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IN SILICO ANALYSIS OF FIG (*Ficus carica* L.) BIOACTIVE COMPOUNDS AS MULTITARGET THERAPEUTIC CANDIDATE AGAINST HIV-1

Analisis *In Silico* Senyawa Bioaktif Buah Tin (*Ficus carica* L.) sebagai Kandidat Terapi Multitarget HIV-1

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ABSTRACT

Antiretroviral drugs (ARV) to treat HIV-1 infection which causes AIDS are predominantly monotargeted so it is considered less effective. Long-term use of this drug may also lead to side effects and the HIV-1 resistance to drug. Thereby highlighting the need for developing more effective multitarget drug candidates. Herbal-based medicine have potential to be developed into multitarget drugs due to its diverse bioactive compounds. In silico approaches are used for initial screening in new drug development. This study aimed to evaluate the potential of fig (*Ficus carica* L.)-derived bioactive compounds as multitarget antiretroviral therapy candidates against three key HIV-1 proteins: Gp120, HIV-1 reverse transcriptase, and HIV-1 protease, in silico. Fourteen bioactive compounds consisting of anthocyanin, flavonoid, and terpenoid derivatives were analyzed for their physicochemical properties, pharmacokinetic profiles, toxicity, and molecular docking interactions. The results revealed that five compounds of flavonoid group: apigenin, catechin, epicatechin, kaempferol, and luteolin, fulfilled the criteria as potential oral multitarget drug candidates with relatively low binding affinity (ΔG) values toward all three HIV-1 target proteins. Notably, luteolin exhibited the strongest binding affinity toward Gp120 (-7.2 kcal/mol), HIV-1 reverse transcriptase (-8.8 kcal/mol) and HIV-1 protease (-8.5 kcal/mol), while also complying Lipinski's, ADMET parameters, and low-toxicity predictions. These findings suggest that luteolin considerable as a safe natural-based multitarget antiretroviral candidate derived from *Ficus carica* L.

Keywords: *Anthocyanin, Flavonoid, Gp-120 protein, HIV-1 protease, HIV-1 reverse transcriptase, Molecular docking, Terpenoid*

ABSTRAK

Obat antiretroviral (ARV) untuk mengatasi Infeksi HIV-1 penyebab AIDS sebagian besar bersifat monotarget sehingga dinilai kurang efektif. Penggunaan jangka panjang obat ini juga dapat menimbulkan efek samping dan dapat menimbulkan resistensi virus HIV-1. Oleh sebab itu diperlukan pengembangan kandidat obat multitarget yang lebih efektif. Obat berbasis herbal memiliki potensi dikembangkan menjadi obat multitarget karena memiliki banyak senyawa bioaktif. Metode in-silico digunakan untuk screening awal dalam pengembangan obat baru. Penelitian ini bertujuan untuk menganalisis potensi senyawa bioaktif buah tin (*Ficus carica* L.) sebagai kandidat terapi antiretroviral multitarget terhadap tiga protein kunci HIV-1, yaitu: Gp120, HIV-1 reverse transcriptase dan HIV-1 protease secara in silico. Sebanyak empat belas senyawa bioaktif dari kelompok antosianin, flavonoid, dan terpenoid dianalisis berdasarkan sifat fisikokimia, profil farmakokinetik,

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toksisitas, serta interaksi molecular docking. Hasil penelitian menunjukkan bahwa lima turunan senyawa flavonoid, yaitu: apigenin, katekin, epikatekin, kaempferol, dan luteolin, memenuhi kriteria sebagai kandidat obat oral multitarget potensial, dengan nilai afinitas pengikatan (ΔG) yang relatif rendah terhadap ketiga protein target HIV-1. Diantara senyawa tersebut, luteolin menunjukkan afinitas pengikatan terkuat dengan nilai ΔG sebesar: -7,2 kcal/mol (Gp120); -8,8 kcal/mol (HIV-1 RT); dan -8,5 kcal/mol (HIV-1 PR). Selain itu, luteolin juga memenuhi kriteria Lipinski's Rule, ADMET, serta memiliki tingkat toksisitas yang rendah. Temuan ini mengindikasikan bahwa luteolin potensi besar sebagai kandidat antiretroviral multitarget berbasis bahan alam yang aman dan efektif yang berasal dari buah tin (*Ficus carica* L.).

Kata kunci: *Antosianin, Flavonoid, HIV-1 protease, HIV-1 reverse transcriptase, Penambatan molekuler, Protein Gp-120, Terpenoid*

INTRODUCTION

Human Immunodeficiency Virus (HIV) is a retrovirus that infects immune cells, particularly $CD4^+$ T helper cells and dendritic cells (Serna-Arbeláez et al., 2023; Xavier Siwe-Noundou et al., 2019) and causes decreased immunity to develop into Acquired Immunodeficiency's Syndrome (AIDS) (Prasetiyo et al., 2024). This condition increasing the risk of opportunistic infections (Chai et al., 2022). Among the two viral strains, HIV-1 is more virulent, transmissible, and globally prevalent than HIV type 2 (Hokello et al., 2024). Current therapy, such as antiretroviral drugs (ARVs) work by inhibit the HIV-1 life cycle. But, the mechanisms specifically on one target (monotargeted) inhibition only, for example efavirenz which only inhibits HIV-1 reverse transcriptase (RT), so its effectiveness is limited. Furthermore, long-term use of these drugs often induces resistance due to virus mutations (Bhajantri & Pushkala, 2024; Nadia et al., 2022; Zubair et al., 2020). Therefore, the development of multitarget drug candidates capable of inhibiting multiple essential proteins in the HIV replication cycle has become an urgent necessity.

The HIV-1 replication cycle relies on several essential protein, such as Gp120, HIV-1 reverse transcriptase (HIV-1 RT), and HIV-1 protease (HIV-1 PR) which plays a vital role in distinct stage: viral attachment, replication, and maturation, respectively (Alves et al., 2021; Ghosh et al., 2016; Governa & Manetti, 2022; Hsieh et al., 2023). Gp120 is a glycoprotein located on the viral envelope. It forms a trimeric spike complex and facilitates viral infection by mediating the penetration of HIV into host cells (Alves et al., 2021; Governa & Manetti, 2022). HIV-1 RT is essential for converting viral RNA into complementary DNA (cDNA), enabling integration of the viral genome into the host chromosomes (Hsieh et al., 2023). Meanwhile, HIV-1 PR function in the late stage of viral maturation by cleaving viral polyproteins into functional proteins and peptides required to produce new virions (Aziz et al., 2024; Ghosh et al., 2016; Kim & Shan, 2022). Therefore, concurrent inhibition of these proteins may more effectively suppress HIV-1 replication.

Natural product-based strategies offer a promising alternative due to their diverse bioactive contents, which exert various pharmacological activities through complex and multitarget mechanisms, including antiviral activity (Chaachouay & Zidane, 2024). Each active molecule in a natural product possesses a unique structure, and even compounds within the same chemical class often appear in various derivatives, allowing for more complex antiviral mechanisms compared to synthetic ones. This potential was demonstrated by (Masduki et al., 2024), who reported that the flavonoid derivatives quercetrin and hyperoside from neem leaves could concurrently inhibit RdRp and Mpro protein of SARS-CoV-2 in silico with binding affinity value of -5,70 and -8,7 Kcal /mol for quercetin and -5,75 and -7,06 Kcal/mol for hyperoside.

Ficus carica L. (fig) contains diverse bioactive compounds with antiviral properties, including alkaloids, flavonoids, phytosterols, polyphenols, steroids,

terpenoids, phenolic acids, phenols, anthocyanins, fatty acids, and volatile compounds (Fazel et al., 2024; Ichsani & Indradi, 2024). This plant has been reported to have many biological activities that are beneficial for health, including high antioxidant, anti-inflammatory, anti-bacterial, anti-fungal, anti-parasitic and anti-diabetic, anti-cholinesterases, and anti-cancer through in vitro and in vivo approaches (Dogara et al., 2024). Moreover, Flavonoids, terpenoids, and anthocyanins from fig fruits have been demonstrated to possess antiviral activity. Ali et al., (2020) reported that terpenoids such as lupeol and α-amyrin (ΔG, and the flavonoids like luteolin, show potential as antiviral against SARS-CoV-2 by inhibiting protease enzymes (MPro) through in silico approaches with each binding affinity value (ΔG) of -12,5 Kcal/mol, -7,9 Kcal/mol and -7,4 Kcal/mol. Furthermore, the anthocyanin derivatives: Cyanidin-3-rhamnoglucoside has also been reported to inhibit viral protease and possess antiviral potential against COVID-19 and SARS-COV-2 by targeting protease and ACE2 enzymes (Hamed et al., 2023). In vitro studies have further confirmed that hexanic and hexane-ethyl acetate exctract of *Ficus carica* L. exhibits antiviral activity against several viruses, including Echovirus (ECV), Adenovirus (ADV) and Herpes Simplex Virus (HSV). These two extracts inhibited viruse multiplication at concentration of 78 µg/ml (Badgujar et al., 2014). Although many studies have been carried out to analyze the antiviral potential of figs, there are still no studies analyzing the effectiveness of fig compounds in inhibiting more than one target protein that is important in the HIV-1 life cycle as a basis for developing multitarget drugs. Therefore, exploring the bioactive compounds of *F. carica* as candidates for multitarget antiretroviral agents, using molecular docking against HIV-1 proteins, is crucial for developing more effective and resistance-resilient alternative therapies.

MATERIALS AND METHODS

This study employed computational approach using bioinformatics tools to predict the potential of fig (*Ficus carica* L.)-derived compounds as a multitarget therapeutic candidate against HIV-1. The research involved analyses of physicochemical properties, pharmacokinetic profiles, and molecular docking of 14 fig fruit's bioactive compounds against three target proteins involved in the HIV-1 replication.

Retrieval and Selection of Ligands and Target Proteins

Test ligands (L) were chosen based on a reported phytochemical constituents of *Ficus carica* L. and target proteins were selected from recent HIV-1 studies published within the past 5–10 years in credible and reputable scientific journals using appropriate queries on search engines such as "*Ficus carica* as antiviral", "bioactive compound of *Ficus carica*", "HIV-1", "molecular docking of Fig as anti-HIV", etc. The appropriate articles were then downloaded and analysed, resulting in three target proteins: Gp120, HIV-1 RT, and HIV-1 PR as receptors, and 14 fig-derived compounds (three anthocyanins, six flavonoids, and five terpenoids) as test ligands.

Target proteins were selected based on reference studies related to the HIV-1 life cycle and the key enzyme related at each stage: Gp120 (viral entry), HIV-1 RT (RNA-to-cDNA conversion and genome integration), and HIV-1 PR (polyprotein cleavage during viral maturation) (Aziz et al., 2024; Hsieh et al., 2023; Governa & Manetti, 2022; Kim & Shan, 2022; Alves et al., 2021; Ghosh et al., 2016). Therefore, concurrent inhibition of these proteins may more effectively. While the test ligands were selected based on reference studies (Fazel et al., 2024; Ichsani & Indradi, 2024; Hamed et al., 2023; Ali et al., 2020; Badgujar et al., 2014;). also the presence of its structure in the database. The 3D structures of receptors were obtained and downloaded from Protein Data Bank (RCSB PDB), while the native ligands (NL) and fig-derived compounds were retrieved from PubChem database. The detailed structures of the target proteins, test and native ligands are shown in Figure 1.

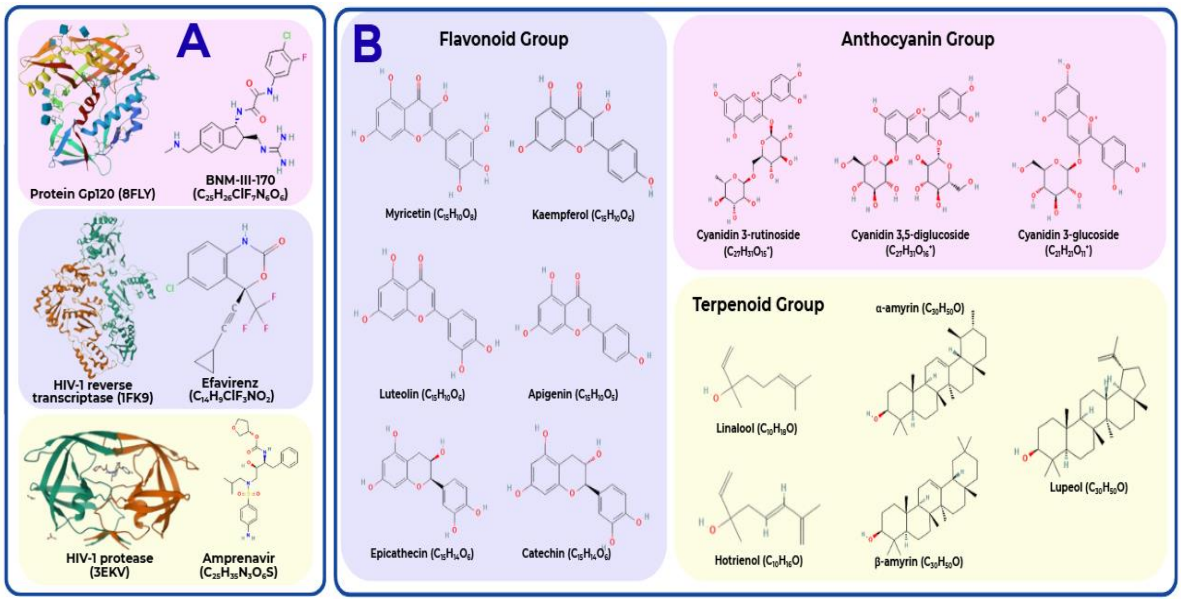

Figure 1. 3D and 2D Structures of research materials A) Targeted protein and their native ligands B) tested ligands from bioactive compound of *Ficus carica* L.

Preparation of Ligands and Target Proteins

Preparation of the target proteins was carried out using PyMOL. The water molecules were removed by selecting *action* > *remove waters*. The native ligand was then separated by selecting *actions* > *preset* > *ligand site* > *cartoon*, followed by *select native ligand* > *actions* > *extract object*, then saved in .pdb format. These water molecules removal and native ligands separation was performed to ensuring unobstructed access to the protein's active site for test compounds (Sari et al., 2020). Test ligands (.sdf) format were imported into PyRx, subjected to energy minimization to achieve their most stable conformations, then saved in .pdb format to enhance the reliability and accuracy of the docking results (Hanif et al., 2020).

Prediction of Physicochemical and Pharmacokinetic Properties (ADMET)

The physicochemical properties of compounds were assessed according Lipinski's Rule of Five (LRF), encompassing molecular weight (MW), partition coefficient (Log P), hydrogen bond acceptors and donors (HBA and HBD). The 3D structures of all test compounds (.sdf) were analyzed using SCFBio web server. Meanwhile, pharmacokinetic properties' prediction was analyzed using pkCSM and Protox server. The canonical SMILES of the ligands were input in the pkCSM to evaluate ADMET profiles: absorption, distribution, metabolism, excretion, and toxicity. The Protox server provided predictive information regarding compound toxicity, including skin sensitization, Ames toxicity, hepatotoxicity, and LD_{50} values. Compounds that do not pass Toxicity Test are not selected for further testing.

Method Validation by Setting the grid center and grid size

Prior to molecular docking, the grid center and grid size were adjusted by performing **redocking** of the native ligand (NL), including BNM-III-170 as the native ligand for the Gp120 protein, efavirenz (HIV-1 RT), and amprenavir (HIV-1 PR) into each receptor using PyRX. The grid center defined the coordinates of receptor (target protein) active site, while the grid size specifies the dimensions of the search space used for molecular docking (Indah Kurnia Klara et al., 2023). It was conducted by selecting *Vina Wizard* > *select molecules* > *forward* until grid box appeared. The grid box was then positioned at the center of the NL > *Run Vina* then saved in .pdb format. The docking resut was then validated by PyMOL to calculate the Root Mean Square Deviation (RMSD) value. The grid center and grid size numbers will be used as docking locations for the test ligand and target protein, if they

meet the requirements. The redocking process and coordinate adjustment must be repeated by defining the grid center and grid size until the required RMSD value is met. The protocol was considered valid if the RMSD value was below 2 Å. The *grid center* and *grid size* in this study are shown in Table 1.

Table 1. Validation results of molecular docking protocols

Native ligand	Target Protein	Grid Center			Grid Size			RMSD
		X	Y	Z	X	Y	Z	
BNM-III-170	GP120	-26,330	1,421	-74,969	12,000	17,405	14,728	0,672 Å
Efavirenz	HIV-1 RT	1,406	-37,006	20,376	10,087	9,536	10,522	0,872 Å
Amprenavir	HIV-1 Protease	19,836	30,879	14,743	14,748	13,447	12,910	0,702 Å

Molecular Docking

The Docking was assessed using PyRX software. the prepared test compounds or ligand (L) were docked with the target proteins one by one and each docking simulation was performed in triplicate. The procedure followed the same parameters as the validation process, including grid box dimensions and docking settings.

Data Visualization and Analysis

The data obtained from the molecular docking process were visualized with *Discovery Studio Visualizer* (DSV). The data were presented in visualized figures, tables and heatmap dendrograms generated using ClustVis (https://biit.cs.ut.ee/clustvis/) and subsequently analyzed descriptively.

RESULTS AND DISCUSSION

Physicochemical properties of *Ficus carica* Bioactive Compounds

In drug development, analysis of physicochemical properties is essential to evaluate oral drug-likeness. This analysis was carried out using Lipinski's Rule of Five (LRF), which analyzed molecular weight (MW), logP, number of hydrogen bond donors (HBD), and number of hydrogen bond acceptors (HBA) (Masduki et al., 2024). The result of Physicochemical test is presented in the figure 2.

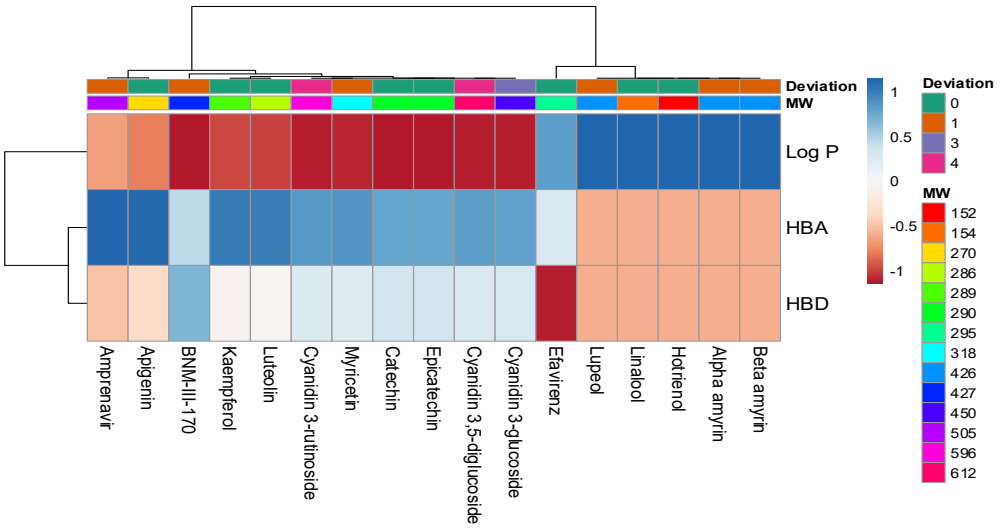

Figure 2. Prediction of the Physicochemical Properties of Fig (*Ficus carica*) Bioactive Compounds Based on Lipinski's Rule of Five (LRF)

Based on result, most of the ligands had regarding MW values < 500 g/mol (complied with LRF) and also lower than amprenavir (one of the ARVs), except two kinds of anthocyanin (*cyanidin 3,5-rutinoside* and *cyanidin 3-diglucoside*) which had MW > 500 g/mol. MW affects cellular uptake, as compounds exceeding 500 g/mol generally show reduced membrane permeability, while smaller molecules are more easily

absorbed (Adriani, 2024). For the logP parameter, the ideal value for oral drug candidates is ≤ 5 (Masduki et al., 2024). Compounds that exceed this threshold included all anthocyanins and three terpenoids (*α-amyrin, β-amyrin*, and *lupeol*), reflecting increased lipophilicity that can impede solubility and absorption, while logP that is too low indicates high hydrophilicity and limited membrane permeability (Klara et al., 2023).

The hydrogen bond acceptors (HBA) and donors (HBD) also play a crucial role in membrane permeability. The result shows that all anthocyanin compounds violated the Lipinski's rule for both parameters, while *myricetin* and the native ligand BNM-III-170 exceeded the HBD threshold. According to LRF, compounds with >10 HBAs and >5 HBDs generally exhibit low membrane permeability due to higher energetic requirements for absorption (Klara et al., 2023). In general, LRF describes a compound's ability to cross cell membranes via passive diffusion, based on its absorption and permeability characteristics. Compounds that comply all parameters are considered suitable for oral administration, while those that do not are better delivered through non-oral routes (Karami et al., 2022). A compound is considered as a potential oral-drug candidate if it violates no more than one LRF (Ekawasti et al., 2021). From figure 2 we can see that all anthocyanin ligands did not pass the LRF test because they had more than 1 violations from the LRF rules. While other compounds still pass the LRF because they have no violation or only have 1 violation from the LRF which is summarized in Table 2.

Tabel 2. summary of Fig Bioactive compound's physicochemical properties

Group Compound	Ligand	MW (g/mol)	Log P	HBA	HBD	Σ Violation
	LRF Standart	< 500	< 5	≤ 10	≤ 5	
Native Ligands	BNM-III-170	427	0.27	7	8*	1
	Efavirenz	295	3.72	3	1	0
	Amprenavir	505*	3.48	9	4	1
Antosianin	*Cyanidin 3,5-diglucoside*	612*	-2,37*	16*	11*	4*
	Cyanidin 3-glucoside	450	-0,76*	11*	8*	3*
	Cyanidin 3-rutinoside	596*	-1,91*	15*	10*	4*
Flavonoid	*Apigenin*	270	2,41	5	3	0
	Catechin	290	1,54	6	5	0
	Epicatechin	290	1,54	6	5	0
	Kaempferol	289	2,30	6	4	0
	Luteolin	286	2,12	6	4	0
	Myricetin	318	1,71	8	6*	1
Terpenoid	*Alpha amyrin*	426	8,02*	1	1	1
	Beta amyrin	426	8,16*	1	1	1
	Hotrienol	152	2,44	1	1	0
	Linalool	154	2,66	1	1	0
	Lupeol	426	8,02*	1	1	1

Note:
* = did not pass the LRF standart

Moreover, it can be seen that only five flavonoid derivatives *apigenin, catechin, epicatechin, kaempferol,* and *luteolin*, as well as the terpenoids *hotrienol* and *linalool*, comply with these rules. These compounds exhibit better physicochemical characteristics than BNM-III-170 and amprenavir, suggesting potential as oral-drug candidates.

Pharmacokinetic and Toxicity Profile of *Ficus carica* Bioactive Compounds

Pharmacokinetic and toxicity properties were evaluated through ADMET analysis to assess compound efficacy and safety. Predictions were performed using the pkCSM and ProTox web servers and visualized using ClustVis, as presented in Figure 3.

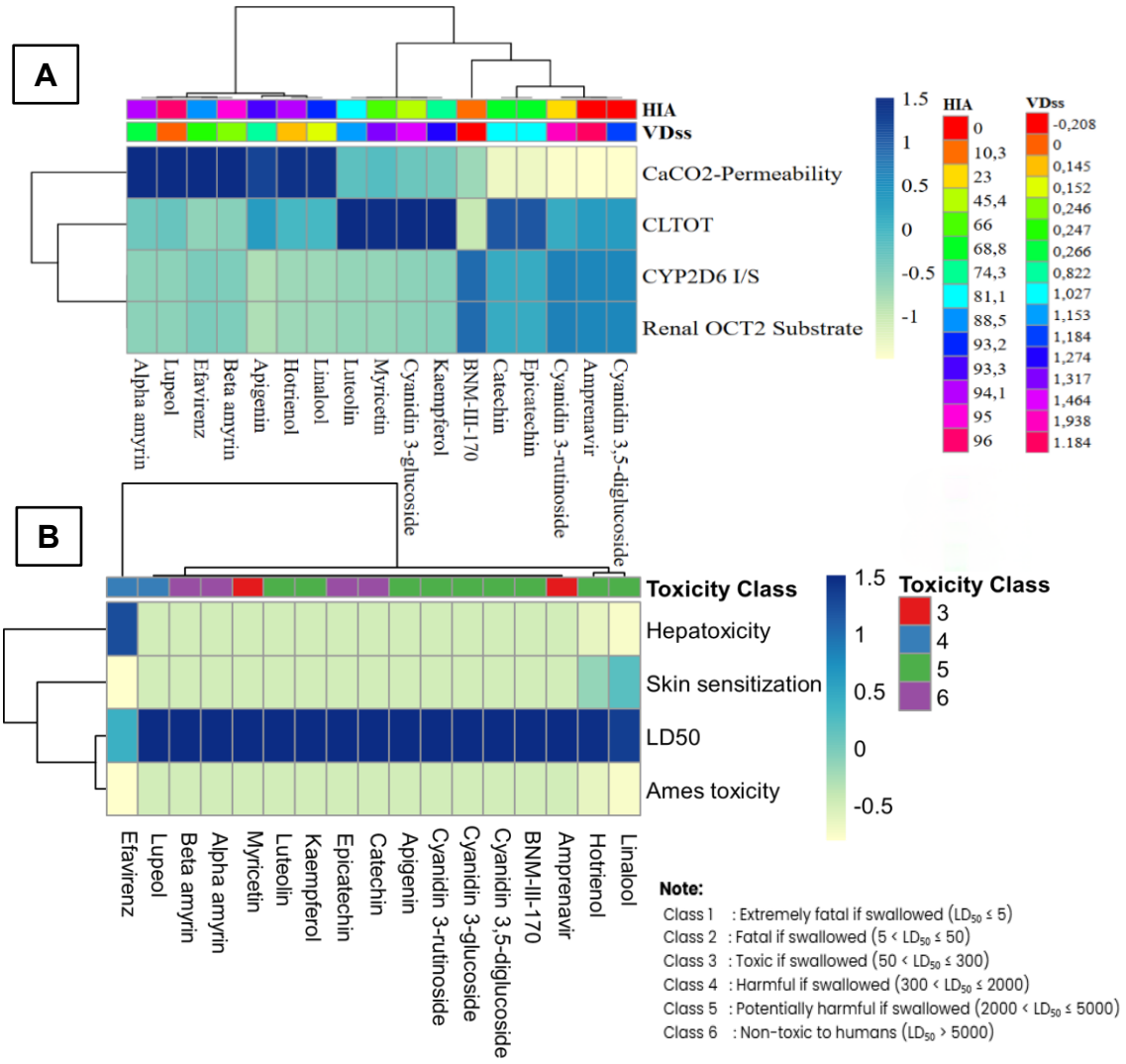

Figure 3. Pharmacokinetic Properties of Ligand Compounds: a) ADME; b) Toxicity

Intestinal absorption was evaluated using $CaCO_2$ permeability and Human Intestinal Absorption (HIA) as indicators of a compound's ability to penetrate the intestinal membrane. Compounds with $CaCO_2$ permeability > 0.90 in the pkCSM model are considered highly permeable (Abdullah et al., 2021). As shown in Figure 3a, all terpenoids and apigenin exhibited values above 0.90, indicating superior absorption potential relative to other compounds and native ligands (BNM-III-170 and amprenavir). HIA reflects the percentage of a compound absorbed via the gastrointestinal tract, with values below 30% indicating poor absorption(Abdullah et al., 2021; Hakiki et al., 2024). Most tested compounds showed HIA >30%, except *cyanidin 3,5-diglucoside* (0%) and *cyanidin 3-rutinoside* (23%), This limited is likely attribute to their significant molecular weight (>500 g/mol) and poor permeability in the $CaCO_2$ model, which restrict passive diffusion. Notably, several compounds, including cyanidin 3-glucoside, catechin, epicatechin, kaempferol, luteolin, and myricetin, displayed low $CaCO_2$ permeability (<0.90) but high HIA (>30%), suggesting that active transport mechanisms may facilitate their intestinal absorption (Artursson et al., 2001).

The Volume of Distribution at Steady State (VDss) reflects compound's ability to distribute into tissues relative to plasma. The Log VDss < -0.15 indicates low and Log VD > 0.45 indicates high tissue distribution (Prasetiyo et al., 2024). In this study, all ligands showed VDss values between 0 to 1.938 log L/kg, suggesting favorable tissue distribu-

tion, while the native ligand BNM-III-170 exhibited limited distribution (Log VD < -0.15). Distribution of a compound is influenced by lipophilicity, molecular size, pH, and plasma protein binding (Prasetiyo et al., 2024). Then for metabolism parameter, none of the tested compounds were predicted to interact with cytochrome P450 enzymes, particularly CYP2D6, indicating a stable metabolic profile with minimal risk of enzymatic interference. Total clearance (CLTOT) values ranged from –0.27 to 0.566 log mL/min/kg, with apigenin showing the highest clearance, suggesting faster elimination. Additionally, none of the compounds were identified as renal OCT2 substrates, implying a low potential for drug–drug interactions(Abdullah et al., 2021; Morrissey et al., 2013).

Toxicity evaluation using the Protox3 platform (Figure 3b) indicated that most tested compounds exhibited low toxicity, based on: LD_{50}, Ames mutagenicity, hepatotoxicity and skin sensitization. LD_{50} estimates the dose causing death in 50% of test subjects and defines toxicity classes (Prasetiyo et al., 2024). Most ligands fell into class 5 (LD_{50} = 2000–5000 mg/kg) or class 6 (LD_{50} > 5000 mg/kg), indicating low or negligible toxicity. Lupeol and efavirenz were class 4 (LD_{50} = 300–2000 mg/kg), while myricetin and amprenavir were class 3 (LD_{50} = 50–300 mg/kg), reflecting higher toxicity, although amprenavir remains clinically safe due to therapeutic doses being well below toxic levels (Hidayah et al., 2024). All compounds tested negative for skin sensitization, Ames mutagenicity, and hepatotoxicity, except hotrienol and linalool, which were positive for skin sensitization, likely due to oxidation forming reactive species (Wang et al., 2025). Efavirenz showed hepatotoxicity, consistent with clinical reports, particularly when co-administered with other hepatotoxic drugs such as lamivudine (Apriali et al., 2022; Zakiyah et al., 2022).

Re-Docking of Native Ligand and Targeted Protein

The RMSD value is the primary parameter for evaluating the docking protocols, which shows the extent of deviation between the re-docked native ligand and its original crystallographic conformation within the target protein. Docking is considered closely resemble the crystallographic ligand conformation when the RMSD value is <2 Å, indicating minimal positional deviation of the ligand (Apriali et al., 2022). A low RMSD suggests that the ligand occupies the same active site as its original position, whereas a high RMSD indicates an incorrect orientation or binding site, potentially leading to biologically irrelevant interactions (Aggarwal & Koes, 2020). If the RMSD exceeds 2 Å, grid parameters optimization is required.

As summarized in Table 1, all docking protocols met the acceptance criteria, with RMSD values below 2 Å. The highest validation accuracy was obtained for the Gp120 protein-BNM-III-170 complexed (RMSD = 0.672 Å). A lower RMSD value indicates greater accuracy in reproducing the native ligand binding pose, whereas higher values reflect increased deviation and potential error in predicting ligand-protein interactions (Susanti et al., 2019). Visual inspection of ligand conformations before and after redocking (Figure 4) further confirmed the reliability of the docking approach, supporting its suitability for subsequent molecular docking studies of test ligands with Gp120, HIV-1 RT, and HIV-1 PR.

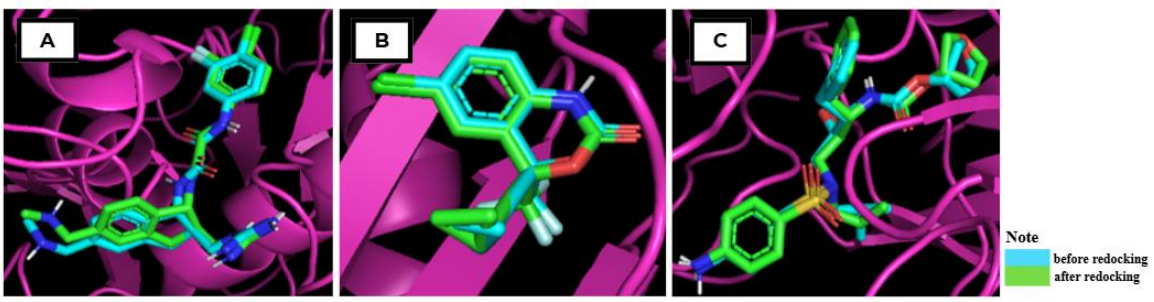

Figure 4. Visualization of the native ligands before (blue) and after redocking (green): (a) BNM-III-170, (b) Efavirenz, and (c) Amprenavir.

Molecular Docking of Bioactive Compounds from Fig (*Ficus carica* L.) to HIV-1 Target Proteins

Molecular docking simulations were conducted for 14 bioactive compounds derived from fig (*Ficus carica* L.), which belong to the anthocyanin, flavonoid, and terpenoid classes against three main HIV-1 target protein at the same time: Gp120, HIV-1 RT, and HIV-1 PR. This approach aims to evaluate the potential of fig compounds as candidates for multitarget therapy in HIV-1 infection, which is new in this research, considering that the common molecular docking study is only carried out on one candidate protein target. Docking was performed using the PyRx software with grid parameters as those in Table 1. These target proteins were selected to assess the multitarget potential of fig-derivedd compounds against HIV-1. The docking results for all compounds against the three proteins are summarized in Table 3.

Table 3. Molecular docking result of 14 Fig bioactive compounds to the three HIV-1 Proteins

Groups	Ligands	Gp120		HIV-1 RT		HIV-1 PR	
		ΔG (kcal/mol)	IC (μM)	ΔG (kcal/mol)	IC (μM)	ΔG (kcal/mol)	IC (μM)
Native	BNM-III-170	-10,1	0,039	-	-	-	-
	Efavirenz	-	-	-12,2	0,001	-	-
	Amprenavir	-	-	-	-	-9,7	0,076
Antosianin	*Cyanidin 3-glucoside*	-6,6	14,348	-3,4	3384,354	-8,8	0,349
	Cyanidin 3,5-diglucoside	-7,6	2,648	4,8*	ND	-8,8	0,349
	Cyanidin 3-rutinoside	-7,0	7,299	4,7*	ND	-8,7	0,413
Flavonoid	*Apigenin*	-7,0	7,299	-8,5	0,579	-8,2	0,961
	Catechin	-7,1	6,164	-8,2	0,961	-7,9	1,595
	Epicatechin	-7,4	3,713	-8,7	0,413	-8,2	0,961
	Kaempferol	-6,7	12,117	-8,5	0,579	-8,3	0,812
	Luteolin	-7,2	5,206	-8,8	0,369	-8,5	0,579
	Myricetin	-7,1	6,164	-8,1	1,138	-8,5	0,579
Terpenoid	*Alpha amyrin*	-6,7	12,117	18,2*	ND	-8,5	0,579
	Beta amyrin	-6,7	12,117	22,3*	ND	-8,4	0,685
	Hotrienol	-6,0	39,544	-6,8	10,234	-5,2	152,806
	Linalool	-6,2	28,205	-7,1	6,164	-4,9	253,680
	Lupeol	-6,6	10,234	8,9*	ND	-10,3	0,028

Note:
ΔG = Binding affinity values; IC = Inhibition constant; * = ΔG positive; ND= Not Detected; (-) = not analyzed; = candidate for multitarget antiretroviral

The docking results showed that all test ligands from fig (*Ficus carica* L.) exhibited negative (low) binding affinity energy (ΔG) toward the Gp120 protein target (ranging from -7.6 to -6.0 kcal/mol) and HIV-1 protease (-10.3 to -4.9 kcal/mol). In contrast, docking with the HIV-1 reverse transcriptase protein revealed five compounds with positive ΔG: *cyanidin 3,5-diglucoside* (4.8 kcal/mol), *cyanidin 3-rutinoside* (4.7 kcal/mol), both belonging to the anthocyanin group and three terpenoid derivatives: *α-amyrin, β-amyrin*, and *lupeol* with ΔG of 18.2, 22.3, and 8.9 kcal/mol, respectively. Lower ΔG generally indicate stronger and more stable ligand-receptor interactions. ΔG is influenced by the nature and strength of intermolecular interactions, the ligand's binding position relative to key residues, and the molecule's size and flexibility. Ligands that are excessively large or highly flexible tend to exhibit weaker binding affinities (Shamim et al., 2024). Meanwhile, the inhibition constant (IC) is directly related to ΔG; a lower IC values indicates that smaller ligand concentrations are required to effectively inhibit the enzymatic or receptor activity. Therefore, lower IC values reflect higher

ligand affinity and stronger, more stable binding to the target receptor (Puspita et al., 2022). In summary, both lower ΔG and Ki values suggest a more potent and stable ligand–receptor interaction.

Molecular docking interactions producing the lowest binding affinity energy indicate the strongest and most favorable ligand-receptor affinity (Mohanty & Mohanty, 2023). Accordingly, as shown in Table 2, several bioactive compounds from fig demonstrated good binding affinity toward all three HIV-1 target proteins. These include *cyanidin 3-glucoside* (anthocyanin group), all flavonoid derivatives, and two terpenoid compounds (*hotrienol* and *linalool*), which exhibited low binding affinity and inhibition constant (Ki) values. Among these compounds, *epicatechin* and *luteolin*, both belonging to the flavonoid class, showed the strongest and most stable binding to all three target proteins compared to other tested compounds, as indicated by their lowest binding affinity energies. Although their affinity values were slightly higher (less negative) than those of the respective native ligands, they remain within a favorable range, from -8.7 to -7.4 kcal/mol for epicatechin and -8.8 to -7.2 kcal/mol for luteolin. According to (Thahara et al., 2022), three bioactive compounds from red ginger, gingerol, 6-shogaol, and 8-shogaol were reported to inhibit the SARS-CoV-2 Mpro protein with ΔG ranging from –5.5 to –6.0 kcal/mol. These findings suggest that epicatechin and luteolin from fig fruit may also possess strong inhibitory potential against Gp120, HIV-1 RT, and HIV-1 PR due to their lower binding affinity values (more negative) compared to those of the red ginger metabolites, indicating a potentially stronger interaction with HIV-1 target proteins.

In addition, diverse intermolecular interactions—including hydrogen bonds (HB), hydrophobic interactions (HFI), Van der Waals (VDW), and electrostatic interactions (EI), contributes to the stability and strength of ligand-receptor complex, thereby enhancing ligand binding effectiveness. Molecular interactions between the tested compounds and target proteins were analyzed by visualizing the docking results using DSV. Representative interaction profiles of compounds with the highest binding affinities for each target protein are visualized in Figure 5.

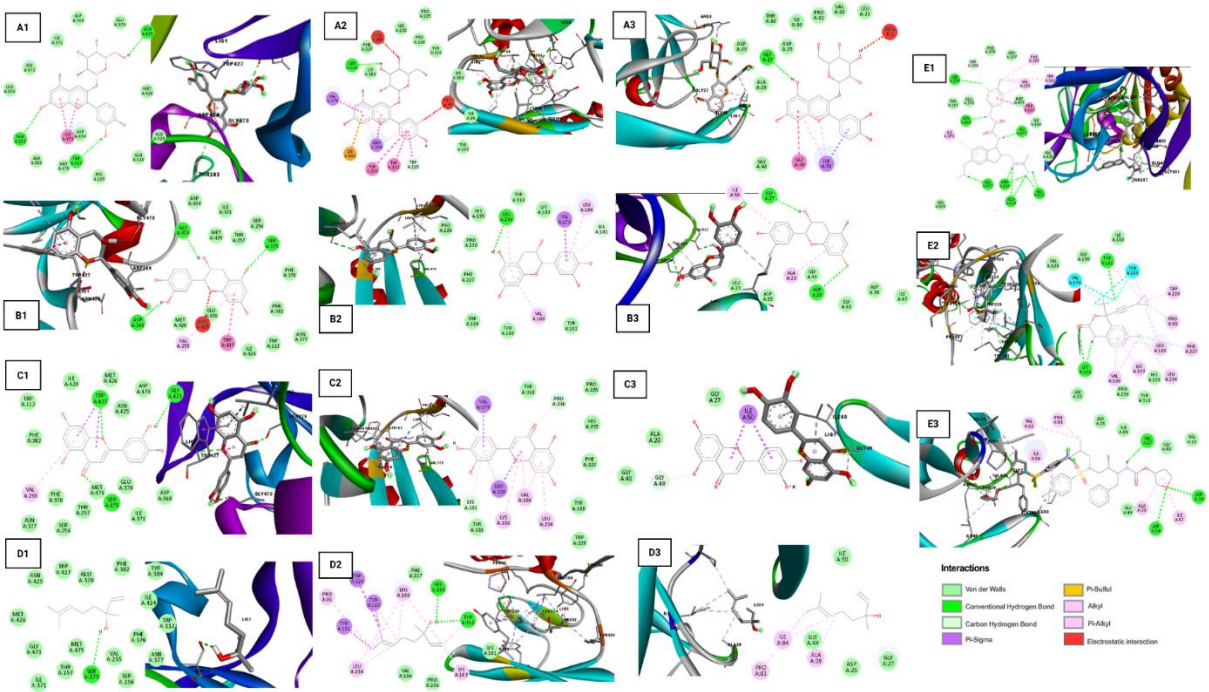

Figure 5. 2D visualization of the molecular interactions of several ligands with three HIV-1 proteins:1) Gp 120; 2) HIV-1 RT; 3) HIV-1 PR; (A) Cyanidin, 3 glucoside; (B) epicatechin, (C) luteolin, (D) linalool, (E) native ligand

The 2D interaction profiles (Figure 5) were further analyzed to determine and quantify the number of bonds formed for each type of interaction, as well as the similarity of interacting amino acid residues. The results are summarized in Tables 3 and 4. Table 3 shows the variation in both the type and number of bonds formed in each molecular docking result between ligands and the target proteins. Anthocyanin derivatives exhibited the highest total number of bonds with the receptors compared to other compound classes. However, based on the binding affinity values, these compounds did not exhibit the strongest binding for each protein target (Table 2). This finding indicates that interaction stability and strength are not determined solely by the total number of bonds. Interaction type, bond distance, and binding location also play critical roles. Consequently, identifying ligand interactions with key active-site amino acid residues of the target proteins is essential, as these residues define the specific binding sites engaged by the test ligands (Bare et al., 2019).

Tabel 3. Types of interactions and number of bonds formed in molecular docking of ligands and target protein

Ligands	Total Number of Bond											
	GP120				HIV-1 RT				HIV-1 PR			
	HB	HFI	VDW	EI	HB	HFI	VDW	EI	HB	HFI	VDW	EI
BNM-III-170	8	5	8	0	-	-	-	-	-	-	-	-
Efavirenz	-	-	-	-	2	7	6	0	-	-	-	-
Amprenavir	-	-	-	-	-	-	-	-	3	5	6	0
Cyanidin 3-glucoside	3	1	12	0	2	4	9	1	1	2	9	0
Cyanidin 3,5-diglucoside	4	1	14	1	3	3	14	1	3	2	12	0
Cyanidin 3-rutinoside	4	1	12	0	4	5	11	0	1	3	12	0
Apigenin	2	1	14	0	2	5	6	0	2	1	2	0
Catechin	2	1	13	0	2	5	8	0	1	2	2	0
Epicatechin	3	2	12	0	2	3	9	0	2	2	6	0
Kaempferol	3	1	12	0	2	4	8	0	0	2	3	0
Luteolin	3	1	14	0	2	5	7	0	1	1	3	0
Myricetin	4	1	12	0	1	4	10	0	2	1	5	0
Alpha amyrin	3	0	9	0	0	1	14	0	1	0	11	0
Beta amyrin	1	0	11	0	0	2	9	0	1	0	11	0
Hotrienol	1	4	12	0	2	5	7	0	0	1	3	0
Linalool	1	0	16	0	2	7	4	0	0	3	4	0
Lupeol	1	0	12	0	0	4	8	0	0	1	7	0

note:
(-) = Not analyzed; = the most total bonds formed; HB = Hydrogen bond; HFI = Hydrophobic interaction; VDW = Van der Walls interaction; EI = Electrostatic interaction

Amino acid residues involved in interaction between the native ligand and the receptor were compared with those formed by the test ligand. The degree of residue similarity is used as an indicator of comparable interaction types and binding strength at the target receptor (Lailiyyah et al., 2023). Higher similarity in interacting residues suggests a greater potential of the compound to function as an effective inhibitor (Sinurat et al., 2021). The Binding Site Similarity (BSS) values were calculated using the BSS equation (Amal & Hayati, 2025). the numbers of shared residues along with the corresponding BSS values are presented in Table 4.

Table 4. Similarity of amino acid residues of test ligands in each target protein

Ligands	Σ Similarity of AA recidues			BSS (%)		
	Gp120	HIV-1 RT	HIV-1 PR	Gp120	HIV-1 RT	HIV-1 PR
Cyanidin 3,5-diglucoside	7	3	6	33,33	20,00	42,86
Cyanidin 3-glucoside	4	4	6	19,05	26,67	42,86
Cyanidin 3-rutinoside	4	3	9	19,05	20,00	64,29
Apigenin	8	7	3	38,10	46,67	21,43
Catechin	8	3	2	38,10	20,00	14,29
Epicatechin	9	5	8	42,86	33,33	57,14
Kaempferol	8	6	2	38,10	40,00	14,29
Luteolin	9	7	2	42,86	46,67	14,29
Myricetin	8	8	5	38,10	53,33	35,71
Alpha amyrin	3	4	5	14,29	26,67	35,71
Beta amyrin	1	6	5	4,76	40,00	35,71
Hotrienol	11	5	2	52,38	33,33	14,29
Linalool	7	6	4	33,33	40,00	28,57
Lupeol	3	6	5	14,29	40,00	35,71

■ = BSS > 50% ■ = BSS > 40% and <50%

In this study, amino acid residue similarity was classified into three categories to streamline the analysis: Group 1 comprised compounds with BSS values >50%, Group 2 included those with BSS values between >40% and <50%, and Group 3 consisted of compounds with BSS values ≤40%. As shown in Table 4, only four compounds belongs to Group 1, Cyanidin 3-rutinoside (64.29%), Epicatechin (57.14%), Myricetin (53.33%), and Hotrienol (52.38%). Group 2 contained six compounds, including Luteolin (46.67% with HIV-1 RT; 42.86% with gp120), Apigenin (46.67% with HIV-1 RT), Cyanidin 3,5-diglucoside and Cyanidin 3-glucoside (42.86% with HIV-1 protease), as well as Epicatechin (42.86% with gp120). The remaining compounds exhibited BSS values ranging from 4.76% to 40.00%.

Notably, BSS values did not always correlate with other interaction parameters. For instance, Cyanidin 3-rutinoside showed the highest BSS value (64.29%) with HIV-1 protease yet did not exhibit the greatest number of interactions; Table 3 shows only 16 total interactions for this ligand, whereas Cyanidin 3,5-diglucoside achieved the highest interaction count (20) with HIV-1 reverse transcriptase. These findings indicate that residue-based analysis alone cannot capture the full complexity of intermolecular interactions. A holistic evaluation incorporating total interaction, interaction types, and residue bond relationships is therefore essential. A complete analysis of docking results, physicochemical properties, pharmacokinetics, and toxicity for both test and native ligands is presented in the table 5.

Tabel 5. analysis results of potential compounds as multitarget hiv-1 therapy candidates

Groups	Ligands	ΔG (kcal/mol)			LRF	ADME	Toxicity Class
		Gp120	HIV-1 RT	HIV-1 PR			
Antosianin	*Cyanidin 3-glucoside*	-6.6	-3.4	-8.8	-	0	5
	Cyanidin 3,5-diglucoside	-7.6	4.8	-8.8	-	1	5
	Cyanidin 3-rutinoside	-7.0	4.7	-8.7	-	1	5
Flavonoid	*Apigenin*	-7.0	-8.5	-8.2	+	0	5
	Catechin	-7.1	-8.2	-7.9	+	0	6
	Epicatechin	-7.4	-8.7	-8.2	+	0	6
	Kaempferol	-6.7	-8.5	-8.3	+	0	5
	*Luteolin**	-7.2	-8.8	-8.5	+	0	5
	Myricetin	-7.1	-8.1	-8.5	+	1	3

Groups	Ligands	ΔG (kcal/mol)			LRF	ADME	Toxicity Class
		Gp120	HIV-1 RT	HIV-1 PR			
Terpenoid	*Alpha amyrin*	-6.7	18.2	-8.5	+	0	6
	Beta amyrin	-6.7	22.3	-8.4	+	0	6
	Hotrienol	-6.0	-6.8	-5.2	+	1	5
	Linalool	-6.2	-7.1	-4.9	+	1	5
	Lupeol	-6.6	8.9	-10.3	+	0	4

note:
- = Did not pass Lipinski's rule
+ = passed Lipinski's rule
0 = passed ADMET evaluation
1 = Did not passed ADMET evaluation (1 parameter did not meet criteria)

Based on the results of molecular docking, physicochemical property analysis, pharmacokinetic profiling, and toxicity evaluation, several bioactive compounds from fig, specifically five flavonoid derivatives (Apigenin, Catechin, Epicatechin, Kaempferol, and Luteolin), are predicted to be potential multitarget HIV-1 therapy candidates by inhibiting the activity of Gp120 protein, HIV-1 reverse transcriptase, and HIV-1 protease. In silico analysis in this study indicates that these five compounds are predicted to bind effectively to Gp120, thereby blocking the adhesion of HIV to $CD4^+$ T cell receptors; inhibit HIV-1 reverse transcriptase, preventing the synthesis of viral cDNA from RNA and halting viral replication; and suppress HIV-1 protease activity, interfering with viral protein maturation. However, this study only tested three target proteins, so it is necessary to carry out further analysis involving other proteins that play a role in the HIV-1 life cycle to ensure the compound's potential as a multitarget therapy candidate.

CONCLUSION

The result of this research, indicate that five out of six flavonoid derivatives (*Apigenin, Catechin, Epicatechin, Kaempferol*, and *Luteolin*) from fig (*Ficus carica* L.) exhibit potential as multitarget agents against HIV-1, as indicated by their relatively low binding affinity energies and inhibition constants across all three target proteins. Among these compounds, *Luteolin* demonstrated the highest potential, showing the lowest (most negative) binding affinity values with all three targets: Gp120 (-7.2 kcal/mol), HIV-1 reverse transcriptase (-8.8 kcal/mol), and HIV-1 protease (-8.5 kcal/mol) along with low inhibition constants. Luteolin also formed strong interactions with nine, seven, and two amino acid residues at the active sites of Gp120, HIV-1 reverse transcriptase, and HIV-1 protease, respectively. Furthermore, luteolin (flavonoid) from fig emerges as the most promising safe oral multitarget therapy candidate against HIV-1, because it has favorable physicochemical and pharmacokinetic properties. However, this result still needed further analysis such as molecular dynamics simulation to evaluate the stability of dynamic ligand-protein interactions in conditions close to real biological systems, so as to strengthen static docking results. In addition, in vitro and in vivo laboratory tests are still needed to confirm the effectiveness of the compound as a candidate for HIV antiviral drugs.

CONFLICT OF INTEREST

The author declares the absence of any conflicts of interest concerning this article's publication. All authors contributed to this study. M. was responsible for research design, supervised the study and manuscript drafting; A.A. contributed to data analysis; R.T.N. conducted the molecular docking analysis, data validation, and visualization; while Y.S. and R.A.U. contributed to physicochemical and pharmacokinetic analysis and provided critical input for the interpretation and discussion of the results.

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