal pKd	Predicted average pKd	Drugscore	Druggability
6Y2E	1	11.57	6.91	-185	Weak
	2	9.66	5.93	-143	Medium
	3	9.50	5.87	-273	Weak
	4	8.89	5.67	-1012	Weak
	5	8.57	5.56	-1033	Weak
	6	8.57	5.55	-607	Weak
	7	7.58	5.22	-901	Weak
	8	7.04	5.03	-1336	Weak
	9	6.58	4.87	-1334	Weak
	10	6.41	4.82	-1181	Weak
	11	5.53	4.52	-1430	Weak
	12	5.51	4.51	-1602	Weak

Table 2. Potential binding sites.

PDB ID	Amino acid residues
6Y2E	VAL-297-A,PHE-294-A,PHE-8-A,ASP-197-A,ASN-203-A,ASN-151-A,ASP-245-A,HIS-246-A,PRO-241-A,ARG-131-A,ILE-200-A,PHE-112-A,LEU-250-A,GLU-240-A,ILE-249-A,ASP-295-A,PHE-134-A,ARG-298-A,THR-201-A,ASN-133-A,THR-111-A,PRO-132-A,ILE-106-A,THR-198-A,GLN-110-A,GLY-109-A,PRO-108-A,VAL-202-A,PHE-291-A,GLN-107-A,THR-243-A,GLN-127-A,LEU-242-A,THR-199-A,THR-292-A,MET-130-A,PRO-293-A

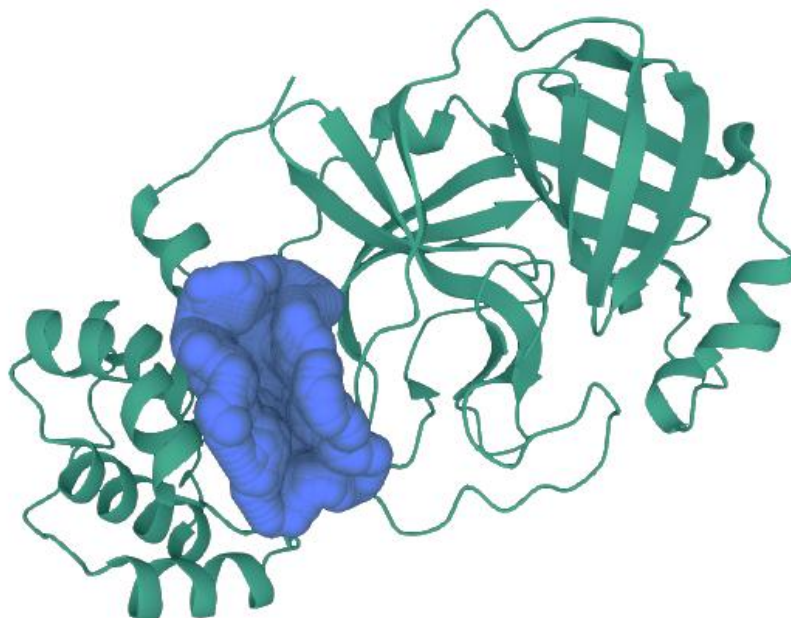


Figure 2. Cavity number 2 visualization.

3.2. Molecular docking.

After obtaining the surface of the protein that displays critical residues of Mpro, the docking is run to see more deeply how the interactions formed between the test ligand and the target Mpro. The molecular docking results of date polyphenols against Mpro of SARS-CoV-2 using the YASARA structure are presented in Table 3. This study used control drugs, such

as tipranavir, ritonavir, and raltegravir, to compare the binding energy, dissociation constant (Kd), and contact receptor residues. Tipranavir had the highest binding energy of 9,575 kcal/mol, followed by flavoxanthin, with a binding energy of 9,092 kcal/mol. The difference in the binding energies between the two ligands was 0.483 kcal/mol, and their Kd values were 95814.6563 pM and 216508.8438 pM, respectively. Other test ligands, including violaxanthin, lutein, and neoxanthin, had higher binding energies than the control drugs, ritonavir and raltegravir. In general, a higher kcal/mol binding energy (more positive) indicates a stronger ligand binding to the target receptor (Figure 3). In addition, we analyzed differences in the number of contact residues between the ligands and the control. For example, the control drug tipranavir had 17 residues in contact, ritonavir had 13 amino acid contact residues, and raltegravir had 18 amino acid contact residues. In contrast, the test ligands with high binding energies had more contact residues: flavoxanthin had twenty-five, violaxanthin had twenty-four, lutein had twenty-four, and neoxanthin had twenty-two contact residues. Thus, it can be concluded that the test ligand interacted with a broader range of contact residues than did the control. However, we not only observed the number of amino acid residues but also analyzed the interactions formed in the docking complex.

This study employed a molecular docking approach as a preliminary framework for evaluating the strength of interactions within protein–ligand complexes. Docking is widely used because it provides valuable early insights into potential binding affinities between ligands and target proteins. However, this method has inherent limitations. Therefore, molecular dynamics (MD) validation serves as an appropriate follow-up step, as it addresses key weaknesses of docking, such as the lack of dynamic flexibility and limited ability to simulate protein behavior within a biological environment [90,91].

Table 3. Analysis results of molecular docking using the YASARA structure. The binding results include binding energy, dissociation constants, and contacting receptor residues.

CID	Name	Binding energy (kcal/mol)	Dissoc. constant (pM)	Contacting receptor residues
54682461	Tipranavir (Control drug)	9.575	95814.6563	A LYS 102 A VAL 104 A ARG 105 A ILE 106 A GLN 110 A THR 111 A ASN 151 A ILE 152 A ASP 153 A SER 158 A CYS 160 A VAL 202 A ILE 249 A THR 292 A PRO 293 A PHE 294 A VAL 297
5281238	Flavoxanthin	9.092	216508.8438	A PHE 8 A GLN 107 A PRO 108 A GLY 109 A GLN 110 A THR 111 A PRO 132 A ASN 151 A ILE 152 A ASP 153 A TYR 154 A ILE 200, A VAL 202 A ASN 203 A GLU 240 A PRO 241 A THR 243 A HIS 246 A ILE 249 A THR 292 A PRO 293 A PHE 294 A ARG 298 A VAL 303 A PHE 305
448438	Violaxanthin	8.487	601099.6875	A PHE 8 A GLN 107 A PRO 108 A GLY 109 A GLN 110 A ASN 151 A ILE 152 A ASP 153 A TYR 154 A ILE 200 A VAL 202 A ASN 203 A GLU 240 A PRO 241 A THR 243 A HIS 246 A ILE 249 A THR 292 A PRO 293 A PHE 294 A ARG 298 A VAL 303 A THR 304 A PHE 305
5281243	Lutein	8.388	710418.875	A PHE 8 A GLN 107 A PRO 108 A GLY 109 A GLN 110 A PRO 132 A ASN 151 A ILE 152 A ASP 153 A TYR 154 A VAL 202 A ASN 203 A GLU 240 A PRO 241 A THR 243 A HIS 246 A ILE 249 A THR 292 A PRO 293 A PHE 294 A ARG 298 A VAL 303 A THR 304 A PHE 305
5282217	Neoxanthin	8.28	852470.8125	A LYS 102 A VAL 104 A ILE 106 A GLN 107 A PRO 108 A GLY 109 A GLN 110 A ASN 151 A ASP 153 A SER 158 A ILE 200 A THR 201 A VAL 202 A ASN 203 A GLU 240 A PRO 241 A THR 243 A HIS 246 A ILE 249 A THR 292 A PRO 293 A PHE 294

CID	Name	Binding energy (kcal/mol)	Dissoc. constant (pM)	Contacting receptor residues
39611	Ritonavir (control drug)	8.217	948110.875	A VAL 104 A ILE 106 A GLY 109 A GLN 110 A THR 111 A ASN 151 A SER 158 A VAL 202 A ASN 203 A ILE 249 A THR 292 A PRO 293 A PHE 294
54671008	Raltegravir (control drug)	7.864	1720329.25	A VAL 104 A ILE 106 A PRO 108 A GLY 109 A GLN 110 A THR 111 A PRO 132 A ASN 151 A ILE 200 A VAL 202 A ASN 203 A GLU 240 A ASP 245 A HIS 246 A ILE 249 A THR 292 A PRO 293 A PHE 294
5280489	beta-carotene	7.853	1752567.125	A PHE 8 A GLN 107 A PRO 108 A GLY 109 A GLN 110 A PRO 132 A ILE 152 A ASP 153 A TYR 154 A VAL 202 A ASN 203 A GLU 240 A PRO 241 A THR 243 A HIS 246 A ILE 249 A THR 292 A PRO 293 A PHE 294 A ARG 298 A VAL 303 A THR 304 A PHE 305
107876	Procyanidin	7.634	2536318.5	A ILE 106 A GLY 109 A GLN 110 A THR 111 A PHE 112 A ASN 151 A VAL 202 A ASN 203 A HIS 246 A ILE 249 A PRO 252 A THR 292 A PRO 293 A PHE 294
5280445	Luteolin	7.328	4251134	A ILE 106 A PRO 108 A GLY 109 A GLN 110 A THR 111 A PHE 112 A ASN 151 A VAL 202 A HIS 246 A ILE 249 A THR 292 A PRO 293 A PHE 294
5280343	Quercetin	7.17	5550349.5	A ILE 106 A PRO 108 A GLY 109 A GLN 110 A THR 111 A PHE 112 A ASN 151 A VAL 202 A HIS 246 A ILE 249 A THR 292 A PRO 293 A PHE 294
5280443	Apigenin	7.144	5799340	A ILE 106 A GLN 110 A THR 111 A ASN 151 A VAL 202 A HIS 246 A ILE 249 A THR 292 A PRO 293 A PHE 294
446925	Lycopene	7.098	6267538.5	A PHE 8 A GLN 107 A PRO 108 A GLY 109 A GLN 110 A PRO 132 A PHE 134 A ASN 151 A ILE 152 A ASP 153 A TYR 154 A VAL 202 A ASN 203 A GLU 240 A HIS 246 A ILE 249 A THR 292 A PRO 293 A PHE 294 A ARG 298 A VAL 303 A THR 304 A PHE 305
443013	Lignans	7.093	6320654.5	A GLN 110 A THR 111 A ASN 151 A ILE 249 A PRO 252 A LEU 253 A THR 292 A PRO 293 A PHE 294 A VAL 297
72276	Epicatechin	7.047	6830940.5	A ILE 106 A GLY 109 A GLN 110 A THR 111 A PHE 112 A ASN 151 A VAL 202 A ASP 245 A HIS 246 A ILE 249 A THR 292 A PRO 293 A PHE 294
689043	Caffeic	6.166	30217746	A ILE 106 A GLN 110 A THR 111 A PHE 112 A ASN 151 A ILE 249 A THR 292 A PRO 293 A PHE 294
445858	Ferulic acid	5.953	43290552	A GLY 109 A GLN 110 A THR 111 A PHE 112 A ASN 151 A VAL 202 A ASN 203 A HIS 246 A ILE 249 A THR 292 A PRO 293 A PHE 294
637540	o-Coumaric	5.865	50222460	A PHE 8 A VAL 104 A ILE 106 A GLN 110 A THR 111 A ASN 151 A SER 158 A CYS 160 A THR 292 A PHE 294
637542	p-Coumaric	5.799	56140548	A GLY 109 A GLN 110 A THR 111 A PHE 112 A ASN 151 A VAL 202 A ILE 249 A THR 292 A PRO 293 A PHE 294
135	4-Hydroxybenzoic	5.501	92835384	A LEU 220 A ASN 221 A ARG 222 A PHE 223 A GLY 258 A ILE 259 A ALA 260 A ASP 263 A ALA 266 A SER 267
72	Protocatechuic	5.359	117977968	A LEU 220 A ASN 221 A ARG 222 A PHE 223 A THR 224 A GLY 258 A ILE 259 A ALA 260 A ASP 263 A SER 267
8468	Vanillic	5.338	122234592	A LEU 220 A ASN 221 A ARG 222 A PHE 223 A THR 224 A GLY 258 A ILE 259 A ALA 260 A ASP 263 A SER 267
370	Gallic	5.298	130771920	A LEU 220 A ASN 221 A ARG 222 A PHE 223 A GLY 258 A ILE 259 A ALA 260 A ASP 263 A MET 264 A ALA 266 A SER 267
10742	Syringic acid	4.934	241729712	A VAL 104 A ILE 106 A GLN 110 A THR 111 A ASN 151 A ASP 153 A SER 158 A THR 292 A PHE 294

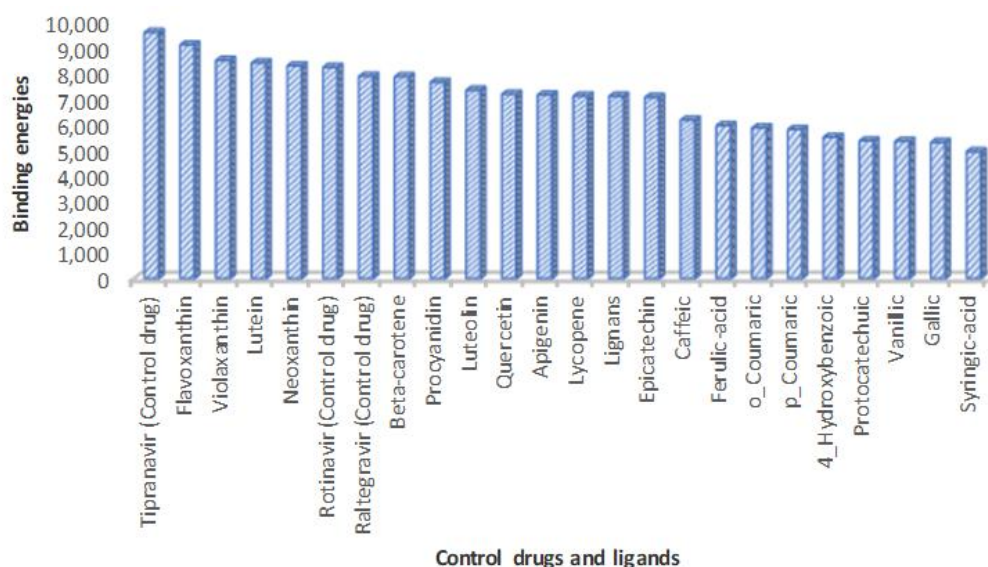


Figure 3. Charts showing the energy binding values of controls and date polyphenols against SARS-CoV-2 Mpro. The docking results show a positive binding energy value in units of kcal/mol in the YASARA structure. The values were sorted from highest to lowest. Tipranavir had the highest binding energy (control drug), and the lowest was syringic acid (ligand).

3.3. Interaction analysis of controls against SARS-CoV-2 Mpro.

We used Discovery Studio Visualizer to visualize and analyze the interaction between polyphenol compounds and controls against SARS-CoV-2 Mpro. The drugs selected as controls are tipranavir, ritonavir, and raltegravir because they are FDA-approved, well-studied antiviral drugs that show strong, stable, and flexible binding results for SARS-CoV-2 Mpro, as reported by Mengist *et al.* [1] and Kumar *et al.* [85]. Tipranavir, as the first control, showed a good docking pose. The analysis results are presented in Figure 4A and Table 4. In the tipranavir-Mpro complex, eight types of interactions were formed, including a Conventional hydrogen bond between A: LYS102: HZ1 as a donor and A: UNK1: O as an acceptor, with a distance of 3.07 Å. The distance in the carbon-hydrogen bond interaction ranges from 2.86 to 2.93 Å, which is less than the distance in the Conventional hydrogen bond. The three carbon-hydrogen bonds are formed due to the interaction of A: ILE106: HA as a donor and A: UNK1: F as an acceptor, A: SER158: HB1 as a donor and A: UNK1: O as an acceptor, and A: THR292: HB as a donor and A: UNK1: O as an acceptor. Thus, in this case, the Conventional hydrogen bond has a greater distance than the carbon-hydrogen bond type, both of which are included in the hydrogen bond category. Three categories of halogens with halogen type (Fluorine) are formed in this complex. These interactions involved A: VAL104: O, A: ARG105: C, and A: GLN110: OE1 as donors and A: UNK1: F as an acceptor, with a distance of 3.04-3.47 Å. There are four types of hydrophobic interactions: π - π stacked, amide- π stacked, alkyl, and π -alkyl. However, we found an unfavorable interaction that would reduce the stability of the tipranavir-Mpro complex, which was formed between A: THR292: OG1 and A: UNK1: O.

Table 4. Interaction analysis of controls and date polyphenols against Mpro. Analysis was done using Discovery Studio Visualizer.

Ligand	Distance (Å)	Category	Types	Donor atom/From	Acceptor atom/To
Tripanavir (Control drug)	3,07252	Hydrogen bond	Conventional hydrogen bond	A: LYS102: HZ1	A: UNK1: O
	2,93924	Hydrogen bond	Carbon hydrogen bond; Halogen (Fluorine)	A: ILE106: HA	A: UNK1: F

Ligand	Distance (Å)	Category	Types	Donor atom/From	Acceptor atom/To
	2,86218	Hydrogen bond	Carbon-hydrogen bond	A: SER158: HB1	A: UNK1: O
	2,90333	Hydrogen bond	Carbon-hydrogen bond	A: THR292: HB	A: UNK1: O
	3,36767	Halogen	Halogen (Fluorine)	A: VAL104: O	A: UNK1: F
	3,47209	Halogen	Halogen (Fluorine)	A: ARG105: C	A: UNK1: F
	3,04649	Halogen	Halogen (Fluorine)	A: GLN110: OE1	A: UNK1: F
	3,86607	Hydrophobic	π - π Stacked	A: PHE294	A: UNK1
	4,13892	Hydrophobic	Amide- π Stacked	A: PRO293: C,O;PHE294: N	A: UNK1
	5,0602	Hydrophobic	Alkyl	A: UNK1: C	A: ILE249
	4,14928	Hydrophobic	Alkyl	A: UNK1: C	A: PRO293
	4,09021	Hydrophobic	Alkyl	A: UNK1: C	A: VAL104
	5,30956	Hydrophobic	Alkyl	A: UNK1: C	A: ILE106
	4,12712	Hydrophobic	π -alkyl	A: UNK1	A: VAL104
	5,13583	Hydrophobic	π -alkyl	A: UNK1	A: VAL297
	2,96239	Unfavorable	Unfavorable acceptor-acceptor	A: THR292: OG1	A: UNK1: O
Flavoxanthin Violaxanthin	3,06498	H-bond	Carbon H-bond	A: UNK1: H	A: ASP153: OD1
	5,18466	Hydrophobic	Alkyl	A: PRO108	A: UNK1
	4,27886	Hydrophobic	Alkyl	A: UNK1: C	A: ARG298
	4,12371	Hydrophobic	Alkyl	A: UNK1: C	A: VAL303
	4,45625	Hydrophobic	Alkyl	A: UNK1: C	A: VAL303
	4,53252	Hydrophobic	Alkyl	A: UNK1: C	A: PRO132
	4,22196	Hydrophobic	Alkyl	A: UNK1: C	A: ILE200
	4,10144	Hydrophobic	π -alkyl	A: HIS246	A: UNK1: C
	5,40883	Hydrophobic	π -alkyl	A: HIS246	A: UNK1: C
	4,08099	Hydrophobic	π -alkyl	A: PHE294	A: UNK1
	4,69011	Hydrophobic	π -alkyl	A: PHE294	A: UNK1: C
	4,75169	Hydrophobic	π -alkyl	A: PHE294	A: UNK1: C
	4,88299	Hydrophobic	π -alkyl	A: PHE294	A: UNK1
	4,70434	Hydrophobic	π -alkyl	A: PHE305	A: UNK1: C
	4,89232	Hydrophobic	π -alkyl	A: PHE305	A: UNK1: C
	2,63505	H-bond	Conventional H-bond	A: TYR154: H	A: UNK1: O
	2,48896	Hydrophobic	π -Sigma	A: UNK1: H	A: PHE294
	4,14275	Hydrophobic	Alkyl	A: UNK1: C	A: PRO108
	4,71784	Hydrophobic	Alkyl	A: UNK1: C	A: ARG298
	4,15391	Hydrophobic	Alkyl	A: UNK1: C	A: VAL303
	4,33801	Hydrophobic	Alkyl	A: UNK1: C	A: PRO293
	4,22506	Hydrophobic	π -alkyl	A: HIS246	A: UNK1
	4,64948	Hydrophobic	π -alkyl	A: HIS246	A: UNK1: C
	4,25102	Hydrophobic	π -alkyl	A: HIS246	A: UNK1: C
	4,91005	Hydrophobic	π -alkyl	A: HIS246	A: UNK1: C
	5,06074	Hydrophobic	π -alkyl	A: PHE294	A: UNK1: C
	5,1473	Hydrophobic	π -alkyl	A: PHE294	A: UNK1: C
	5,05307	Hydrophobic	π -alkyl	A: PHE294	A: UNK1
	4,70152	Hydrophobic	π -alkyl	A: PHE305	A: UNK1: C
Lutein	3,01408	H-bond	Carbon H-bond	A: UNK1: H	A: PRO241: O
	2,51181	Hydrophobic	π -Sigma	A: UNK1: H	A: PHE294
	5,37455	Hydrophobic	Alkyl	A: VAL303	A: UNK1
	3,94814	Hydrophobic	Alkyl	A: UNK1: C	A: PRO108
	4,40788	Hydrophobic	Alkyl	A: UNK1: C	A: ARG298
	4,03328	Hydrophobic	Alkyl	A: UNK1: C	A: VAL303
	4,53951	Hydrophobic	Alkyl	A: UNK1: C	A: VAL303
	4,55049	Hydrophobic	Alkyl	A: UNK1: C	A: PRO293
	4,86318	Hydrophobic	π -alkyl	A: HIS246	A: UNK1
	4,7542	Hydrophobic	π -alkyl	A: HIS246	A: UNK1
	4,73439	Hydrophobic	π -alkyl	A: HIS246	A: UNK1: C
	4,90014	Hydrophobic	π -alkyl	A: PHE294	A: UNK1: C
	4,00978	Hydrophobic	π -alkyl	A: PHE294	A: UNK1
	5,0152	Hydrophobic	π -alkyl	A: PHE294	A: UNK1: C
	4,62244	Hydrophobic	π -alkyl	A: PHE305	A: UNK1: C
Neoxanthin	2,6918	Hydrophobic	π -Sigma	A: UNK1: H	A: PHE294
	5,20644	Hydrophobic	Alkyl	A: VAL104	A: UNK1

Ligand	Distance (Å)	Category	Types	Donor atom/From	Acceptor atom/To
	4,81617	Hydrophobic	Alkyl	A: VAL202	A: UNK1
	4,61154	Hydrophobic	Alkyl	A: UNK1: C	A: ILE249
	3,95935	Hydrophobic	Alkyl	A: UNK1: C	A: PRO293
	4,57029	Hydrophobic	π -alkyl	A: HIS246	A: UNK1: C
	4,94059	Hydrophobic	π -alkyl	A: HIS246	A: UNK1: C
	4,96283	Hydrophobic	π -alkyl	A: HIS246	A: UNK1
	4,42469	Hydrophobic	π -alkyl	A: PHE294	A: UNK1
	4,81391	Hydrophobic	π -alkyl	A: PHE294	A: UNK1: C
Ritonavir (Control drug)	2,75201	Hydrogen Bond	Carbon-hydrogen bond	A: SER158: HB2	A: UNK1: F
	4,51242	Hydrophobic	π - π Stacked	A: UNK1	A: PHE294
	5,29914	Hydrophobic	Alkyl	A: PRO293	A: UNK1
	4,00635	Hydrophobic	π -alkyl	A: PHE294	A: UNK1
	5,49644	Hydrophobic	π -alkyl	A: UNK1	A: ILE106
Raltegravir (Control drug)	2,29336	Hydrogen Bond	Carbon-hydrogen bond	A: GLY109: HA2	A: UNK1: O
	3,62397	Halogen	Halogen (Fluorine)	A: ASN151: CG	A: UNK1: F
	3,35089	Hydrogen Bond	π -donor hydrogen bond	A: GLN110: HE22	A: UNK1
	2,73769	Hydrogen Bond	π -donor hydrogen bond	A: UNK1: H	A: HIS246
	2,82426	Hydrophobic	π -Sigma	A: GLY109: HA2	A: UNK1
	4,48713	Hydrophobic	π - π T-shaped	A: HIS246	A: UNK1
	4,08267	Hydrophobic	Alkyl	A: UNK1: C	A: VAL202
	3,72792	Hydrophobic	Alkyl	A: UNK1: C	A: ILE249
	3,70685	Hydrophobic	Alkyl	A: UNK1: C	A: VAL202
	4,18836	Hydrophobic	Alkyl	A: UNK1: C	A: PRO293
	4,81844	Hydrophobic	Alkyl	A: UNK1: C	A: ILE200
	3,88773	Hydrophobic	π -alkyl	A: HIS246	A: UNK1: C
	5,49775	Hydrophobic	π -alkyl	A: UNK1	A: ILE249

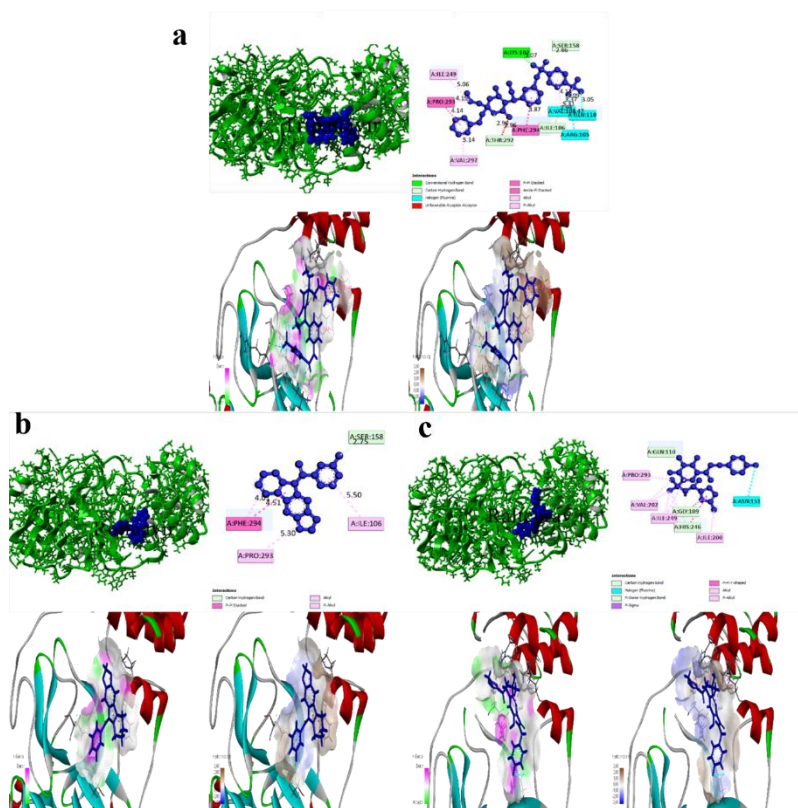


Figure 4. Analysis and Visualization of the docking results of controls against SARS-CoV-2 Mpro. Visualization was done using Discovery Studio Visualizer. Visualization in 2D and 3D. **(A)** Mpro complex against tipranavir; **(B)** Mpro complex against ritonavir; **(C)** Mpro complex against raltegravir.

Ritonavir, as the second control, also showed a good docking pose. The analysis results can be seen in Figure 4B and Table 4. In the ritonavir-Mpro complex, we found only four types of interactions. These included a carbon-hydrogen bond formed by the interaction of A: SER158: HB2 as a donor and A: UNK1: F as an acceptor, a π - π stacked hydrophobic interaction formed by the interaction of A: UNK1 with A: PHE294, an alkyl-type interaction formed by A: PRO293 with A: UNK1, and a π -alkyl interaction formed on two residues, A: ILE106 and A: PHE294.

Raltegravir, as the third control, also showed a good docking pose. The analysis results can be seen in Figure 4C and Table 4. In the raltegravir-Mpro complex, we observed three types of hydrogen bonds, including a carbon-hydrogen bond between A: GLY109: HA2 (donor) and A: UNK1: O (acceptor) with a distance of 2.29 Å, a π -donor hydrogen interaction between A: GLN110: HE22 (donor) and A: UNK1 (acceptor) with a distance of 3.35 Å, and a π -sigma, π - π T-shaped, and alkyl hydrophobic interactions. The distance of the π -donor hydrogen bond was 2.73 Å between A: UNK1: H and A: HIS246. The analysis results can be seen in Figure 3 and Table 4.

3.4. Interaction analysis of date polyphenols against SARS-CoV-2 Mpro.

We analyzed four ligands with binding energies higher than the control. The first ligand, flavoxanthin, had one hydrogen bond and fourteen hydrophobic interactions (Figure 5A), with hydrophobic interactions being the predominant type.

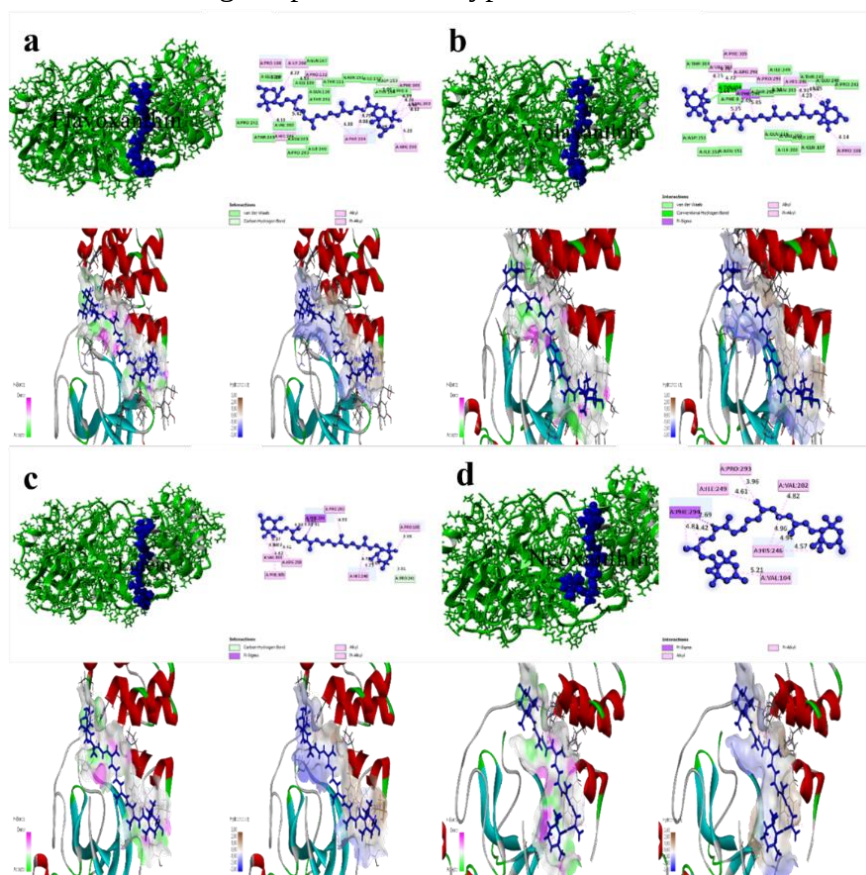


Figure 5. Analysis and visualization of four test ligands against SARS-CoV-2 Mpro. Visualization was done using Discovery Studio Visualizer. Visualization in 2D and 3D. (A) Mpro complex against flavoxanthin; (B) Mpro complex against violaxanthin; (C) Mpro complex against lutein; (D) Mpro complex against neoxanthin.

A: UNK1: H donated a hydrogen bond to A: ASP153: OD1, forming a distance of 3.06 Å. The hydrophobic interactions occur in A: PRO108-A: UNK1 (alkyl), A: UNK1: C-A:

ARG298; A: VAL303; A: PRO132; A: ILE200 (alkyl), A: HIS246-A: UNK1: C (π -alkyl), A: PHE294-A: UNK1; A: UNK1: C (π -alkyl), and A: PHE305-A: UNK1: C (π -alkyl). The distance of hydrophobic interactions in this complex ranged from 4.08 to 5.18 Å. The second ligand, violaxanthin, had a dominant hydrophobic interaction and one hydrogen bond (Figure 5B). A: TYR154: H donated a hydrogen bond to A: UNK1: O, forming a distance of 2.63 Å. The hydrophobic interactions occurred in A: UNK1: H-A: PHE294 (π -sigma), A: UNK1: C-A: PRO108; A: ARG298; A: VAL303; A: PRO293 (alkyl), A: HIS246-A: UNK1; A: UNK1: C (π -alkyl), A: PHE294-A: UNK1: C (π -alkyl), and A: PHE305-A: UNK1: C (π -alkyl). The distance of hydrophobic interactions in this complex ranged from 2.48 to 5.14 Å.

The third ligand, lutein, had a dominant hydrophobic interaction, and one hydrogen bond (Figure 5C) was formed between A: UNK1: H as a donor and A: PRO241: O as an acceptor. The hydrophobic interactions formed in this complex are of the π -sigma, alkyl, and π -alkyl types. The hydrophobic interaction occurs in A: UNK1: H-A: PHE294 (π -sigma), A: VAL303-A: UNK1(alkyl), A: UNK1: C-A: PRO108; A: ARG298; A: VAL303; A: PRO293 (alkyl), A: HIS246-A: UNK1; A: UNK1: C (π -alkyl), A: PHE294-A: UNK1: C; A: UNK1 (π -alkyl), and A: PHE305-A: UNK1: C (π -alkyl). The distance of hydrophobic interactions in this complex ranged from 2.51 to 5.37 Å.

Our present study shows that the fourth ligand, neoxanthin, had only hydrophobic interactions (Figure 5D), and no hydrogen bonds were formed in this complex. However, it is believed that there were π interactions in this complex that significantly contributed to the binding energies of the ligand to the receptor. Chaari *et al.* [31] show that polyphenols are able to bind to proteins to form soluble or insoluble complexes and that the binding strength is positively correlated with the hydrophobicity of polyphenols. Furthermore, in his research, the presence of an aromatic group and one or more hydroxy groups was able to provide inhibition of the hIAAP target protein. The interactions formed were classified as having little contact with Mpro amino acid residues. Details of the hydrophobic interactions in this complex are A: UNK1: H-A: PHE294 (π -sigma), A: VAL104-A: UNK1 (alkyl), A: VAL202-A: UNK1(alkyl), A: UNK1: C-A: ILE249; A: PRO293 (alkyl), A: HIS246-A: UNK1: C; A: UNK1 (π -alkyl), A: PHE294-A: UNK1; A: UNK1: C (π -alkyl). The distance formed ranges from 2.69 to 5.20 Å. The presence of π -alkyl contributes to the binding energies through dispersion forces. Notably, from all of the results here, complexes with a bond-on interaction distance between 2.5 Å and 3.1 Å were considered a strong bond-on interaction [68,85,92,93].

In this study, the test ligands formed hydrogen bonds through hydroxyl groups (O – H) to help stabilize the complex. It should be noted that our analysis of the control tipranavir revealed unfavorable acceptor-acceptor binding at A: THR292: OG1-A: UNK1: O, which could potentially destabilize the complex. This finding emphasizes the need for a new drug candidate to maintain better complex stability and effectively inhibit Mpro. Furthermore, we observed that the π -Sigma type, which belongs to the hydrophobic category, always has a fairly close bond distance. We observed π -Sigma bonds in the Mpro-violaxanthin, Mpro-lutein, and Mpro-neoxanthin complexes. Interestingly, the bond distance in π -Sigma bonds was much closer than the bond spacing formed in hydrogen bonds.

3.5. Molecular dynamics (MD) simulation.

After the molecular docking, we chose the best complexes, which were selected based on the binding energy values, to carry out Molecular dynamics (MD) simulation. The three complexes are Mpro-flavoxanthin, Mpro-violaxanthin, and Mpro-neoxanthin, while the drug

control used is the Mpro-tipranavir complex because it has the highest binding energy. The combination of docking and MD methods can be used to validate docking results, and MD simulation is an excellent computational method to help understand biomolecular structures, particle properties, and their motions and atomic dynamics in macromolecules [69,94–96]. The MD in this study aims to predict and examine the stability of the Mpro-ligand complex. We use several parameters such as root mean square deviation (RMSD), the radius of gyration (Rg), solvent accessible surface area (SASA), and binding free energy calculation.

Molecular dynamics (MD) simulations have been extensively employed in drug discovery studies, as this approach offers dynamic and comprehensive insights into protein–ligand interactions and the atomic-level behavior of biomolecules. As a result, MD simulations have become an essential tool in computational biophysics. It is important to emphasize that MD simulations operate based on the fundamental principles of classical mechanics, applying Newton’s equations of motion to predict the movement of individual atoms within a molecular system. During the simulation process, force fields are utilized to evaluate interatomic interactions, bond flexibility, and angle bending. In the present study, the AMBER force field was employed, as it is specifically optimized for simulating proteins and nucleic acids. The application of this force field aims to provide accurate and reliable parameterization of biomolecular systems. Proper force field parameterization is crucial for achieving precision in MD simulations [97].

Figure 6 shows the results of the RMSD backbone (RMSDBb) in an MD simulation run for 20 ns. As a control drug, Tipranavir produced an RMSD value that continued to increase from 0 to 16.9 ns, reaching 3.025 Å. This value is the highest in this complex. Interestingly, there was a decrease after that, which caused the RMSD value in this complex to be relatively stable up to 20 ns. It can be seen that the flavoxanthin complex and the neoxanthin complex have good stability after 0 to 6 ns; besides that, the two complexes do not touch above the value of 3 Å. For violaxanthin, the complex is not very stable. However, the violaxanthin complex also does not exceed 3 Å. RMSD is used to investigate structural deviations and dynamics of the enzyme-ligand complex over time [66,69,70,98,99]. For the RMSDBb value, the three complexes derived from the test ligands did not exceed 3 Å, and only the drug control complex exceeded 3 Å. The (Tipranavir, flavoxanthin, violaxanthin, neoxanthin) – enzyme complexes had mean values of 2.409, 2.143, 2.226, and 2.094 Å, respectively, and did not show significant deviations. The average values of each complex are 1.936, 2.014, 2.105, and 2.251 Å.

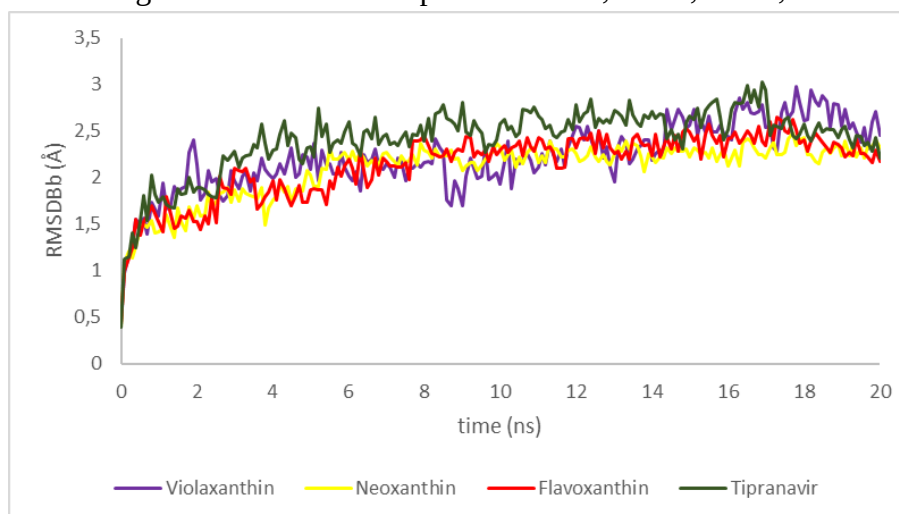


Figure 6. The four violaxanthin (purple), neoxanthin (yellow), flavoxanthin (red), and tipranavir (green) complexes were analyzed using the RMSDBb value with a time of 20 ns during the MD simulation.

Figure 7 shows the RMSD results of C-alpha atoms (RMSDCa) in an MD simulation that was run for 20 ns. We use these parameters to evaluate RMSDCa fluctuations to determine the stability of each enzyme-ligand complex. The results show that tipranavir has poor stability compared to the ligands. Tipranavir produced the highest value at 2,868 Å, while the three test ligands did not produce values higher than this value. The RMSDCa graphs produced in this study's best sequence of enzyme-ligand complexes were neoxanthin, flavoxanthin, violaxanthin, and tipranavir. Overall, the RMSDCa graph does not exceed the value of 2.5 Å; this indicates that there is a slight fluctuation in the C-alpha carbon because an RMSDCa value produced from a high complex is an indicator of low stability [66,69,100]. The RMSD value from the MD simulation was calculated using Yasara using the following equation:

$$\text{RMSD} = \sqrt{\frac{\sum_{i=1}^n R_i^* R_i}{n}} \quad (1)$$

R_i is a vector connecting the positions of I atoms (of N atoms) in the reference snapshot and the current snapshot after the optimal superposition [53,57].

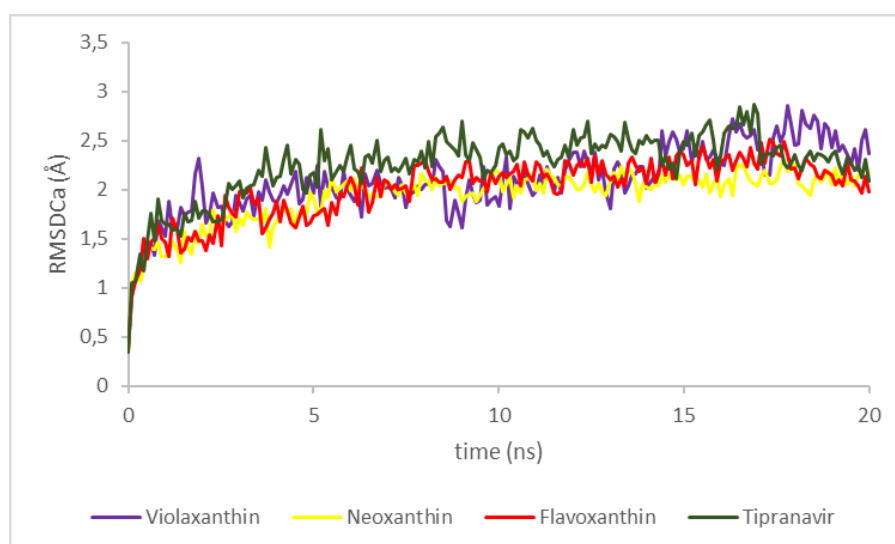


Figure 7. The four violaxanthin (purple), neoxanthin (yellow), flavoxanthin (red), and tipranavir (green) complexes were analyzed using RMSDCa values over a time of 20 ns during the MD simulation.

Figure 8 shows the SASA values. The four Mpro-ligand complexes showed a stable graph between 10 and 15 ns. After 15 ns, the fluctuations of tipranavir increased, and flavoxanthin decreased. However, all four Mpro-ligand complexes stabilized until 20 ns. We performed a complex analysis by looking at the SASA value to examine changes in the Mpro SARS-CoV-2 surface in response to binding with ligands [69,98]. The four complexes of tipranavir, violaxanthin, neoxanthin, and flavoxanthin have an average of 13.984, 13.931, 13.832, and 13.886 Å², respectively. Based on these averages, it is also known that the SASA values of the four complexes do not show many different trends. Figure 6 shows that violaxanthin and neoxanthin have fairly good stability compared to tipranavir and flavoxanthin. Figure 9 shows that during the 20 ns time, the fluctuation of tipranavir reached its highest value at 22.44 Å at 17.6 ns. Violaxanthin showed the highest Rg value at 3.3 ns with a value of 22.35 Å, neoxanthin had the highest Rg value at 2.4 ns with a value of 22.33 Å, and flavoxanthin had the highest Rg value at 0.6 and 15.5 ns with a value of 22.19 Å. The radius of gyration (Rg) is used to evaluate protein motion and stability and to analyze the cohesiveness of the enzyme-

ligand complex. If the Rg value is high, the complex has more unstable properties, but if the Rg value is low, the complex shows firmness [69,98].

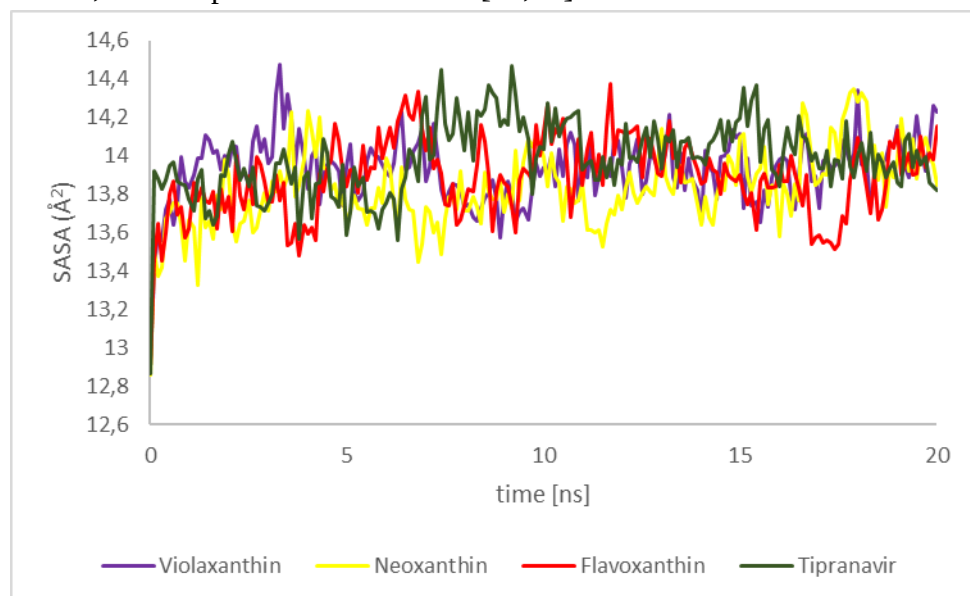


Figure 8. The four violaxanthin (purple), neoxanthin (yellow), flavoxanthin (red), and tipranavir (green) complexes were analyzed using SASA values with a time of 20 ns during the MD simulation.

The average values of the tipranavir, violaxanthin, neoxanthin, and flavoxanthin complexes were 22,075, 22,078, 22,065, and 22,007 Å, respectively. Based on Rg analysis, the flavoxanthin complex showed a better value than the other three complexes. Rg is calculated and plotted using the formula below:

$$Radius_{gyr,Mass} = \sqrt{\frac{\sum_{i=1}^N Mass_i (\vec{R}_i - \vec{C})^2}{\sum_{i=1}^N Mass_i}} \quad (2)$$

In the formula, C is the center of mass, and Ri is the position of the i atom of N.

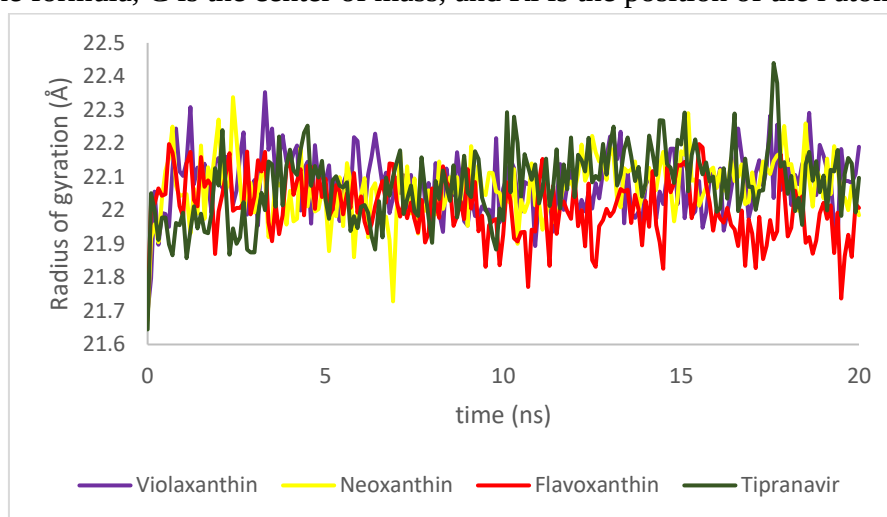


Figure 9. The four violaxanthin (purple), neoxanthin (yellow), flavoxanthin (red), and tipranavir (green) complexes were analyzed using Rg values with a time of 20 ns during the MD simulation.

The simulated trajectory is set for a time of 20 ns. Figure 10 shows the value of the most negative bond-free energy, the violaxanthin complex, with a value of -2589.73 kJ/mol at 2.4 ns. The free binding energies of the four complexes (tipranavir, flavoxanthin, violaxanthin, neoxanthin) were calculated using the BoundaryFast approach [71]. The other three complexes, tipranavir, flavoxanthin, and neoxanthin, showed stable plot trends. The average bond-free

energies of the four complexes were the tipranavir complex with a value of 32.095 kJ/mol, the flavoxanthin complex with a value of 61.946 kJ/mol, the neoxanthin complex with a value of -30.301 kJ/mol, and the violaxanthin complex with a value of -54.3957 kJ/mol. The YASARA macro was used to calculate the binding energy value of BoundaryFast. Complexes with positive values have good binding power [71]. Thus, the flavoxanthin complex has a better binding capacity than the others. The Molecular Mechanics/Poisson–Boltzmann Surface Area (MM-PBSA) method is a computational approach widely utilized in drug design to evaluate the binding strength between drug candidates and their target proteins [39,101].

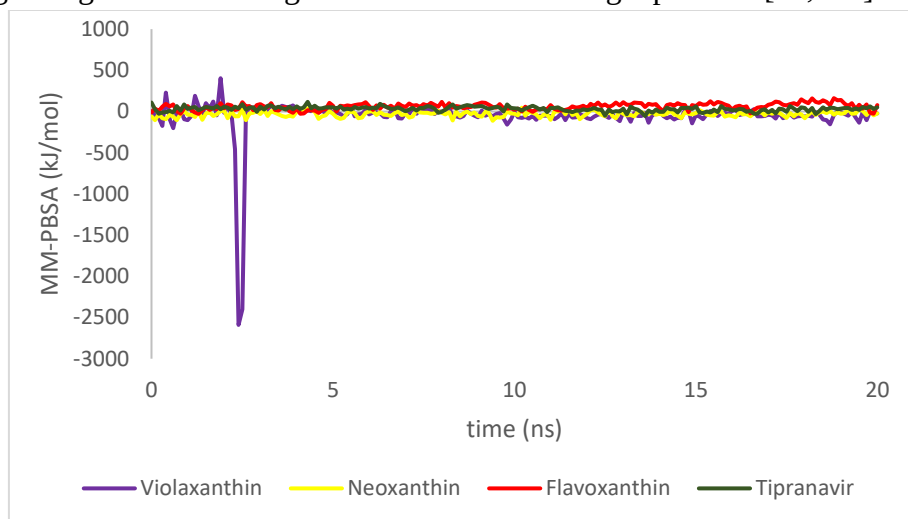


Figure 10. The four violaxanthin (purple), neoxanthin (yellow), flavoxanthin (red), and tipranavir (green) complexes were analyzed using BoundaryFast values with a time of 20 ns during the MD simulation.

3.6. Principal component analysis (PCA) of molecular dynamics (MD) simulation.

This study divides feasibility into PC1, PC2, PC3, PC4, and PC5. PC1 represents 99%, PC2 0.7%, PC3 0.3%, while 0% for PC4 and PC5. Thus, this study showed that the four ligands tethered to Mpro did not significantly change the trajectory compared with the negative control (Apo) or the positive control (tipranavir). In addition, the scores plot value validates the RMSDBb value, where there is no significant difference across all trajectories. The results can be seen in Figure 11A and Figure 11B.

This study uses PCA analysis to examine the structural and energy changes in the Mpro-ligand and apo-protein complexes during the MD simulation. PCA is an unsupervised data reduction method used extensively to describe the variation in the collective energy profile of MD trajectory data, as well as a method that minimizes data complexity and selects the different modes involved in protein motion. This PCA helps analyze any conformational changes during MD that can be categorized by analyzing protein and drug complexes. In addition, PCA can also help in learning the direction and level of movement of the MD trajectory [72,73]. (PCA) has also been applied in studies related to SARS-CoV-2. Wang *et al.* [102] utilized the 3CL protease as the target protein, which had undergone molecular dynamics (MD) simulations. They employed MD trajectories from 120 ns to 300 ns to perform PCA on both the unbound 3CL protease and the Nirmatrelvir-bound 3CL protease complex. PCA enabled the reduction of dimensionality in high-dimensional datasets, facilitated the identification of clusters, and provided insight into significant collective motions within the protein molecule [103].

Principal Component Analysis (PCA) was applied to the molecular dynamics trajectories to identify the dominant modes of molecular motion. This analysis yields eigenvector matrices and their corresponding eigenvalues, which together describe the

amplitude and direction of the principal internal motions within the protein. Conformationally more stable complexes typically occupy a more restricted phase space and form more compact clusters in two-dimensional projections (PC1 vs. PC2). In contrast, less stable complexes tend to exhibit broader conformational distributions and less densely packed clusters [104–106]. The biological interpretation of these findings is highly relevant to antiviral potential. A more stable inhibitor–protease (Mpro) complex—characterized by a confined phase space and dampened collective motions—suggests that the inhibitor effectively “locks” the enzyme conformation. This restriction may hinder the intrinsic flexibility required by Mpro for substrate binding or catalytic conformational transitions. Consequently, higher conformational stability of the ligand-bound complex may directly correlate with improved inhibitory potency by reducing the likelihood of the enzyme reverting to its active state. In this context, inhibitors that produce the most compact and concentrated PCA clusters, particularly those overlapping with or closely approaching the apo-Mpro conformational space, may be considered the most promising candidates due to their ability to stabilize less active or catalytically unproductive conformations.

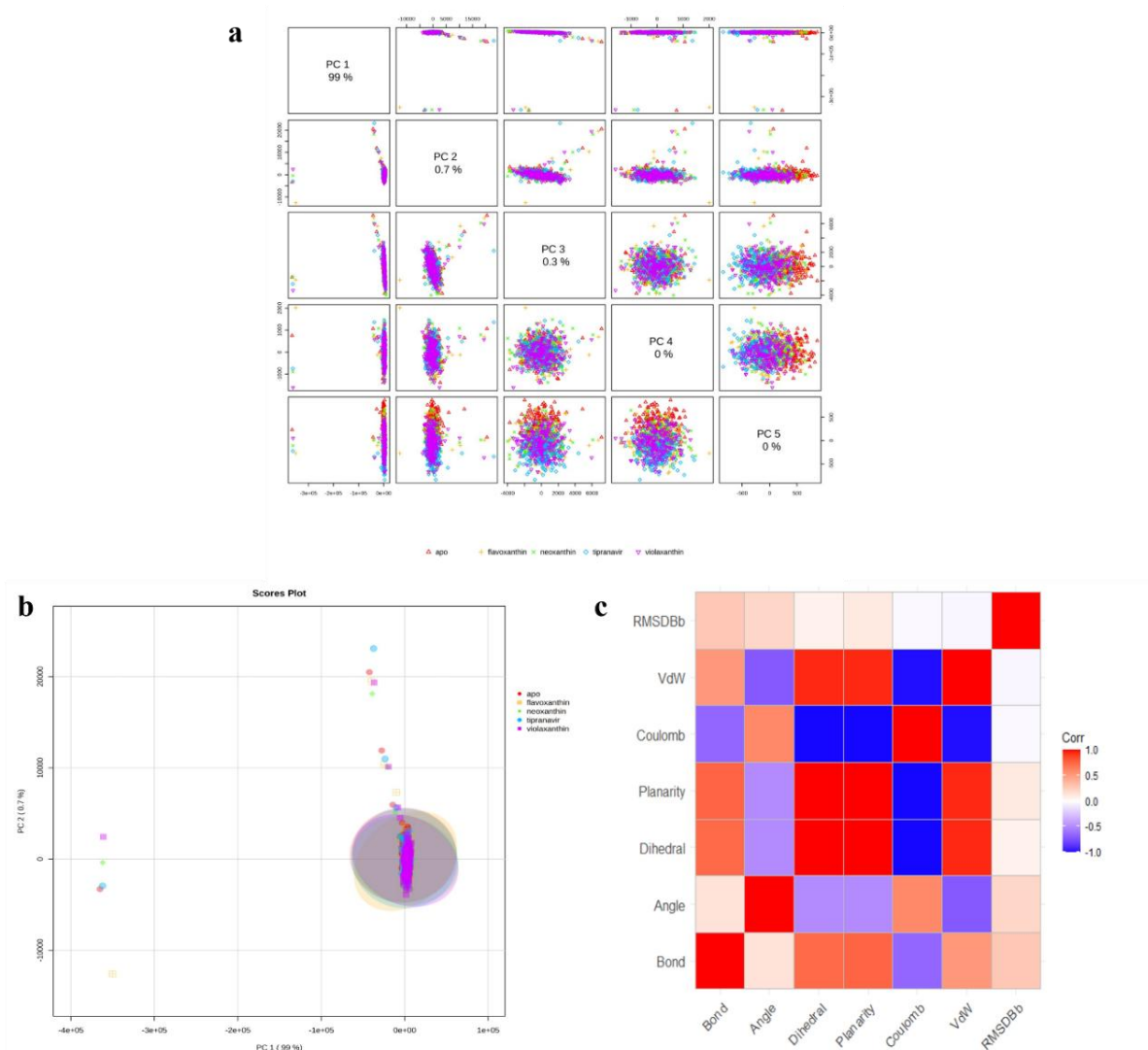


Figure 11. PCA analysis on MD. (A) PC eligibility results; (B) Plot score results; (C) Correlation results. The variables analyzed include bond, angle, dihedral, planarity, Coulomb, and van der Waals.

Figure 11C shows the correlation results for the variables analyzed, namely bond, angle, dihedral, planarity, Coulomb, van der Waals (VdW), and RMSD backbone of the four complexes, namely Mpro-violaxanthin, Mpro-neoxanthin, Mpro-flavoxanthin, and Mpro-

tipranavir that MD has simulated. Positive correlation values from 0.1 to 1.0 are colored red. It is known that planarity has a very high positive correlation with the dihedral and van der Wall; the dihedral also has a high correlation with the van der Wall. A negative correlation with values of -0.1 to -1.0 is colored blue. It is known that the Coulomb has a very negative correlation with van der Wall, dihedral, and planarity.

3.7. ADMET analysis.

The results are presented in Table 5. The human intestinal absorption prediction results show that all ligands can be categorized as ligands that can be absorbed well through the human intestine. This is because there is no value with a percentage below 30%. For the blood-brain barrier (BBB), if the logBB value is > 0.3 , it is predicted that it will cross the blood-brain barrier easily, whereas for values < -1 , it is predicted to have a poor distribution to the brain. The oral rat acute toxicity parameter indicates the toxicity level of the compounds. CYP3A4 was chosen due to 3A4 being one of the main isoforms responsible for drug metabolism. The last parameter was hepatotoxicity, to find out whether a compound has the possibility of interfering with normal liver function.

Various software tools have been developed to assist the drug development process in predicting bioactive molecules' pharmacokinetic and physicochemical characteristics [78,107,108]. All matters related to pharmacokinetics (ADMET), pharmacodynamics, and physicochemical properties relate to the effectiveness of phytoconstituents, which are included in the process of new drug discovery. The study of mechanisms that require the movement of molecules to various physiological compartments, and how new drug candidates function/affect when utilized. The bioavailability of phytoconstituents to target cells and their absorption and metabolism in the human body are important factors in enhancing bioactivity. Therefore, poor and toxic phytoconstituents must be removed during the drug discovery process, because natural molecules must be therapeutically active and have relevant pharmacokinetic properties. The application of ADME-based approaches has served as a key method in accelerating drug discovery efforts against SARS-CoV-2. For instance, in a study conducted by Geedkar *et al.* [109], their computational predictions indicated that the synthesized azo-anchored 3,4-dihydroimidazo[4,5-b]indole derivatives 5(a–r) demonstrated zero violations of Lipinski's rule and exhibited favorable pharmacokinetic property predictions.

With numerous phytocompounds available for exploration, computer technology simulations provide a viable alternative to animal experiments, and *in silico* predictions can minimize the costs and time associated with *in vivo* experiments [76,78,110].

Table 5. ADMET results from the pkCSM webpage. All data, polyphenols, and controls were analyzed for ADMET properties.

Ligands	HIA	BBB	Oral rat acute toxicity (LD ₅₀) (mol/kg)	CYP3A4 substrate (categorical)	CYP3A4 inhibitor (categorical)	Hepatotoxicity (categorical)
Flavoxanthin	90.466	-0.082	2.222	Yes	No	No
Violaxanthin	90.257	-0.175	2.259	Yes	No	No
Lutein	89.781	-0.215	3.491	Yes	No	No
Neoxanthin	91.585	-0.581	2.32	Yes	No	No
Beta carotene	90.393	0.92	2.134	Yes	No	No
Procyanidin	55.527	-1.783	2.482	No	No	No
Luteolin	81.13	-0.907	2.455	No	No	No
Quercetin	77.207	-1.098	2.471	No	No	No
Apigenin	93.25	-0.734	2.45	No	No	No

Ligands	HIA	BBB	Oral rat acute toxicity (LD ₅₀) (mol/kg)	CYP3A4 substrate (categorical)	CYP3A4 inhibitor (categorical)	Hepatotoxicity (categorical)
Lycopene	89.02	1.024	2.224	Yes	No	No
Lignans	96.109	-0.861	2.216	Yes	No	No
Epicatechin	68.829	-1.054	2.428	No	No	No
Caffeic	69.407	-0.647	2.383	No	No	No
Ferulic acid	93.685	-0.239	2.282	No	No	No
o-Coumaric	93.494	-0.225	2.192	No	No	No
p-Coumaric	93.494	-0.225	2.155	No	No	No
4-Hydroxybenzoic	83.961	-0.334	2.255	No	No	No
Protocatechuic	71.174	-0.683	2.423	No	No	No
Vanillic	78.152	-0.38	2.454	No	No	No
Gallic	43.374	-1.102	2.218	No	No	No
Syringic acid	73.076	-0.191	2.157	No	No	No

3.8. QSAR analysis and drug-likeness analysis.

We analyzed each test ligand to determine its drug-likeness and potential activity as an antiviral. Table 6 shows the results of the prediction analysis of the Lipinski rules of five. The results of the QSAR analysis can be seen in Figure 12.

From the results of the drug-likeness analysis of the twenty-one compounds used in the Mpro SARS-CoV-2 docking study, it turns out that three compounds do not comply with the Lipinski rule of five. These three compounds include beta-carotene, procyanidin, and lycopene. All three compounds show a molecular weight of over 500 Daltons. The molecular weight is expected to be under 500 Daltons because a molecule with a low molecular weight will be easily absorbed, so the compound is easily transported and dispersed, compared to a compound with a high molecular weight. Much literature has explained that if a molecule violates the Lipinski rule of five, it is likely to have problems with bioavailability and its ability to display drug-like properties [81,83]. In addition, a compound that follows the Lipinski rule of five is predicted to be considered a drug-like molecule and is expected to trigger a response of biological activity when it interacts with target proteins in the cytoplasm [111]. The results from the PASS web server show that it can be predicted that the compounds tested in this simulation have a chance of being antivirals. These results refer to the Pa (potential activity) score of each compound. A Pa value greater than 0.3 is categorized as capable of activity as an antiviral [83,111].

Structure-based drug design plays a vital role in novel drug development [93]. The relationship between the receptor and the ligand plays an important role in drug formulation. Some drugs are isolated from natural products based on bioactivity-guided fractionation. Natural products have helped cure various diseases suffered by humans [26,112,113]. We used molecular docking as an early prediction because protein-ligand docking is an essential tool for computational drug design and has been widely used in pharmaceutical companies. This method was chosen to help predict the position and orientation of the ligand when it binds to the target receptor. Currently, there are many applications available to perform molecular docking. This method has various purposes in pharmaceutical research, but most are used to help filter the vast virtual database of available chemicals for drug candidate development [114]. Here, Mpro has been analyzed as our target for inhibiting SARS-CoV-2 using data on polyphenolic compounds through the molecular docking method with the aid of the YASARA structure. We explained several crucial parameters in the molecular docking method to understand the interactions formed.

Table 6. Results from the PubChem (SMILES) and SCFBIO (Lipinski) web servers.

Compounds	CID	Canonical SMILES	Lipinski rule of five					Passed?
			MW (<500 Dalton)	LOGP (<5)	HBA (<5)	HBD (<10)	MR (40-130)	
Flavoxanthin	5281238	<chem>CC1=CC(CC(C1C=CC(=CC=CC(=CC=CC=C(C)C=CC=C(C)C2C=C3C(CC(CC3(O2)C)O)(C)C)C)C)C)O</chem>	312	-0.053	6	5	77.145	Yes
Violaxanthin	448438	<chem>CC(=CC=CC=C(C)C=CC=C(C)C=CC12C(CC(CC1(O2)C)O)(C)C)C=CC=C(C)C=CC34C(CC(CC3(O4)C)O)(C)C</chem>	312	-0.053	6	5	77.145	Yes
Lutein	528124	<chem>CC1=C(C(CC(C1)O)(C)C)C=CC(=CC=CC(=CC=CC=C(C)C=CC=C(C)C=CC2C(=CC(CC2(C)C)O)C)C)C</chem>	568	10.403	2	2	184.101	No
Neoxanthin	5282217	<chem>CC(=CC=CC=C(C)C=CC=C(C)C=C=C1C(CC(CC1(C)O)O)(C)C)C=CC=C(C)C=CC23C(CC(CC2(O3)C)O)(C)C</chem>	312	-0.053	6	5	77.145	Yes
beta-carotene	5280489	<chem>CC1=C(C(CCC1)(C)C)C=CC(=CC=CC(=CC=CC=C(C)C=CC=C(C)C=CC2=C(CCCC2(C)C)C)C)C</chem>	536	12.605	0	0	181.392	No
Procyanidin	107876	<chem>C1C(C(OC2=CC(=CC(=C21)O)O)C3=CC(=C(C=C3)O)O)OC4(C(C(C5=C(C=C(C=C5O4)O)O)O)O)C6=C(C(=C(C=C6)O)O)O</chem>	594	2.732	13	10	144.305	No
Luteolin	5280445	<chem>C1=CC(=C(C=C1C2=CC(=O)C3=C(C=C(C=C3O2)O)O)O)O</chem>	286	2.125	6	4	72.478	Yes
Quercetin	5280343	<chem>C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O)O</chem>	302	2.01	7	5	74.05	Yes
Apigenin	5280443	<chem>C1=CC(=CC=C1C2=CC(=O)C3=C(C=C(C=C3O2)O)O)O</chem>	270	2.419	5	3	70.813	Yes
Lycopene	446925	<chem>CC(=CCCC(=CC=CC(=CC=CC(=CC=CC=C(C)C=CC=C(C)C=CC=C(C)CCC=C(C)C)C)C)C</chem>	536	10.073	0	0	186.486	No
Lignans	443013	<chem>COC1=CC(=CC(=C1OC)OC)C2C3C(COC3=O)C(C4=CC5=C(C=C24)OCOC5)O</chem>	414	2.176	8	1	102.471	Yes
Epicatechin	72276	<chem>C1C(C(OC2=CC(=CC(=C21)O)O)C3=CC(=C(C=C3)O)O)O</chem>	290	1.546	6	5	72.622	Yes
Caffeic acid	689043	<chem>C1=CC(=C(C=C1C=CC(=O)O)O)O</chem>	180	1.195	4	3	46.441	Yes
Ferulic acid	445858	<chem>COC1=C(C=CC(=C1)C=CC(=O)O)O</chem>	194	1.498	4	2	51.328	Yes
o-Coumaric	637540	<chem>C1=CC=C(C(=C1)C=CC(=O)O)O</chem>	164	1.49	3	2	44.776	Yes
p-Coumaric	637542	<chem>C1=CC(=CC=C1C=CC(=O)O)O</chem>	164	1.49	3	2	44.776	Yes
4-Hydroxybenzoic acid	135	<chem>C1=CC(=CC=C1C(=O)O)O</chem>	138	1.09	3	2	35.066	Yes
Protocatechuic	72	<chem>C1=CC(=C(C=C1C(=O)O)O)O</chem>	154	0.796	4	3	36.730	Yes
Vanillic acid	8468	<chem>COC1=C(C=CC(=C1)C(=O)O)O</chem>	168	1.099	4	2	41.618	Yes
Gallic acid	370	<chem>C1=C(C=C(C(=C1O)O)O)C(=O)O</chem>	170	0.501	5	4	38.395	Yes
Syringic acid	10742	<chem>COC1=CC(=CC(=C1O)OC)C(=O)O</chem>	198	1.107	5	2	48.17	Yes

Mpro-ligand interactions occur due to recognition of specific molecules at the atomic level; at this level, a docking algorithm can be used to assist [31]. Our analysis revealed that date polyphenols can inhibit Mpro, which inhibits viral replication and transcription [115].

Collectively, previous studies reinforce the potential of *Phoenix dactylifera* (date palm) as a rich source of bioactive compounds with broad biological activities. Experimental evidence has demonstrated that date extracts exhibit direct antiviral activity against bacteriophages through virus-binding mechanisms, as well as the capacity to promote tissue repair via progenitor cell mobilization. In parallel, *in silico* studies have mapped specific phytochemicals in dates—such as coumestrol, pinoresinol, and isofucosterol—that are computationally predicted to exhibit strong binding affinities toward viral targets (e.g., proteases or envelope proteins) and vectors (e.g., proteins in *Aedes aegypti* mosquitoes).

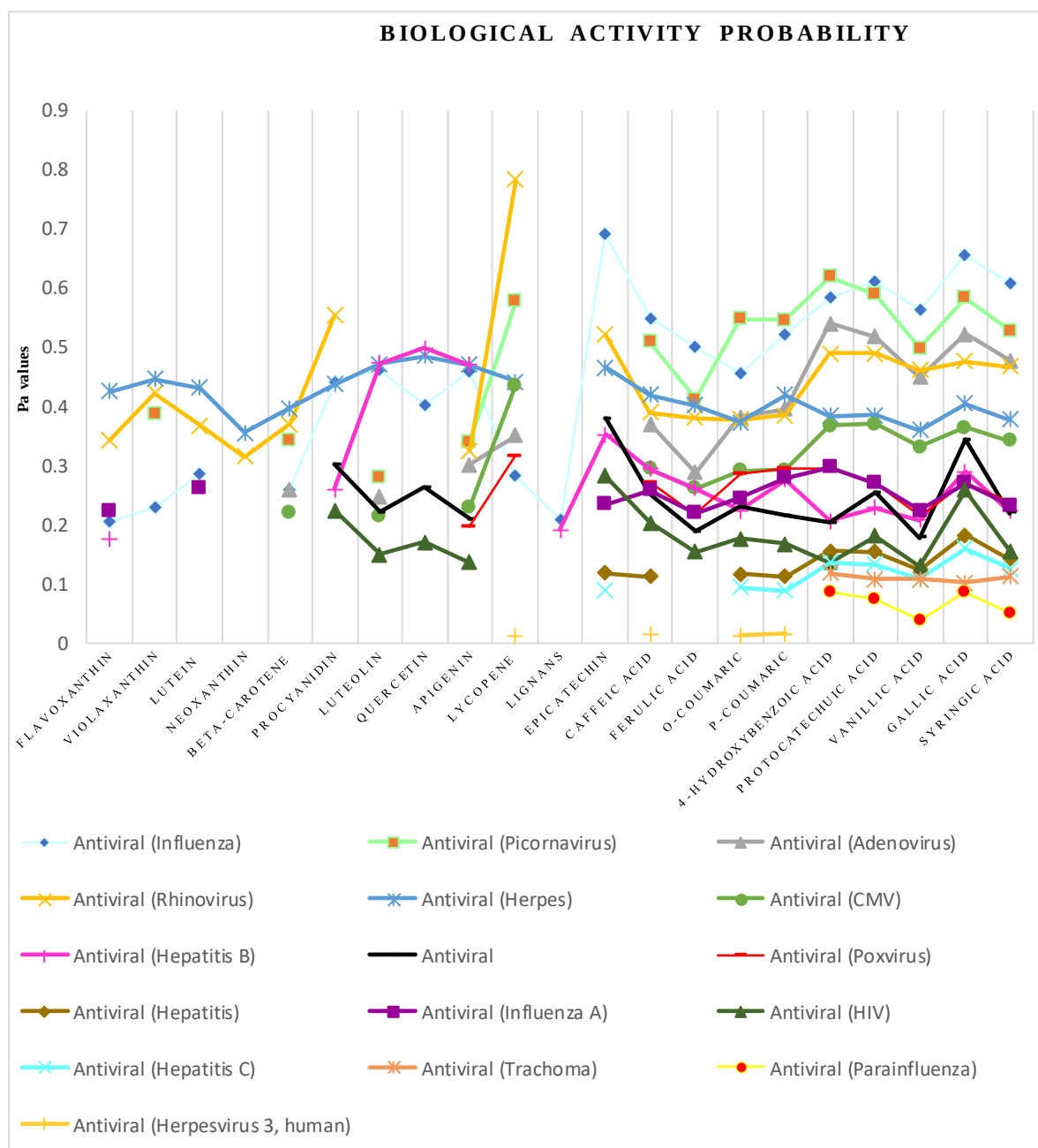


Figure 12. Results from the PASS web server.

Accordingly, the computational findings of the present study, which identify date-derived polyphenolic compounds as potential inhibitors of the SARS-CoV-2 protease, do not stand in isolation but rather form part of a broader scientific narrative supporting the promise of dates as a source of antiviral and regenerative compounds [116–118].

4. Conclusions

Flavoxanthin, neoxanthin, and violaxanthin are predicted to provide interactions and energy in inhibiting the main protease. The results of the three ligands, especially the best flavoxanthin among the three, are predicted to form good stability in terms of RMSDBb, RMSDCa, SASA, radius of gyration, and BoundaryFast. They are not toxic to the body. The three ligands tethered to Mpro did not change the trajectory significantly. Therefore, our study suggests that flavoxanthin can be developed as a promising drug candidate for the SARS-CoV-2 main protease inhibitor. This study has a limitation related to the relatively short simulation timescale of 20 ns, which may be insufficient for accurately capturing thermodynamic properties or for fully sampling all binding-pocket configurations relevant to the conformational states of the protein during molecular dynamics simulations. However, to validate its potential, further investigations using *in vitro* and *in vivo* studies are necessary in addition to this *in silico* analysis.

Author Contributions

Conceptualization, G.M.G., F.R.M., R.A.P.I. and I.M.A.; methodology, G.M.G., F.R.M. and R.A.P.I.; software, G.M.G., F.R.M., R.A.P.I. and I.M.A.; validation, G.M.G., F.R.M., R.A.P.I., I.A.F., O.R., I.P., J.E.S. and I.M.A.; formal analysis, G.M.G., F.R.M., R.A.P.I., I.A.F., O.R., I.P., J.E.S. and I.M.A.; investigation, G.M.G., F.R.M. and R.A.P.I.; resources, G.M.G., R.A.P.I. and I.M.A.; data curation, G.M.G. and R.A.P.I.; writing—original draft preparation, G.M.G. and R.A.P.I.; writing—review and editing, G.M.G., F.R.M., R.A.P.I., I.A.F., O.R., I.P., J.E.S. and I.M.A.; visualization, G.M.G., F.R.M. and R.A.P.I.; supervision, I.M.A. All authors have read and agreed to the published version of the manuscript.

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All research data have been presented in this research paper.

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Conflicts of Interest

The authors declare no conflict of interest.

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