International Journal of Public Health Science (IJPHS)
Vol. 13, No. 3, September 2024, pp. 1019~1029
ISSN: 2252-8806, DOI: 10.11591/ijphs.v13i3.23822

Interactions and mechanisms of phenolic compounds with human immunodeficiency virus-1 Tat protein

Cherry May S. Delos Santos[1], June Alexis A. Santos[2], Danilet Vi M. Mendoza[3]
[1]College of Arts and Sciences, Nueva Ecija University of Science and Technology, Cabanatuan City, Philippines
[2]Department of Environment and Natural Resources, Mines and Geosciences Bureau-Region III, San Fernando City, Philippines
[3]Department of Natural and Applied Sciences, College of Arts and Sciences, Nueva Ecija University of Science and Technology, Cabanatuan City, Philippines

Article Info

Article history:

Received Aug 23, 2023
Revised Jan 2, 2024
Accepted Jan 9, 2024

Keywords:

HIV-1
In silico
Molecular docking
Phenolic compounds
Tat protein

ABSTRACT

Human immunodeficiency virus remains a serious health threat, with an increase of 24% newly cases globally. Targeting Tat protein is an emerging therapeutic strategy for inhibiting the feedback loop that drives the exponential increase in viral transcription and particle production of the virus. The study aimed to determine the inhibitory potential of phenolic compounds from *Ricinus communis* L. and *Jatropha curcas* L., against the Tat C protein using in silico techniques. Phenolic compounds identified from both plants were screened by absorption-distribution-metabolism-excretion (ADME) analysis using drug-likeness prediction. Molecular docking analysis of the compounds with drug-like properties against the receptor and ligand-protein complexes' analysis and visualization were performed. The results revealed three phenolic compounds with the highest negative binding affinity to the receptor's active site: ellagic and neochlorogenic acids with -7.2 kcal/mol and isohemiphloin with -7.3 kcal/mol. The interacting amino acids of the complexes were majorly His13, Lys19, Lys28, Thr64, His65, Gln66, Pro70, Gln72, and Pro73 via non-covalent interactions: hydrogen bonds, hydrophobic, and electrostatic interactions. The identified phenolic compounds provide a core structure that can be candidate for plant-based antiviral drugs development to potentially aiding in the virus's therapeutic challenge.

Corresponding Author:

Danilet Vi M. Mendoza
Department of Natural and Applied Sciences, College of Arts and Sciences
Nueva Ecija University of Science and Technology
Cabanatuan City, Nueva Ecija, Philippines
Email: niletmendoza@yahoo.com

1. INTRODUCTION

The human immunodeficiency virus (HIV) remains a major public health concern, with 84.2 million people infected since the epidemic's inception and approximately 38.4 million people worldwide living with HIV in 2021 with an increase of 24% relative to 2010. According to the World Health Organization (WHO), the African region remains the most severely affected with the highest number of HIV-infected people, approximately 25.6 million; and in the Asia and Pacific Region, the Philippines has the fastest-growing case with a 237% increase in annual new HIV infections from 2010 to 2021. The Department of Health of the Philippines recorded 14, 970 cases of HIV infection in 2022, which is 21% higher than the previous year, and stated that the number of HIV diagnoses in the country fluctuated over the past seven years. This continuous increase in HIV cases necessitates a more aggressive response and increased focus on HIV/AIDS.

The human immunodeficiency virus is a retrovirus that attacks immune cells, primarily the CD4+ T cells, which are the helper cells that initiates the body's response to infection and diseases. HIV structure is similar to the simple retrovirus with a small number of differences: i) the HIV capsid is cone-shaped and is an elongated deviation of a spherical icosahedral capsid, which is unique among animal viruses, and ii) accessory proteins, such as Vpr, are enclosed inside the nucleocapsid. The genome of HIV provirus (proviral deoxyribonucleic acid (DNA)) consists of thousands of nucleotides and is produced through reverse transcription of the viral RNA genome into DNA, ribonucleic acid (RNA) degradation, and integration of the double-stranded HIV DNA into the human genome. The DNA genome is flanked at both ends by long terminal repeat (LTR) sequences, encoding the different structural proteins. In addition to structural proteins, the sub-genomic RNAs: singly spliced RNA and double spliced RNA encodes six accessory proteins, two of which are required for the initiation of HIV replication: transactivator protein (Tat) and RNA splicing-regulator (Rev), while the other proteins influence viral replication, virus budding, and pathogenesis [1]–[5].

Antiretroviral therapy (ART) is the most significant advancement in the medical management of infection [6]. With ART, it is expected to reduce HIV transmission by decreasing the concentration of the virus in the blood and genital secretions of the person with HIV infection [7], and is possible to extend the phase without or with only slight symptoms for years. However, it is a life-long treatment, and drugs with a new mode of action are required due to the failure of permanently eradicating the virus, issues such as drug resistance, adverse side effects contributing to ART failure, and the fact that there is still no cure for HIV infection. New drugs and novel targets are required to overcome HIV, with an ideal drug candidate being able to inhibit viral production from integrated viral genomes and permanently silence HIV transcription [8]–[11].

Most current antiviral medications are based on the inhibition of viral protein activity, which can lead to drug resistance through mutation of these protein targets. Targeting alternative splicing pathways can avoid this problem in two ways: i) many of the targets in this pathway are host cellular proteins that are less prone to mutation due to rapid replication, and ii) it would be more difficult for the virus to adapt to these compounds because changes in the splicing sequences would result in the virus failing to complete the transcription of all the mRNAs that are required to be replicated. Tat is a regulatory protein that facilitates viral transcription and modulates cellular structures, particularly the nucleus [12], [13]. Given Tat's importance in viral gene expression and its role in latency maintenance or reactivation, the search for Tat inhibitors has been a focus of recent research. However, small molecules that inhibit Tat, either by direct interaction, by its degradation, or by structurally modifying it, are limited. Direct inhibition of Tat blocks the feedback loop that drives an exponential increase in viral transcription and particle production. It has also been suggested that blocking Tat activity might help block viral reactivation and maintain the virus in a state of prolonged silencing. Although the dependence of HIV transcription on Tat has made it an attractive drug target, no approved Tat inhibitor therapeutics are currently available in the clinic [14]. Since new drugs will be needed for the management of HIV, the WHO has suggested that ethnomedicines and other natural products should be systematically evaluated against HIV as they may yield effective and more affordable therapeutic agents.

Ricinus communis L., commonly known as castor plant, is native to Africa and Asia, which is commonly known as "tangan-tangan" in the Philippines and is often abundant along watercourses and floodplains, distributed or wasteland, and roadside areas, which may be common after heavy rains or floods. *R. communis* extracts possess significant pharmacological activities, including anti-fungal and antimicrobial, antioxidant, anticancer, hepatoprotective, antidiabetic, wound healing and bone regenerative properties, and antiviral [15], [16]. Its antiviral activity has been attributed to the plants' rich phenolic compounds, flavonoids, and alkaloid contents [17]. Similarly, *Jatropha curcas* L., a member of the Euphorbiaceae family has been used in Asia for the treatment of a wide spectrum of ailments related to skin, cancer, digestive, respiratory, and infectious diseases. Previous studies revealed that the spectrophotometric determination of leaf extracts of *J. curcas* showed higher total phenolic content (TPC) and total flavonoid content (TFC) and concluded to possess significantly higher total phenolic compounds [18]. Various studies found that *J. curcas* was being used for the treatment of HIV-related conditions such as skin rash and oral candidiasis and was found to possess anti-HIV activities by inhibiting HIV-1 cell entry. However, there is an extremely limited number of previous reports on the specific anti-HIV activity of *J. curcas* [19]. With this background, the current study was designed to evaluate the potential antiviral activity of the phenolic compounds from *J. curcas* leaves against the Tat C protein.

The study aimed to determine the inhibitory potential of phenolic compounds from the leaves of the medicinal plants, *Ricinus communis* L. and *Jatropha curcas* L., against the HIV-1 subtype C Tat protein using in silico techniques. Specifically it aimed: i) to screen the phenolic compounds from *R. communis* and *J. curcas* leaves through ADME analysis using drug-likeness prediction; and ii) to visualize and analyze the ligand-protein complexes by utilizing computational software, specifically: binding affinity (kcal/mol); interacting sites; and intermolecular forces of attraction of the complexes.

2. METHOD

2.1. Ethical consideration

There is no ethical clearance sought for the study since the study involved in silico analysis and no biological samples were extracted and obtained. The study purely used computers and softwares and no living organism was involved. Thus, no ethical clearance number was obtained.

2.2. Selection and retrieval of ligands and protein

Phytochemical constituents, primarily the phenolic compounds present in *R. communis* and *J. curcas* leaves were selected using previous literature studies [20]–[22] and were retrieved from the PubChem database (htttps://pubchem.ncbi.nlm.nih.gov) in structure data format (.sdf) and converted to molecular structure format (.mol2) using the UCSF chimera. It is an extensive molecular modeling system developed by the University of California, San Francisco. Other compounds that were not available on the database were drawn with ChemSketch software and saved into .sk2 and .mol file format for the compounds' two- and three-dimensional structures, respectively. Protein models from previous studies were stored in Protein Data Bank (PDB) and were given specific PDB identification number to be utilized by future researchers. The receptor, HIV-1 subtype C Tat proteins' PDB Identification was identified from recent literature and was retrieved from the RCSB protein data bank (htttps://www.rcsb.org) in PDB file format using the identified PDB ID: 1TBC [23].

2.3. Absorption-distribution-metabolism-excretion ADME analysis

The identified phenolic compounds were screened and filtered by absorption-distribution-metabolism-excretion (ADME) analysis using drug-likeness prediction in the SwissADME and ADMETlab 2.0 web tools, by following and giving distinct emphasis to its violation in Lipinski's rule of five (RO5) [24]. Lipinski's rule of five was applied in the study to determine a potential drug candidate and filter those chemical compounds that are not likely to be leads or drugs. A violation of any two of these four parameters characterized the chemical compound as an undesirable drug candidate. In order to use the compounds in the softwares, simplified molecular input line entry system (SMILES) were obtained. SMILES are chemical notations that serve as representation of the chemical structure of compounds that can be processed by computers. The canonical SMILES of the compounds obtained from the PubChem database and the .sk2 file of the unregistered compound were used as an input in SwissADME and ADMETlab web tool as each SMILES strings uniquely identify a single molecule structure to analyze and screened the ligands.

2.4. Ligands and protein preparation

After screening or filtration, the three-dimensional structures of the ligands that exhibited drug-like properties were directly downloaded from the PubChem database and stored in a .sdf file and were opened in the UCSF chimera to facilitate ligand optimization by the performed structure minimization and dock prep under the structure editing tools for the preparation of ligands. Default parameters of the UCSF chimera were used except for the steepest descent steps and size (unit Angstrom, Å), which was adjusted to 150 and 0.03 Å, respectively in the minimization structure process. Files for the minimized and dock- prepped ligands were saved in .pdb and .mol2 file format, respectively, and were equipped for molecular docking. Whereas, the retrieved Tat protein was obtained in nuclear magnetic resonance (NMR) structure with ten (10) conformers and was prepared using the UCSF chimera software by the performed structure comparison utilizing the match → align tool with its default parameters to analyze the 10 conformers, followed by the removal of nine out of the 10 NMR structures to obtained one model three-dimensional structure (1 tbc (#0.1)) and thereafter saved into .pdb format for ligand-protein docking.

2.5. Active site prediction

A small region or cleft where the ligand molecule can bind to the receptor protein and produce the preferred outcome is termed an active site or catalytic site. The binding site of the target protein was determined using the PrankWeb tool (https://prankweb.cz/), utilizing the PDB ID (1TBC). The result was downloaded to analyze the produced output in a comma separated values (CSV) file which contains an ordered list of pockets and their scores. The result showed seven pockets arranged in descending order from high to low predicted ligandability and probability score. From these results, pocket 1 showed both a high ligandability and probability value of 13.1 and 0.695, respectively, as compared with other pockets, therefore, the predicted centers and active sites of pocket 1 were used for the molecular docking process, which served as the ligand binding site of the receptor.

2.6. Molecular docking

Molecular docking was performed to evaluate the binding affinity and to provide ligand-protein complexes for analysis. The docking process was carried out using AutoDock vina featured in UCSF Chimera. It was executed using the flexible docking protocol with the flexible ligand-rigid receptor docking method; all

bonds contained in the ligand were allowed to rotate freely, making the receptor rigid. The target protein was first analyzed and prepared for docking and the identified active site was selected and made visible during the process, followed by the optimization of ligands. Default parameters of Vina were used for the docking process, as the scoring matrix in this program is stochastic, and each run uses a random seed position, except for the centers x, y, and z which utilized the identified center values of -5.6684, -0.1148, and 1.8072, respectively, from PrankWeb result and the grid box which was adjusted with extended grid size (12.2746 Å×16.0208 Å×17.4198 Å) to reveal all the possible interacting sites. A total of three docking trials were performed and after docking analysis, 10 configurations or poses for each ligand-protein complexes were generated, the docking session for each of the analyzed ligands was then saved in a phyton (.py) file, and the Vina result was recorded and saved in Autodock structure (.pdbqt) format.

2.7. Ligand-protein complex visualization

To compare the docking trials, root-mean-square deviation (RSMD) analysis was conducted. This served as a means to measure the similarities and differences between the docking results. Biovia discovery studio visualizer was used to perform RMSD analysis to identify which of the result in the three docking trials was used for the analysis and visualization of the complexes. Similar software was equipped to display and analyze the two- and three- dimensional structures of the ligand-protein complexes, including the interacting sites and formed intermolecular forces of attraction (IMFA).

3. RESULTS AND DISCUSSION

3.1. Absorption, distribution, excretion properties, metabolism, and excretion properties

The 19 phenolic compounds obtained from the leaves of *R. communis* are the selected ligands that were subjected to the ADME analysis, and the results presented in Table 1 revealed that of the 19 phenolic compounds, eight compounds violated more than one rule. These were filtered out as these are considered undesirable drug candidates. Three of the remaining 11 compounds violated only one rule including compounds 3, 12, and 14, whereas the other eight compounds did not violate any of the four parameters in Lipinski's RO5. Four of these eight phenolic compounds including ellagic acid, ferulic acid, gallic acid, and kaempferol also resulted in previous studies with no violations and matched the drug-like properties [25]. Similarly, previous studies obtained findings that epicatechin, gentisic acid, and quercetin resulted in no violation, and chlorogenic acid with one violation [26]. Neochlorogenic acid also resulted in one violation of Lipinski's criteria in a previous study [27].

Table 1. Lipinski's rule of five for ADME analysis of *Ricinus communis* L.

Phenolic compound	Lipinski's rule of five				Number of violation	Druglikeness: (Yes for<or=1 violation; No for>1 violation
	MW<or=to 500 Da	Log (P)< or=to 5	HBDs< or=to 5	HBAs< or=to 10		
(-)-Epicatechin	√	√	√	√	0	Yes
2,5-Dihydroxybenzoic acid	√	√	√	√	0	Yes
Chlorogenic acid	√	√		√	1	Yes
Corilagin		√			3	No
Ellagic acid	√	√	√	√	0	Yes
Ferulic acid	√	√	√	√	0	Yes
Gallic acid	√	√	√	√	0	Yes
Hyperoside	√	√			2	No
Kaempferol	√	√	√	√	0	Yes
Kaempferol-3-O-B-D-glucopyranoside		√			3	No
Kaempferol-3-O-B-rutinoside		√			3	No
Kaempferol-3-O-B-D-xylopyranoside	√	√		√	1	Yes
Methyl gallate	√	√	√	√	0	Yes
Neochlorogenic acid	√	√		√	1	Yes
Quercetin	√	√	√	√	0	Yes
Quercetin-3-O-B-D-glucopyranoside	√	√			2	No
Quercetin-3-O-B-rutinoside		√			3	No
Quercetin-3-O-B-D-xylopyranoside	√	√			2	No
Tannins		√			3	No

*The compound name in the bold letter indicates that the phenolic compound violated more than one (> 1) rule of Lipinski's rule of five and did not proceed with the docking process.

The results of the analysis of *J. curcas'* phenolic compounds presented in Table 2 showed that 27 compounds with less than or equal to one (≤1) violation exhibited drug-likeness and proceeded as ligands in the molecular docking process, whereas 12 compounds that contain more than one (>1) violation were filtered out as these are considered as undesirable drug candidates. Of the 27 drug candidates, seven compounds violated one rule, which mostly violates the third rule having an excessive value of H-bond donors (HBDs>5), except for 3',5-Dimethoxy-4'-hydroxy-7-[(beta-D-glucopyranosyl) oxy] flavone with more than 10 hydrogen bond acceptors. Previous studies also obtained similar results. Apigenin derivatives including cosmosiin (apigenin-7-O-glucoside) and vitexin (apigenin-8-C-glucoside) also resulted in one violation and bergenin and luteolin resulted in no violation. While the remaining 20 compounds did not violate any of the four parameters in Lipinski's rule of five. Catechin, epicatechin, eriodictoyl, luteolin, naringenin, and quercetin resulted in no violation and matched the drug- like properties.

Table 2. Lipinski's rule of five for ADME analysis of *Jatropha curcas* L.

Phenolic compound	Lipinski's rule of five				Number of violations	Druglikeness: (Yes for<or=1 violation; No for>1 violation
	MW<or =to 500 Da	Log (P)<or=to 5	HBDs< or=to 5	HBAs< or=to 10		
3,3',4,4'-tetra-O-methylellagic acid	√	√	√	√	0	Yes
3',5-dimethoxy-4'-hydroxy-7-[(beta-D-glucopyranosyl)oxy]flavone	√	√	√		1	Yes
5,7,2'-trihydroxy-8,6'-dimethoxyflavone	√	√	√	√	0	Yes
Apigenin	√	√	√	√	0	Yes
Apigenin-C-hexoside-O-hexoside		√			3	No
Bergenin	√	√	√	√	0	Yes
Catechin	√	√	√	√	0	Yes
Chrysoeriol	√	√	√	√	0	Yes
Cosmosiin	√	√		√	1	Yes
Coumarin	√	√	√	√	0	Yes
Epicatechin	√	√	√	√	0	Yes
Eriodictyol	√	√	√	√	0	Yes
Fraxetin	√	√	√	√	0	Yes
Hemiphloin	√	√		√	1	Yes
Isohemiphloin	√	√		√	1	Yes
Isoorientin	√	√			2	No
Isoquercetin	√	√			2	No
Isoscoparin	√	√			2	No
Isovitexin	√	√		√	1	Yes
Jatrophenol I		√			3	No
Jatrophenol II		√			3	No
Jatrophenol III		√			3	No
Luteolin	√	√	√	√	0	Yes
Naringenin	√	√	√	√	0	Yes
Naringenin-C-hexoside	√	√		√	1	Yes
N-trans-feruloyltyramine	√	√	√	√	0	Yes
Orientin	√	√			2	No
Quercetin	√	√	√	√	0	Yes
Quercetin-3-O-methylether	√	√	√	√	0	Yes
Rhoifolin		√			3	No
Scoparin	√	√			2	No
Scopoletin	√	√	√	√	0	Yes
Scopolin	√	√	√	√	0	Yes
Taxifolin	√	√	√	√	0	Yes
Tomenin	√	√	√	√	0	Yes
Tomentin	√	√	√	√	0	Yes
Vicenin-1		√			3	No
Vicenin-3		√			3	No
Vitexin	√	√		√	1	Yes

*The compound name in the bold letter indicates that the phenolic compound violated more than one (>1) rule of Lipinski's rule of five and did not proceed with the docking process.

3.2. Interactions and mechanisms of the ligand- protein complexes

3.2.1. Binding affinity of the ligand-protein complexes

A total of 36 phenolic compounds from both plants, which showed effective ADME properties were bonded to the active site of the Tat C protein. The results of the average binding affinity of the phenolic compounds of the castor plant (*Ricinus communis* L.) and physic nut (*Jatropha curcas* L.) to the active site of HIV-1 Tat C were shown in Table 3. The binding affinity (or free energy of binding) is the sum of the final intermolecular energy and torsion-free energy. The negative value of binding affinity depicts that the reaction between bioactive components bonded to the active site occurs spontaneously due to this change in total intermolecular and torsional energies [28]. Therefore, a better inhibitor of the Tat C protein among the selected ligands is the phenolic compound(s) with a high negative value of binding affinity as this corresponds to better bonding of phytochemical components with the receptor; better inhibition of the viral transcription, which then a better inhibition of the virus. The binding affinities of the phenolic compounds ranged from -5.3 to -7.3 kcal/mol. There was no control analyzed in the study for the comparison of the result as there were no clinically available Tat inhibitors [29]. The docking analysis revealed that the best inhibitors are ellagic acid and neochlorogenic acid from the castor plant, and isohemiphloin from physic nut to the Tat C protein with a binding affinity of -7.2 kcal/mol and -7.3 kcal/mol, respectively.

Table 3. The binding affinity of *R. communis* and *J. curcas* Phenolic compounds with HIV-1 subtype C Tat protein

Plant source	Phenolic compound	Binding affinity with Tat c protein (kcal/mol)
R. communis	(-)-Epicatechin	-6.6
	2,5-Dihydroxybenzoic acid (Gentisic acid)	-5.4
	Chlorogenic acid	-6.9667
	Ellagic acid	**-7.2**
	Ferulic acid	-5.8
	Gallic acid	-5.3
	Kaempferol	-6.4667
	Kaempferol-3-O-β-D-xylopyranoside	-7.0
	Methyl gallate	-5.4
	Neochlorogenic acid	**-7.2**
	Quercetin	-7.1667
Jatropha curcas L.	3,3’, 4,4’-Tetra-O-methylellagic acid	-5.6
	3',5-Dimethoxy-4'-hydroxy-7-[(beta-D-glucopyranosyl)oxy]flavone	-6.5
	5,7,2'-Trihydroxy-8,6'-dimethoxyflavone	-6.2
	Apigenin	-6.6
	Bergenin	-5.6
	Catechin	-7.0
	Chrysoeriol	-6.2
	Cosmosiin	-6.8333
	Coumarin	-5.4
	Epicatechin	-6.6
	Eriodictyol	-7.0
	Fraxetin	-6.1
	Hemiphloin	-5.6
	Isohemiphloin	**-7.3**
	Isovitexin	-5.3667
	Luteolin	-7.0
	Naringenin	-6.5
	Naringenin-C-hexoside isomer 3	-6.8667
	N-trans-Feruloyltyramine	-6.8
	Quercetin	-7.1667
	Quercetin-3-O-methyl ether	-7.2
	Scopoletin	-5.8333
	Scopolin	-6.4
	Taxifolin	-7.1
	Tomenin	-6.1667
	Tomentin	-5.8
	Vitexin	-7.1

*The compound name in the bold letter indicates that the phenolic compound with the highest negative value of binding affinity in kcal/mol for each of the plant source.

A previous study performed in silico approach to find an efficacious inhibitor from the phytoconstituents of Moringa oleifera leaves extract against a synthetic HIV-1 Tat, which specifically targeted the subtype B Tat protein (PDB: 1JFW) resulted in two best compounds: aurantiamide acetate and

kaempferol with a binding affinity of -9.99 kcal/mol and -9.82 kcal/mol, respectively. In comparison with the present study, aurantiamide acetate was not utilized and the binding affinity of kaempferol is -6.4667 kcal/mol, which signified that kaempferol phenolic compound might be a possible inhibitor for the Tat B, but was not in the case for the Tat C. However, in comparison with the present study, ellagic acid from the castor plant is one of the best inhibitors bonded to Tat C. Despite having a similar function in the viral transcription, both studies showed different results and these differences may be explained due to the different sequence alignment of both Tat protein.

The docking analysis showed that of the 36 phenolic compounds bonded with Tat C, 11 compounds are included in the top 5 highest negative binding affinities. These were ranked and included in Table 3. It can be observed that seven of which are from Physic nut; three compounds are from Castor plant; and one phenolic compound existed on both plants.

3.2.2. Interactions of the phenolic compounds with amino acids of the Tat C protein

Determining the amino acid residues of the active site where the inhibitors are attached can help in the development of an antiviral drug. It provides data on how to modify the structure of the inhibitor for enhancing its bonding with the target protein. The amino acid interactions of the Tat C protein with plant-derived phenolic compounds that demonstrated high negative binding affinity are presented in Table 4. To assess interaction strength, numerous specific measures of atom contacts were analyzed, both favorable and unfavorable interactions. These interactions can be classified by whether the interaction geometry is strong or weak. The interacting residues of Tat C with respective ligands were majorly through hydrogen bonds, hydrophobic interactions, electrostatic interactions, and van der Waals forces. Moreover, there is an unfavorable interaction in the three phenolic compounds including quercetin with unfavorable acceptor-acceptor interaction, taxifolin, and catechin, both with unfavorable donor-donor interaction. This unfavorable interaction means that the potential energy of the system is decreased or less stable because of these interactions, or simply, two (or more) atoms do not like to be where they are. However, unfavorable interaction in molecular docking does not necessarily mean that the compound is not a good inhibitor because of many reasons such as protein flexibility is not taken into account in a commonly used docking protocol, the right binding mode of inhibitor might not be returned by the docking program or not top-scored by the used scoring function, other effects poorly accounted for in docking might play a crucial role in activity (solvent, entropy, and target interaction partners), and compound might have an unexpected mode of action or a different binding site [30].

Table 4. Interacting sites between ligand-protein complexes

Phenolic compound	Interacting amino acids			
	Favorable interactions			Unfavorable interaction
	Hydrogen bonds	Electrostatic/miscellaneous	Hydrophobic	
Isohemiphloin	His13 Lys19 Gln66 Pro70 Gln72 Pro73		Lys19 Lys28 (pi-alkyl)	
Ellagic acid	His13 Lys28 Thr64 Gln72 Pro73	Lys19 (pi-cation)	Lys19 Lys28 (pi-alkyl)	
Neochlorogenic acid	His13 Lys19 Hs65 Pro70 Gln72	Cys34 (pi-sulfur)	Lys19 Lys28 (pi-alkyl)	
Quercetin-3-O-methyl ether	His13 Lys19 Thr64 Gln66 Pro70		Lys19 Lys28 Pro73 (pi-alkyl)	
Quercetin	Lys19 Gln66 Pro70		Lys19 Lys28 Pro73 (pi-alkyl)	Thr64 (unfavorable acceptor-acceptor)
Taxifolin	Lys19 Thr64 Pro70	Lys19 (pi-cation)	Lys28 Pro73 (pi-alkyl)	His13 (unfavorable donor-donor)
Vitexin	His13 Lys19 Gln66 Gln72	Cys34 (pi-sulfur)	Lys19 Lys28 (pi-alkyl)	
Kaempferol-3-O-β-D-xylopyranoside	His13 Lys19 Gln66 Pro70		Lys19 Lys28 Pro73 (pi-alkyl)	
Catechin	His13 Lys19 Thr64 Gln66 Pro70	Lys19 (pi-cation)	Lys28 Pro73 (pi-alkyl)	His13 (unfavorable donor-donor)
Eriodictyol	His13 Lys19 Thr64 Pro70 Pro73	Lys19 (pi-cation)	Lys28 Pro73 (pi-alkyl)	
Luteolin	His13 Lys19 Thr64 (Conventional H bond) Pro70 (C-H bond)		Lys19 Lys28 Pro73 (mixed pi/alkyl hydrophobic)	

Representation of binding interactions of the ligand-protein complexes with the highest negative binding affinity was selected based on the RMSD result of the ligand conformation. RMSD stands for root mean square deviation, which is a numerical measurement representing the difference between two

structures. The values of the RMSD in ligand conformational search are widely used to confirm whether a close-match docked pose was predicted or not by the docking simulation, wherein, an RMSD value of less than or equal to two angstrom (≤2 Å) is good [31]. Out of the 11 compounds with the highest negative binding affinity, any of each trial of the 10 phenolic compounds is a good representation to show the binding interaction of the ligand-protein complexes as each conformation on every trial has less than 2 Å RMSD value, ranging from 0.3193–0.7284 Å, when comparing the three trials, suggesting high structural similarity and conformational stability.

The binding of ellagic acid and neochlorogenic acid from *R. communis* to the Tat C protein showed several types of interactions. Ellagic acid exhibited two types of hydrogen bonds: conventional hydrogen bonds were observed with the hydroxyl groups bonded to His13 and Thr64; and carbon-hydrogen bonds to Lys28, Thr64, Gln72, and Pro73 aided in the stabilization of the ligand at the Tat C binding pockets. A mixed pi-alkyl hydrophobic interaction was also observed in Lys19 and Lys28, while Lys19 of the N-terminus region also showed electrostatic interaction, pi-cation. Along with these interactions, four Van der Waals attractive forces (Lys29, Val36, His65, and Gln66) were shown in the protein-ligand complex. Neochlorogenic acid interacted via conventional H-bonds to His13, Lys19, and His65 and carbon-hydrogen bonds to Pro70, and Gln72, pi-alkyl interactions to Lys19 and Lys28, and a pi-sulfur interaction to Cys34 of the cysteine-rich region. Other interactions with Tat C include Pro18, Val36, Gln66, Thr64, and Pro72, all affected by van der Waals forces. Isohemiphloin with the highest binding affinity to the Tat C protein interacted with different amino acid residues. Isohemiphloin had the most stable positioning in the binding pocket as the interactions observed formed six hydrogen bonds via conventional H-bond of oxygen group to Lys19, and hydroxyl groups bonded to Gln66, and Pro70; carbon-hydrogen bonds to His13, Pro70, Gln72, and Pro73; and a pi- alkyl interaction to Lys was surrounded by Cys31, His33, Cys34, and Val36 of the cysteine-rich region and Thr64 of the glutamine region governed by van der Waals forces.

A distinguished relationship between phenolic compounds of *J. curcas* with the highest negative binding affinity among the docked ligands and the Tat C protein. Quercetin-3-O-methyl ether exhibited conventional H-bond interaction to His13, Lys19, Thr64, and Pro70, carbon-hydrogen bond to Gln66, and Pro70, and Lys19, Lys28, and Pro73 reacted with aromatic rings, all formed a hydrophobic interaction, pi-alkyl with the compound. Other residues include Cys34, Val36, and Gln72 established van der Waals forces. The same pattern of amino acid interactions with that of the quercetin-3-O-methyl ether were observed in catechin, eriodictyol, and luteolin however, there were minimal differences in the exhibited interactions. Catechin had formed unfavorable donor-donor interaction with His13, no carbon-hydrogen bond to Pro70, the aromatic ring of the compound formed pi-cation with Lys19, and Pro18 was also included to form van der Waals force. Eriodictyol exhibited conventional H-bond interaction on both oxygen and terminal hydrogen connected to oxygen to His13, only carbon-hydrogen bond to Pro70, and an additional carbon-hydrogen bond interaction to Pro73. Eriodictyol also formed an electrostatic (pi-cation) interaction with Lys19 instead of pi- alkyl, and similar van der Waals forces (Val36, Gln66, and Gln72) with that of the luteolin. Whereas luteolin phenolic compound established conventional H-bond interaction to His13 on both oxygen and terminal hydrogen connected to oxygen, and there were no formed conventional H-bond and carbon-hydrogen bonds to Pro70 and Gln66, respectively. Instead, Gln66 established van der Waals forces along with Val36 and Gln72 and not Cys34. Attachment of taxifolin to the Tat C protein produced H-bond interactions: a conventional H- bond to Lys19 and Thr64; and a carbon-hydrogen bond to Pro70, a pi-alkyl interaction of the aromatic rings to Lys28 and Pro73, and a pi-cation to Lys19. An unfavorable donor-to-donor interaction was observed between His13, and the terminal hydrogen connected to oxygen, whereas Pro18 of the N-terminus, Cys34, and Val36 of the cysteine-rich region, and Gln66 and Gln72 of glutamine region formed van der Waals interactions. Vitexin established conventional- hydrogen bond interaction to His13, Lys19, and Gln66, a carbon-hydrogen bond to Gln72, a mixed pi-alkyl hydrophobic interaction to Lys19 and Lys28, a pi-sulfur interaction to Cys34, and most of the interactions were van der Waals attraction to Cys31, His33, Val36, Thr64, Pro70, and Pro73.

Kaempferol-3-O-β-D-xylopyranoside from *R. communis* interacted with the Tat C protein via H-bond interactions to His13, Lys19, Gln66 (conventional H-bond), and Pro70 (both conventional H-bond and carbon-hydrogen bond). The aromatic ring system of the compound was responsible for the hydrophobic interaction to Lys19, Lys28, and Pro73, forming a mixed pi-alkyl interaction. Moreover, Cys34, Val36, Thr64, and Gln72 established non-bonded van der Waals forces with the ligand.

Quercetin is the phenolic compound that existed on both plants and had a similar amino acid interaction (with that of the quercetin-3-O-methyl ether to the Tat C protein, except for Gln66. The interactions also showed conventional H-bond interaction to His13, Lys19 Thr64, and Pro70, the carbon-hydrogen bond only to Pro70 making the Gln66 as an exception, and Lys19, Lys28, and Pro73 reacted with aromatic rings, all formed a hydrophobic interaction, pi- alkyl with the compound. Other residues include Cys34, Val36, His65, Gln66, and Gln72 established van der Waals forces.

A literature survey has shown that ellagic acid, neochlorogenic acid, and isohemiphloin contribute to diverse pharmacological properties. Ellagic acid (2,3,7,8-tetrahydroxy[1]-benzopyranol[5,4,3- cde]benzopyran-5,10-dione] is a naturally occurring polyphenolic compound that is found in many plant sources. Structurally, presents four rings representing the lipophilic domain, four phenolic groups, and two lactones, which form hydrogen-bonds sides and act as electron acceptors respectively, and that represents the hydrophilic domain [32]. In addition, ellagic acid has been reported to possess antiviral activity demonstrated by in vitro models [33]. Moreover, in an in vitro study, it was reported that of the identified specialized metabolites in *Punica granatum* (Pomegranate), ellagic acid was one of the compounds that exhibited the most relevant inhibition of HIV-1 RT-associated ribonuclease H (RNase H) and HIV-1 integrase (IN) lens epithelium–derived growth factor (LEDGF)-dependent activities [34]. This compound extracted from *Lagerstroemia speciosa* L. (Banaba) was also reported to have the ability to inhibit HIV-1 protease expression [35]. Ellagic acid isolated from the methanol extract of Diospyros lotus fruits is the second phenolic compound with the strongest antiviral activity against HIV-1 (IIIB strain) [36]. Neochlorogenic acid (5-caffeoylquinic acid) is also a natural polyphenolic compound found in different plant sources and previous studies have shown that this compound has outstanding antiviral activities [37]. A previous study indicated that the performed cell experiments showed that neochlorogenic acid has a good inhibitory effect on the HIV-1 RT enzyme and may also inhibit HIV through four targets: haemopoietic cell kinase (HCK), epidermal growth factor receptor (EGFR), sarcoma (SRC), and 3-phosphoinositide dependent protein kinase 1 (PDPK1) [38]. Moreover, neochlorogenic acid may bind HIV-2 RT. Isohemiphloin (naringenin-8-C-glucoside) is a C-glycosyl compound that is functionally related to (S)-naringenin substituted by a beta-D- glucopyranosyl at position 8 via a C-glycosidic prevents intracellular replication of the chikungunya virus [39] and inhibits assembly and long-term production of infectious hepatitis C virus particles in a dose-dependent manner [40]. Previous study reported that naringenin had a greater antiviral activity to inhibit the replication of the neurovirulent strain of Sindbis virus (NSV) linkage [41], which is a naringenin glycoside form, found in Jatropha species. C-glycosylated flavanones are much less studied than O-glycosides but are endowed with several health benefits or pharmacological functions such as antioxidant, anticancer, antitumor, and anti-diabetic activities [42]. Despite the isohemiphloin (naringenin glycoside form) being less studied, the antiviral effects of naringenin itself have been reported, and the *J. curcas* plant source was found to display antiviral activity on human immunodeficiency virus. Naringenin shows a dose-dependent inhibitory effect against the dengue virus. It has also been demonstrated by previous study that naringenin is one of the nine flavonoid compounds that could block virus replication of human cytomegalovirus (HCMV) [43]. Because naringenin demonstrated potent activity against a wide range of viruses, therefore, one can expect that its derivative will be effective against viruses. Moreover, isohemiphloin is a flavonoid [44], and flavonoids are known to have antiviral activity against herpes simplex 1 and 2, influenza, dengue, and yellow fever, and HIV-1 [45].

4. CONCLUSION

The study successfully utilized in silico methods to identify potential inhibitors or novel anti-HIV drugs that actively target the HIV-1 subtype C trans-activator of transcription protein. From the above references and the research findings, three phenolic compounds exhibited the highest negative binding affinity to the receptor: ellagic and neochlorogenic acids from *R. communis* and isohemiphloin from *J. curcas*, which interacted strongly with the binding site residues. The interacting amino acids between the top identified ligands and the Tat C protein were majorly His13, Lys19, Lys28, Thr64, His65, Gln66, Pro70, Gln72, and Pro73 through non-covalent interactions, including hydrogen bonds, electrostatic interactions, and hydrophobic interactions. The identified phenolic compounds provide a core structure that can be exploited to develop plant-based antiviral drugs with a possible mechanism of action that may potentially block the feedback loop that drives exponential increases in viral transcription and viral particle production, thereby reducing the activity of the Tat protein and preventing the trans-activation response (TAR RNA) from binding. These may also help prevent viral reactivation and possibly keep the virus in a state of prolonged silencing. Furthermore, the use of these compounds would be beneficial to exploit in the development of anti-HIV drugs as they may also possess a multi-target function to avoid the use of several drugs with different activities. They are therefore recommended for further computational methods and in vitro and in vivo clinical studies towards developing new anti-HIV drugs.

REFERENCES

[1] E. Rossi, M. E. Meuser, C. J. Cunanan, and S. Cocklin, "Structure, function, and interactions of the HIV-1 capsid protein," *Life*, vol. 11, no. 2, p. 100, Jan. 2021, doi: 10.3390/life11020100.
[2] S. Wang, H. Li, Z. Lian, and S. Deng, "The role of RNA modification in HIV-1 infection," *International Journal of Molecular Sciences*, vol. 23, no. 14, p. 7571, Jul. 2022, doi: 10.3390/ijms23147571.
[3] M.T. Montemayor, "DOH launches 7th AIDS medium term plan, emphasizes equality to address HIV," Philippine News Agency,

PNA, January, 2023. Accessed: August, 19, 2023. [Online] Available: https://www.pna.gov.ph/articles/1193752.
[4] A. F. Feder, P. S. Pennings, and D. A. Petrov, "The clarifying role of time series data in the population genetics of HIV," *PLOS Genetics*, vol. 17, no. 1, p. e1009050, Jan. 2021, doi: 10.1371/journal.pgen.1009050.
[5] D. Ajasin and E. A. Eugenin, "HIV-1 Tat: role in bystander toxicity," *Frontiers in Cellular and Infection Microbiology*, vol. 10, p. 61, Feb. 2020, doi: 10.3389/fcimb.2020.00061.
[6] A. Rodari, G. Darcis, and C. M. Van Lint, "The current status of latency reversing agents for HIV-1 remission," *Annual Review of Virology*, vol. 8, no. 1, pp. 491–514, Sep. 2021, doi: 10.1146/annurev-virology-091919-103029.
[7] H. Gruell and F. Klein, "Antibody-mediated prevention and treatment of HIV-1 infection," *Retrovirology*, vol. 15, no. 1, p. 73, Dec. 2018, doi: 10.1186/s12977-018-0455-9.
[8] S. Mediouni, S. Lyu, S. M. Schader, and S. T. Valente, "Forging a functional cure for HIV: transcription regulators and inhibitors," *Viruses*, vol. 14, no. 9, p. 1980, Sep. 2022, doi: 10.3390/v14091980.
[9] S. Pawar *et al.*, "Structural studies of antiviral inhibitor with HIV-1 protease bearing drug resistant substitutions of V32I, I47V and V82I," *Biochemical and Biophysical Research Communications*, vol. 514, no. 3, pp. 974–978, Jun. 2019, doi: 10.1016/j.bbrc.2019.05.064.
[10] B. Baruah, I. Ayus, and M. P. Dutta, "Identification of biomarker genes for human immunodeficiency virus using ensemble approach," in *Lecture Notes in Electrical Engineering*, Springer Nature Singapore, 2022, pp. 637–648.
[11] B. Salehi *et al.*, "The therapeutic potential of naringenin: a review of clinical trials," *Pharmaceuticals*, vol. 12, no. 1, p. 11, Jan. 2019, doi: 10.3390/ph12010011.
[12] N. A. Ahmad *et al.*, "Nanocrystalline diamond electrolyte-gates in field effect transistor for a prolific aptasensing HIV-1 Tat on hydrogen-terminated surface," *International Journal of Nanoelectronics and Materials*, vol. 13, no. 2, pp. 295–306, 2020.
[13] M. A. Kurnaeva, E. V Sheval, Y. R. Musinova, and Y. S. Vassetzky, "Tat basic domain: A 'Swiss army knife' of HIV-1 Tat?," *Reviews in Medical Virology*, vol. 29, no. 2, Mar. 2019, doi: 10.1002/rmv.2031.
[14] A. C. Puhl, A. Garzino Demo, V. A. Makarov, and S. Ekins, "New targets for HIV drug discovery," *Drug Discovery Today*, vol. 24, no. 5, pp. 1139–1147, May 2019, doi: 10.1016/j.drudis.2019.03.013.
[15] R. H. Elkousy, Z. N. A. Said, M. A. Ali, O. Kutkat, and S. A. A. El Wafa, "Anti-SARS-CoV-2 in vitro potential of castor oil plant (Ricinus communis) leaf extract: in-silico virtual evidence," in Research Square Platform LLC, North Carolina, United States of America, 2022. [Online]. Available: doi: 10.21203/rs.3.rs-1979637/v1.
[16] W. Abdul *et al.*, "Therapeutic role of Ricinus communis L. and its bioactive compounds in disease prevention and treatment," *Asian Pacific Journal of Tropical Medicine*, vol. 11, no. 3, p. 177, 2018, doi: 10.4103/1995-7645.228431.
[17] H. S. Chouhan, G. Swarnakar, and B. Jogpal, "Medicinal properties of Ricinus communis: a review," *International Journal of Pharmaceutical Sciences and Research*, vol. 12, no. 7, pp. 3632–3642, 2021, doi: 10.13040/IJPSR.0975-8232.12(7).3632-42.
[18] Y. Hu *et al.*, "Jatrophacine, a 4,5- seco -rhamnofolane diterpenoid with potent anti-inflammatory activity from Jatropha curcas," *Natural Product Research*, vol. 35, no. 16, pp. 2748–2752, Aug. 2021, doi: 10.1080/14786419.2019.1660656.
[19] J. de S. F. Elvino and A. D. G. J. Edilson, "Anti-viral compounds from Jatropha curcas seed extract with anti-HIV-1 and anti-SARS-CoV-2 action," *African Journal of Pharmacy and Pharmacology*, vol. 17, no. 1, pp. 1–9, Jan. 2023, doi: 10.5897/AJPP2022.5328.
[20] G. Zengin *et al.*, "Chemical composition and biological properties of two jatropha species: different parts and different extraction methods," *Antioxidants*, vol. 10, no. 5, p. 792, May 2021, doi: 10.3390/antiox10050792.
[21] H. Franke, R. Scholl, and A. Aigner, "Ricin and Ricinus communis in pharmacology and toxicology-from ancient use and 'Papyrus Ebers' to modern perspectives and 'poisonous plant of the year 2018,'" *Naunyn-Schmiedeberg's Archives of Pharmacology*, vol. 392, no. 10, pp. 1181–1208, Oct. 2019, doi: 10.1007/s00210-019-01691-6.
[22] J.A. Duke and M.J. Bogenschutz, "Chemoicals in: Mucuna pruriens (L.) DC.(Fabaceae)-Cowage, Velvetbean," in *Dr. Duke's phytochemical and ethnobotanical databases*, Washington, DC, USA, pp. 1-8.
[23] M. E. Williams and R. Cloete, "Molecular modeling of subtype-specific tat protein signatures to predict Tat-Tar interactions that may be involved in HIV-associated neurocognitive disorders," *Frontiers in Microbiology*, vol. 13, p. 866611, Apr. 2022, doi: 10.3389/fmicb.2022.866611.
[24] S. Stegemann, C. Moreton, S. Svanbäck, K. Box, G. Motte, and A. Paudel, "Trends in oral small-molecule drug discovery and product development based on product launches before and after the rule of five," *Drug Discovery Today*, vol. 28, no. 2, p. 103344, Feb. 2023, doi: 10.1016/j.drudis.2022.103344.
[25] M. Radha, V. Ratnasabapathysarma, and J. Suganya, "In silico approach to inhibit synthetic HIV-TAT activity using Phytoconstituents of Moringa oleifera leaves extract," *Research Journal of Pharmacy and Technology*, vol. 13, no. 8, p. 3610, 2020, doi: 10.5958/0974-360X.2020.00638.1.
[26] T. Rathinavel *et al.*, "Potential COVID-19 drug from natural phenolic compounds through in silico virtual screening approach," *Biointerface Research in Applied Chemistry*, vol. 11, no. 3, pp. 10161–10173, Oct. 2020, doi: 10.33263/BRIAC113.1016110173.
[27] A. Stefaniu and L. C. Pirvu, "In silico study approach on a series of 50 polyphenolic compounds in plants; a comparison on the bioavailability and bioactivity data," *Molecules*, vol. 27, no. 4, p. 1413, Feb. 2022, doi: 10.3390/molecules27041413.
[28] I. J. Arenas Buan and D. V. Muncal Mendoza, "Computational study of bioactive components of sweet basil (Ocimum basilicum Linn.), luyang dilaw (Curcuma longa Linn.) and lagundi (Vitex negundo) as inhibitor against human immunodeficiency virus (Hiv-1)," *Oriental Journal of Chemistry*, vol. 36, no. 04, pp. 767–772, Aug. 2020, doi: 10.13005/ojc/360424.
[29] S. Mediouni *et al.*, "Didehydro-cortistatin a inhibits HIV-1 by specifically binding to the unstructured basic region of Tat," *mBio*, vol. 10, no. 1, pp. e02662-18, Feb. 2019, doi: 10.1128/mBio.02662-18.
[30] E. Edache, A. Uzairu, P. A. Mamza, and G. A. Shallangwa, "Investigation of salicylidene acylhydrazides derivatives: molecular docking, ADMET, and molecular dynamic simulations were used in conjunction towards the design of new yersinia pseudotuberculosis inhibitors," *Turkish Computational and Theoretical Chemistry*, vol. 6, no. 1, pp. 9–30, Jun. 2022, doi: 10.33435/tcandtc.1003157.
[31] G. Grasso *et al.*, "Fragmented blind docking: a novel protein–ligand binding prediction protocol," *Journal of Biomolecular Structure and Dynamics*, vol. 40, no. 24, pp. 13472–13481, Dec. 2022, doi: 10.1080/07391102.2021.1988709.
[32] W. R. García-Niño, L. Ibarra-Lara, M. Y. Cuevas-Magaña, A. Sánchez-Mendoza, and E. Armada, "Protective activities of ellagic acid and urolithins against kidney toxicity of environmental pollutants: A review," *Environmental Toxicology and Pharmacology*, vol. 95, p. 103960, Oct. 2022, doi: 10.1016/j.etap.2022.103960.
[33] M. Kullappan *et al.*, "Ellagic acid as a potential inhibitor against the nonstructural protein NS3 helicase of Zika virus: a molecular modelling study," *BioMed Research International*, vol. 2022, pp. 1–15, Aug. 2022, doi: 10.1155/2022/2044577.
[34] C. Sanna *et al.*, "In vitro anti-HIV-1 reverse transcriptase and integrase properties of Punica granatum l. leaves, bark, and peel extracts and their main compounds," *Plants*, vol. 10, no. 10, p. 2124, Oct. 2021, doi: 10.3390/plants10102124.

[35] E. H. El-Bilawy *et al.*, "Antifungal, antiviral, and HPLC analysis of phenolic and flavonoid compounds of Amphiroa anceps extract," *Sustainability*, vol. 14, no. 19, p. 12253, Sep. 2022, doi: 10.3390/su141912253.
[36] K. Chojnacka, D. Skrzypczak, G. Izydorczyk, K. Mikula, D. Szopa, and A. Witek-Krowiak, "Antiviral properties of polyphenols from plants," *Foods*, vol. 10, no. 10, p. 2277, Sep. 2021, doi: 10.3390/foods10102277.
[37] K. Seo *et al.*, "Anti-inflammatory role of Prunus persica L. Batsch methanol extract on lipopolysaccharide-stimulated glial cells," *Molecular Medicine Reports*, vol. 21, no. 5, pp. 2030–2040, Mar. 2020, doi: 10.3892/mmr.2020.11016.
[38] J. Li, L. Dou, S. Chen, H. Zhou, and F. Mou, "Neochlorogenic acid: an anti-HIV active compound identified by screening of Cortex Mori [Morus Alba L. (Moraceae)]," *Pharmaceutical Biology*, vol. 59, no. 1, pp. 1515–1525, Jan. 2021, doi: 10.1080/13880209.2021.1995005.
[39] L. Albuquerque de Oliveira Mendes *et al.*, "The anti-Zika virus and anti-tumoral activity of the citrus flavanone lipophilic naringenin-based compounds," *Chemico-Biological Interactions*, vol. 331, p. 109218, Nov. 2020, doi: 10.1016/j.cbi.2020.109218.
[40] H. Tutunchi, F. Naeini, A. Ostadrahimi, and M. J. Hosseinzadeh-Attar, "Naringenin, a flavanone with antiviral and anti-inflammatory effects: A promising treatment strategy against COVID-19," *Phytotherapy Research*, vol. 34, no. 12, pp. 3137–3147, Dec. 2020, doi: 10.1002/ptr.6781.
[41] S. Kim, P. A. Thiessen, T. Cheng, J. Zhang, A. Gindulyte, and E. E. Bolton, "PUG-View: programmatic access to chemical annotations integrated in PubChem," *Journal of Cheminformatics*, vol. 11, no. 1, p. 56, Dec. 2019, doi: 10.1186/s13321-019-0375-2.
[42] D. Elkhalifa, I. Al-Hashimi, A.-E. Al Moustafa, and A. Khalil, "A comprehensive review on the antiviral activities of chalcones," *Journal of Drug Targeting*, vol. 29, no. 4, pp. 403–419, Apr. 2021, doi: 10.1080/1061186X.2020.1853759.
[43] M. Kowalczyk *et al.*, "Drug design strategies for the treatment of viral disease. plant phenolic compounds and their derivatives," *Frontiers in Pharmacology*, vol. 12, p. 709104, Jul. 2021, doi: 10.3389/fphar.2021.709104.
[44] I. Najmanová, M. Vopršalová, L. Saso, and P. Mladěnka, "The pharmacokinetics of flavanones," *Critical Reviews in Food Science and Nutrition*, vol. 60, no. 18, pp. 3155–3171, Oct. 2020, doi: 10.1080/10408398.2019.1679085.
[45] A. H. D. Cataneo *et al.*, "The citrus flavonoid naringenin impairs the in vitro infection of human cells by Zika virus," *Scientific Reports*, vol. 9, no. 1, p. 16348, Nov. 2019, doi: 10.1038/s41598-019-52626-3.

BIOGRAPHIES OF AUTHORS

Cherry May S. Delos Santos She finished her Bachelor of Science in Chemistry degree at the Nueva Ecija University of Science and Technology. Her undergraduate research study was a Finalist in the Oral Research Paper Presentation – Student Category in the 8th Central Luzon Health Research Forum in the Philippines. She was a StuFAPs grantee of the Commission on Higher Education (CHED) during her undergraduate program. Her research interests are mainly focused on in silico studies, drug development, cosmetics formulation, genetics, and forensic science. She can be contacted at email: delossantoscherrymay16@gmail.com.

June Alexis A. Santos is a graduate school student at Adamson University, Philippines. He specializes in pharmacoinformatics focusing on employing molecular dynamics to unravel drug-protein receptor interactions. His passion extends to utilizing data science and machine learning for computer-aided drug development. Beyond academia, he serves as a Science Research Specialist II at the Department of Environment and Natural Resources – Mines and Geosciences Bureau, contributing significantly to environmental research and getting involved in many environment-related projects. An avid publisher, he shares his insights on bioinformatics' role in computer-aided drug design, showcasing his commitment to advancing interdisciplinary knowledge. He can be contacted at email: june.alexis.santos@adamson.edu.ph.

Danilet Vi M. Mendoza is an Associate Professor at the Nueva Ecija University of Science and Technology. She is a registered chemist in the Philippines. She finished her Bachelor of Science in Chemistry degree at the University of the Philippines Los Banos and her Master of Science degree at the Ateneo de Manila University. She is currently pursuing her Doctor of Philosophy in Science Education at the Nueva Ecija University of Science and Technology. Her research interests are mainly focused on inorganic materials, nanoparticles, in silico studies and environmental chemistry. She can be contacted at email: niletmendoza@yahoo.com.