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BIOINFORMATICS STUDY OF THE SELECTIVE INHIBITOR FROM *GARCINIA MANGOSTANA* L. TACKLE HIV-1 INFECTION

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KEY WORDS:
antiretroviral, bioinformatics, Garcinia mangostana, HIV-1, protease inhibitor

ABSTRACT

HIV has a host cell, T-cell lymphocytes with CD4+ receptors. HIV drugs have the inhibitory activity on HIV-1 protease by producing chemical bonding interactions such as hydrogen and hydrophobic. However, some cases show long-term side effects that may be harmful from the use of synthetic antiretrovirals. This requires new innovations to make drugs based on natural resources or alternative medicine for handling these cases. Natural-based drugs are claimed to reduce the side effects produced. *Garcinia mangostana* L. or queen of fruit is widely found in Southeast Asia. Many parts of this plant, such as fruits, are used for traditional medicine. Research with *in vitro* and *in vivo* approaches reveals that mangostin compounds from *Garcinia mangostana* L. can be an antiviral candidate. *Garcinia mangostana* L. has the main chemical compounds of garciniaxanthone, garcinone A, and mangostin. This study uses garciniaxanthone, garcinone A, and mangostin compounds to reveal the molecular mechanism of the antiviral activity in *Garcinia mangostana* L. through inhibition of HIV-1 protease with a bioinformatics approach. *In silico* methods used in this study are druglikeness, molecular docking, interactions, visualization, and dynamic simulation. Garciniaxanthon B, garcinone B, and beta-mangostin from *Garcinia mangostana* L. have potential as antiretroviral agents for the treatment of HIV-1 infection. The three compounds are predicted to inhibit the protease activity in HIV-1 with a more negative binding affinity score, form ligand-protein molecular complexes with van der Waals, hydrogen, pi/alkyl/anion/sigma bonds, form stable bonds and drug-like molecules.

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БИОИНФОРМАТИЧЕСКОЕ ИЗУЧЕНИЕ СЕЛЕКТИВНОГО ИНГИБИТОРА ИЗ *GARCINIA MANGOSTANA* L. БОРЬБА С ВИЧ-1-ИНФЕКЦИЕЙ

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КЛЮЧЕВЫЕ СЛОВА:
антиретровирусные препараты, биоинформатика, Garcinia mangostana, ВИЧ-1, ингибитор протеазы

АННОТАЦИЯ

ВИЧ имеет клетку-хозяина, Т-клеточные лимфоциты с рецепторами CD4+. Препараты против ВИЧ обладают ингибирующей активностью в отношении протеазы ВИЧ-1, создавая химические связи, такие как водородные и гидрофобные. Однако в некоторых случаях наблюдаются долгосрочные побочные эффекты, которые могут быть вредными от использования синтетических антиретровирусных препаратов. Это требует новых инноваций для создания лекарств на основе природных ресурсов или альтернативной медицины для лечения этих случаев. Также утверждается, что лекарства на натуральной основе уменьшают возникающие побочные эффекты. *Garcinia mangostana L.* или королева фруктов широко распространена в Юго-Восточной Азии, многие части этого растения, например плоды, используются в традиционной медицине. Исследования *in vitro* и *in vivo* показывают, что соединения мангустина из *Garcinia mangostana* L. могут быть кандидатами на противовирусные препараты. *Garcinia mangostana* L. содержит основные химические соединения гарциниаксантона, гарцинона А и мангостина. В этом исследовании используются соединения гарциниаксантона, гарцинона А и мангустина для выявления молекулярного механизма противовирусной активности *Garcinia mangostana* L. посредством ингибирования протеазы ВИЧ-1 с помощью биоинформатического подхода. Методы *in silico*, используемые в этом исследовании, включают подобие лекарствам, молекулярный докинг, взаимодействия, визуализацию и динамическое моделирование. Гарциниаксантон В, гарцинон В и бета-мангостин из *Garcinia mangostana* L. потенциально могут использоваться в качестве антиретровирусных средств для лечения

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инфекции ВИЧ-1. Предполагается, что эти три соединения ингибируют протеазную активность ВИЧ-1 с более отрицательным показателем аффинности связывания, образуют молекулярные комплексы лиганд-белок с ван-дерваальсовыми, водородными, пи/алкил/анионными/сигма-связями, образуют стабильные связи и подобные лекарствам молекулы.

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1. Introduction

Garcinia mangostana L. or the queen of fruit is widely found in Southeast Asia. Many parts of this plant, such as fruits, are used for traditional medicine. *Garcinia mangostana* L. is a popular plant for alternative medicine found in Asia that contains several chemical compounds such as triterpenoids, flavonoids, and xanthones. Extracts from this plant can be used in traditional medicine for treatment of several diseases such as diarrhea, infection, dysentery, inflammation, cholera, and fever. Compounds from *Garcinia mangostana* such as α-mangostin have pharmacological effects such as the antioxidant activity [1,2]. *Garcinia mangostana* L. has the main chemical compounds of garciniaxanthone, garcinone A, and mangostin [3,4]. The antiviral activity in other cases was also found through *in vivo* research on the administration of the *Garcinia mangostana* L. extract, which can inhibit the replication of the DENV-2 virus. *In vitro* and *in vivo* studies show that α-mangostin from the *Garcinia mangostana* extract can trigger a significant decrease in viral replication in serum and muscle. Previous research reveals that mangostin compounds from *Garcinia mangostana* L. can be an antiviral candidate against chikungunya virus (CHIKV) infection. The cell model in the study was Vero cells (VC). The results show that mangostin with a concentration of 8 μM can increase cell viability and reduce virus replication [5]. The antiviral activity of *Garcinia mangostana* L. may be used as an HIV-1 antiviral candidate, as many previous studies revealed.

Human immunodeficiency virus (HIV) consists of two types, HIV-1 and HIV-2 (only found in West Africa). The first cases of HIV-1 infection were identified in 1981 in San Francisco and New York. HIV was found to be a trigger for opportunistic diseases of the immune system or acquired immune deficiency syndrome (AIDS) based on genomic analysis of the virus [6,7]. HIV-2 has a lower prevalence than HIV-1 and is very slow to initiate AIDS in patients. The protease enzymes of HIV-1 are called aspartic proteases used as the main targets for AIDS treatment. Ten years after the discovery of protease (PR) in HIV-1, a drug with a selective antagonist mechanism was discovered in 1987. Then a few months later, a phase 1 clinical trial was conducted on inhibitor candidates such as saquinavir in 1989 (approved in 1995), as well as ritonavir and indinavir. By 2009, around ten protease inhibitor candidates were launched in the market for HIV treatment [8,9]. However, several reports show that long-term side effects, such as nausea, diarrhea, skin rash, etc., can be caused by protease inhibitors from synthetic drugs. In addition, HIV-1 drugs are expensive and cannot be reached by patients with lower economic conditions [10]. This requires new innovations to make drugs based on natural resources or alternative medicine for handling these cases. Natural-based drugs are claimed to reduce the side effects produced.

HIV-1 is a class of retroviruses with RNA-like genetic material. HIV infects T lymphocyte cells with CD4+ representation on the surface. HIV infects host cells requiring a fusion mechanism at the cell membrane. The first stage of replication is the interaction of envelope spike glycoprotein consisting of gp120 and gp41 on host cell receptors (CCR5 & CXCR4) triggering conformational changes in the envelope spike glycoprotein [11,12]. The process produces a hole for the viral capsid to enter the cell. During the entry process several viral enzymes work such as reverse transcriptase to produce cDNA from ssRNA, and integrase for integration of HIV-1 cDNA to form mRNA [13]. The translational process of viral mRNA produces polypeptides, then proteases cut HIV-1 polypeptides into short peptides for the virus assembly. Protease inhibitors act to inhibit the virus assembly process and trigger the failure of the replication process. The inhibitor binds to the functional domain of the enzyme through hydrogen bonding and hydrophobic interactions to produce the inhibitory activity. Hydrogen and hydrophobic bonds play an important role in drug stability in triggering the inhibitory activity on the target. Both bonds play a role in inducing a specific biological response when a ligand-protein complex is formed [14,15]. Candidate inhibitors of HIV-1 proteases must have hydrogen and hydrophobic interactions when binding to functional domains on the target.

Previous research only revealed the potential of *Garcinia mangostana* L. referring to mangostin compounds and the molecular mechanism of compounds-target interaction is not yet known. Bioinformatics can be used to predict the molecular mechanism of therapeutic effects of drug candidate compounds through bioactivity tests, docking simulations, and molecular dynamics. This study uses garciniaxanthone, garcinone A, and mangostin compounds to reveal the molecular mechanism of the antiviral activity in *Garcinia mangostana* L. through inhibition of HIV-1 protease with a bioinformatics approach.

2. Objects and methods

Garciniaxanthone, garcinone, and mangostin from *Garcinia mangostana* L. consisting of garciniaxanthone A, garciniaxanthone B, garciniaxanthone C, garcinone A, garcinone B, garcinone C, alpha-mangostin, beta-mangostin, and gamma-mangostin as ligands were used in this study. All information on the ligands such as CID, formula, creation, modification, SMILES, and *sdf* files were obtained from PubChem [16]. Minimization of ligands was performed through OpenBabel v2.3.1 software for conversion of *sdf* files to *pdb* and increasing the flexibility of ligand molecules. The target in this study was HIV-1 protease RCSB PDB ID: 1DMP obtained from Protein Databank (PDB; https://www.rcsb.org) [17] with *pdb* file. The removal of water molecules and native ligands on the protein was performed through PyMOL v.2.5.2 software (Schrödinger, Inc., USA) with an academic license to optimize the molecular docking simulation process.

Similarity of physicochemical properties of query compounds with drug molecules in this study was identified through SwissADME (http://www.swissadme.ch) [18] by referring to rules such as Lipinski, Ghose, Veber, Egan, and Muegge. A bioavailability score was used in this study to determine a drug-like molecule. A drug-like molecule is a compound that has similar properties to drug molecules referring to physicochemical properties such as molecular weight, refractivity, number of hydrogen bonds, lipophilicity, and others. Ligands with drug-like molecule properties can circulate in the body, if they have a bioavailability score ⩾0.5 and trigger specific activity on the target [19,20].

Docking simulation in this study aims to identify the inhibitor activity of garcinoxanthone, mangostin, and garcinone derivates from *Garcinia mangostana* L. on HIV-1 protease. Docking is an *in silico* method to determine the level of the ligand activity on the target referring to the binding affinity score [21,22]. Determination of the docking grid on HIV-1 protease in this study was as follows: center (Å) X: −13.452 Y: 19.535 Z: 29.487 and dimensions (Å) X: 30.378 Y: 24.648 Z: 31.525; then docking simulation was performed through PyRx v1.0 software (Scripps Research, USA). Ligand-protein molecular complexes from docking simulations are displayed as transparent surfaces, cartoons, and sticks through structural selection in PyMOL v.2.5.2 software (Schrödinger, Inc., USA) with an academic license for standard publication visualization. Protein coloring is a single color and ligand coloring is based on C, H, N, and O atoms [23,24].

Identification of the position and type of chemical bond interactions in the ligand-protein molecular complex was performed through Discovery Studio Visualizer™ v.16.1 software (Dassault Systèmes SE, France). Weak bond interactions, such as van der Waals, hydrogen, electrostatic, hydrophobic, and pi/alkyl bond interactions, were formed in the ligand-protein complex [25,26]. These bonds contribute to affecting the activity and biological response of the target when an interaction with the ligand is formed [27,28].

Stability analysis of chemical bond interactions in ligand-protein interaction hot spots is performed through molecular dynamic simulation on the CABS-flex 2.0 server (http://biocomp.chem.uw.edu.pl/CABSflex2) [29]. This server identifies the stability of ligand-protein molecular complexes by calculating structural flexibility through large-scale conformational simulations. The output score of the simulation results is the root-mean-square fluctuation (RMSF) for the determination of molecular complex stability [29,30].

3. Results and discussion

3.1. Compound and target collection

Garcinia mangostana L. can act as an antiviral candidate based on the results of the *in vitro* and *in vivo* analysis. Previous studies have shown that compounds from these plants can inhibit target virus replication and increase cell viability. *Garcinia mangostana* L. has other benefits such as the

Table 1. **Ligand information from the chemical compound database**
Таблица 1. **Информация о лигандах из базы данных химических соединений**

Compound	CID	Formula	Created	Modified	SMILES
Garciniaxanthone A	15293708	C23H24O5	2007–02–09	2022–12–24	CC(=CCC1=C(C2=C(C=C1) C(=O)C3=C(C(=CC(=C3O2) O)C(C)(C)C=C)O)O)C
Garciniaxanthone B	10407298	C23H22O5	2006–10–25	2022–12–24	CC1(C=CC2=C(O1) C3=C(C=C2) C(=O)C4=C(C(=CC(=C4O3) O)C(C)(C)C=C)O)C
Garciniaxanthone C	9842847	C23H24O5	2006–10–25	2022–12–24	CC(=CCC1=C(C2=C(C=C1) C(=O)C3=C(C=C(C(=C3O2) O)CC=C(C)C)O)O)C
Garcinone A	70689919	C23H24O5	2013–02–04	2022–12–24	CC(=CCC1=C(C(=C2C(=C1O)C(=O)C3=C(O2) C=C(C=C3) O)CC=C(C)C)O)C
Garcinone B	5495928	C23H22O6	2005–08–01	2022–12–24	CC(=CCC1=C(C2=C(C=C1O)OC3=C(C2=O)C4=C(C(=C3) O)OC(C=C4)(C)C)O)C
Garcinone C	44159808	C23H26O7	2009–08–24	2022–12–24	CC(=CCC1=C(C2=C(C=C1O)OC3=C(C2=O)C(=C(C(=C3) O)O)CCC(C)(C)O)O)C
Alpha-mangostin	5281650	C24H26O6	2005–03–26	2022–12–24	CC(=CCC1=C(C2=C(C=C1O)OC3=C(C2=O)C(=C(C(=C3) O)OC)CC=C(C)C)O)C
Beta-mangostin	5495925	C25H28O6	2005–08–01	2022–12–24	CC(=CCC1=C(C=C2C(=C1O)C(=O)C3=C(O2) C=C(C(=C3CC=C(C)C)OC)O)OC)C
Gamma-mangostin	5464078	C23H24O6	2005–08–01	2022–12–24	CC(=CCC1=C(C2=C(C=C1O)OC3=C(C2=O)C(=C(C(=C3) O)O)CC=C(C)C)O)C

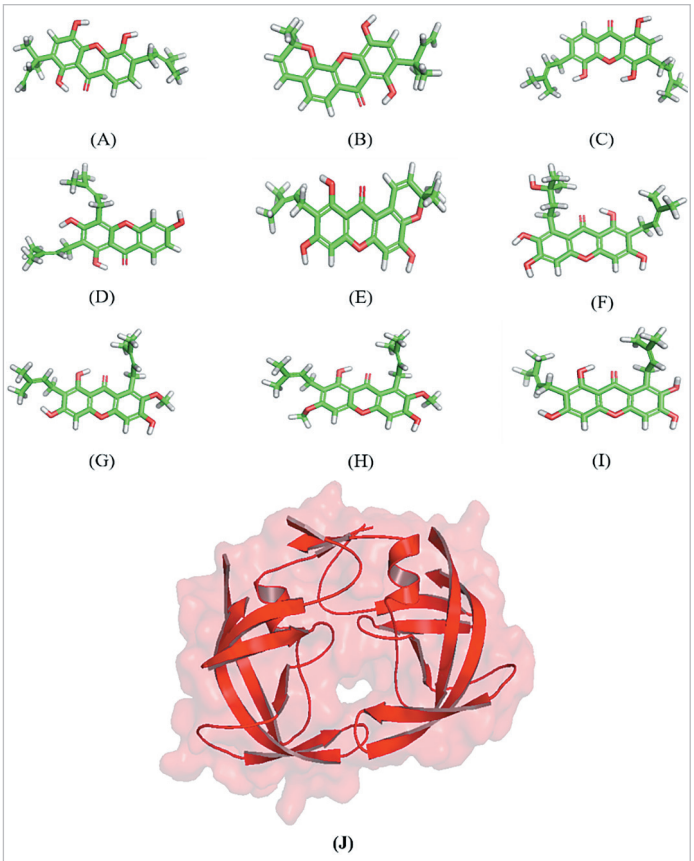

Figure 1. **Structural visualization of ligands and target. (A) garciniaxanthone A, (B) garciniaxanthone B, (C) garciniaxanthone C, (D) garcinone A, (E) garcinone B, (F) garcinone C, (G) alpha-mangostin, (H) beta-mangostin, (I) gamma-mangostin, and (J) HIV-1 protease**
Рисунок 1. **Структурная визуализация лигандов и цели. (A) гарциниаксантон A, (B) гарциниаксантон B, (C) гарциниаксантон C, (D) гарцинон A, (E) гарцинон B, (F) гарцинон C, (G) альфа-мангостин, (H) бета-мангостин, (I) гамма-мангостин и (J) протеаза ВИЧ-1**

anti-inflammatory, antioxidant, antidiabetic, and antimicrobial activities [31–33]. Screening of natural compounds-based HIV-1 antiviral candidates through the computational approach is important in this study for the discovery of new treatment alternatives and prediction of molecular mechanisms of antiviral compounds from *Garcinia mangostana* L. Chemical compounds of garciniaxanthone, garcinone, and mangostin derivatives from *Garcinia mangostana* L. with information on compound name, CID, formula, creation, modification, SMILES, and sdf file were obtained from the database (Table 1). The 3D visualization of ligands was performed with the display of sticks and transparent cartoons on the target (Figure 1).

3.2. Drug-like compounds

The similarity of query ligands with drug molecules in terms of several druglikeness rules such as Lipinski, Ghose, Veber, Egan, and Muegge was analyzed with Canonical SMILES input from garcinoxanthone, mangostin, and garcinone derivative compounds [34–36]. The results of the druglikeness analysis show that all query compounds from *Garcinia mangostana* L. are probable drug-like molecules because they fulfill at least 3 druglikeness rules such as Lipinski, Ghose, Veber, and Egan. All query compounds have a bioavailability score of 0.55 (Table 2). The query compound can have activity similar to drug molecules and can circulate in the body of *Homo sapiens* because it has a bioavailability score of ⩾0.5. The query is also predicted to pass through selectively permeable membranes to the target in cells [37].

Table 2. **The result of drug-like molecule prediction**
Таблица 2. **Результат прогнозирования подобных лекарствам молекул**

Compound	Lipinski	Ghose	Veber	Egan	Muegge	Bioavailability score	Probable
Garciniaxanthone A	Yes	Yes	Yes	Yes	No	0.55	Drug-like molecule
Garciniaxanthone B	Yes	Yes	Yes	Yes	No	0.55	Drug-like molecule
Garciniaxanthone C	Yes	Yes	Yes	Yes	No	0.55	Drug-like molecule
Garcinone A	Yes	Yes	Yes	Yes	No	0.55	Drug-like molecule
Garcinone B	Yes	Yes	Yes	Yes	No	0.55	Drug-like molecule
Garcinone C	Yes	Yes	Yes	Yes	Yes	0.55	Drug-like molecule
Alpha-mangostin	Yes	Yes	Yes	Yes	No	0.55	Drug-like molecule
Beta-mangostin	Yes	Yes	Yes	Yes	No	0.55	Drug-like molecule
Gamma-mangostin	Yes	Yes	Yes	Yes	No	0.55	Drug-like molecule

3.3. Molecular interaction between the HIV-1 protease and query compound

Simulation of ligand-protein molecular interactions in this study was performed through the docking method with grid position: center (Å) X: −13.452 Y: 19.535 Z: 29.487 and dimensions (Å) X: 30.378 Y: 24.648 Z: 31.525 on HIV-1 protease. Molecular docking aims to screen the ligand activity on the target with reference to the binding affinity score [38]. Binding affinity is a negative free energy from the result of ligand-protein complex interaction that works according to the law of thermodynamics [39,40]. This is also proportional to the increase in the inhibitor activity on the target by ligands with more negative binding affinity scores. Docking simulation results show that garciniaxanthone B (−9.3 kcal/mol), garcinone B (−9.4 kcal/mol), and beta-mangostin (−9.3 kcal/mol) have more negative binding affinity scores than other derivative compounds (Table 3). This indicates that the three compounds from *Garcinia mangostana* L. have the potential to be good HIV-1 protease inhibitor candidates. The 3D visualization of ligand-protein complexes from docking results is displayed with the structure of transparent surfaces, cartoons, sticks, and single-color selection (Figure 2).

Table 3. **Comparison of binding affinity scores**
Таблица 3. **Сравнение баллов аффинности связывания**

Compound	CID	Target	PDB ID	Binding affinity (kcal/mol)
Garciniaxanthone A	15293708	HIV-1 protease	1DMP	−8.9
Garciniaxanthone B	10407298	HIV-1 protease	1DMP	**−9.3**
Garciniaxanthone C	9842847	HIV-1 protease	1DMP	−9.1
Garcinone A	70689919	HIV-1 protease	1DMP	−8.8
Garcinone B	5495928	HIV-1 protease	1DMP	**−9.4**
Garcinone C	44159808	HIV-1 protease	1DMP	−8.5
Alpha-mangostin	5281650	HIV-1 protease	1DMP	−8.7
Beta-mangostin	5495925	HIV-1 protease	1DMP	**−9.3**
Gamma-mangostin	5464078	HIV-1 protease	1DMP	−8.7

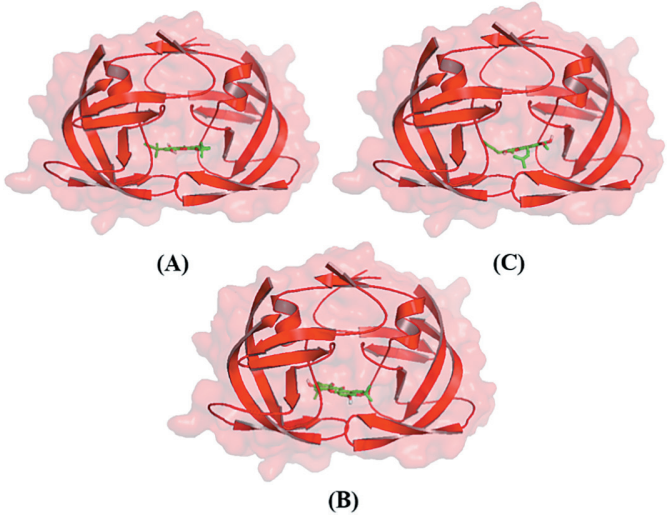

Figure 2. **Ligand (green) and protein (red) complex. (A) garciniaxanthone B_HIV-1 protease, (B) garcinone B_HIV-1 protease, and (C) beta-mangostin_HIV-1 protease**

Рисунок 2. **Комплекс лиганд (зеленый) и белок (красный). (А) гарциниаксантон В _ протеаза ВИЧ-1, (В) гарцинон В_ протеаза ВИЧ-1, и (С) бета-мангостин _ протеаза ВИЧ-1**

Garciniaxanthon B interacts with HIV-1 protease hotspots namely Gly49, Arg8, Gly48, Gly27, Asp29, Asp30, Val32, Gly27, Gly49, Asp29, Gly48, and Asp30 via van der Waals bond, Ile47, Ile84, Ala28, Ile50, Asp25, Ile47, Ile84, Ile50, Val32, and Ala28 via Pi/Alkyl/Anion bond with 0 unfavorable. Garcinone B interacted at the HIV-1 protease hotspot through Asp29, Ile84, Gly49, Gly27, Gly48, Arg8, Asp29, Ile47, Val32, Gly49, Gly48 with van der Waals bond, hydrogen bond identified at Asp30, and Pi/Alkyl/Sigma/Anion at Ala28, Ile47, Ile50, Ile84, and Ala28 with 1 unfavorable. Beta-mangostin interacted at the HIV-1 protease hotspot through Val82, Pro81, Ile84, Val32, Ile47, Gly48, Gly27, Arg8, Gly49, Asp30, Asp29, Gly48, and Gly49 with van der Waals bond, hydrogen bond at Asp30 and Asp29, Pi/Alkyl/Sigma/Anion bond identified at Ile47, Ile50, Ala28, Ile84, Val82, Val32, Pro81, Asp25 (Figure 3). Weak interactions such as hydrogen, van der Waals, hydrophobic, pi, alkyl, electrostatic, and hydrophobic can trigger the ligand activity on targets such as inhibitors [41,42]. Unfavorable bonds can trigger unstable ligand-protein if >3 [43,44]. Garciniaxanthon B, garcinone B, and beta-mangostin can affect the inhibitor activity on the target because they produce weak bonds such as van der Waals, hydrogen, and pi/alkyl/anion/sigma with a number of unfavorable interactions (not more than three).

3.4. Interaction stability

Identification of the chemical bond stability at interaction hotspots in this study was carried out through molecular dynamics simulations. The ligand-protein complexes of garciniaxanthon B_HIV-1 protease, garcinone B_HIV-1 protease, and beta-mangostin_HIV-1 protease (Figure 4) was identified as having RMSF values >3 (Å). Ligand-protein

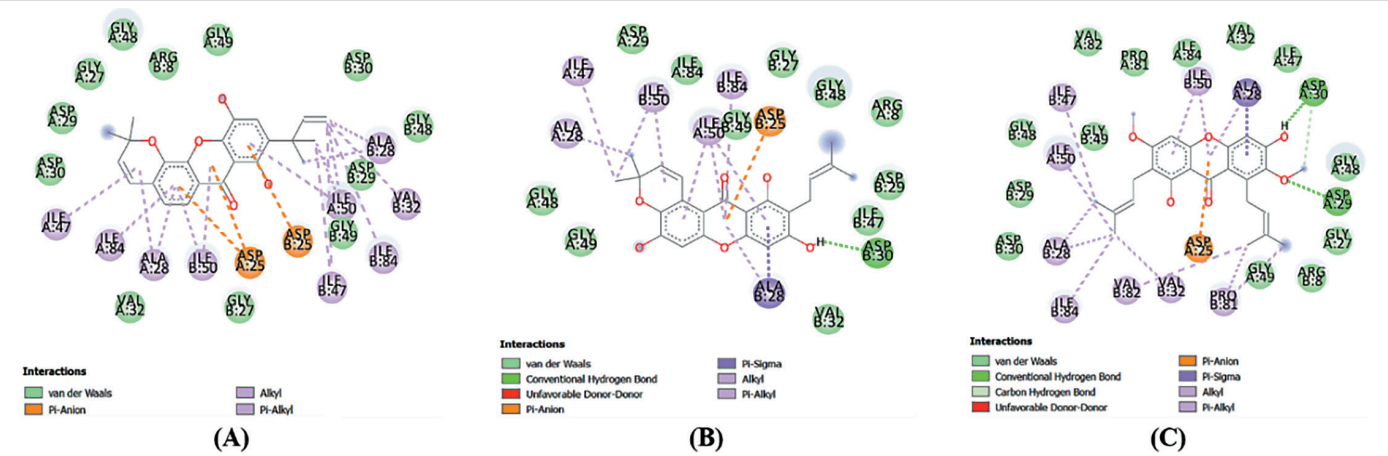

Figure 3. **2D ligand-protein interaction. (A) garciniaxanthone B_HIV-1 protease, (B) garcinone B_HIV-1 protease, and (C) beta-mangostin_HIV-1 protease**

Рисунок 3. **2D взаимодействие лиганд-белок. (А) гарциниаксантон В _ протеаза ВИЧ-1, (В) гарцинон В_ протеаза ВИЧ-1, и (С) бета-мангостин _ протеаза ВИЧ-1**

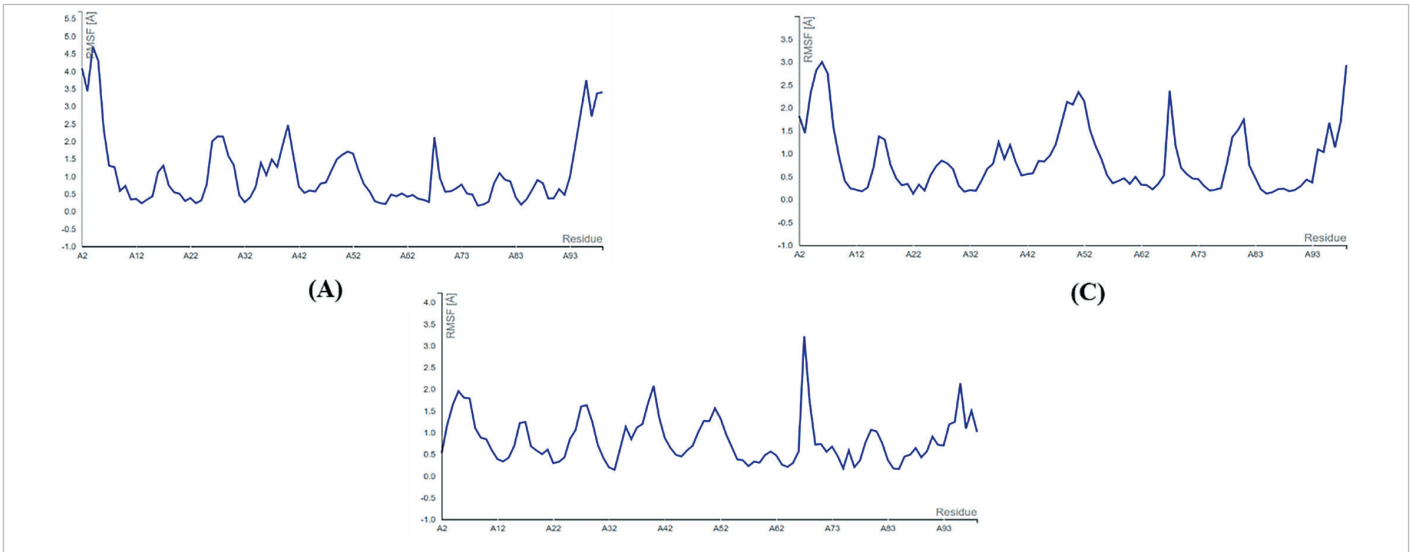

Figure 4. **RMSF fluctuation plot. (A) garciniaxanthone B_HIV-1 protease, (B) garcinone B_HIV-1 protease, and (C) beta-mangostin_HIV-1 protease**

Рисунок 4. **График среднеквадратичных флуктуаций (RMSF) (А) гарциниаксантон В _ протеаза ВИЧ-1, (В) гарцинон В_ протеаза ВИЧ-1, и (С) бета-мангостин _ протеаза ВИЧ-1**

complexes with RMSF values >3 at interaction hotspots show stable properties and may trigger the inhibitory activity on the target [45–47]. RMSF shows the fluctuation of atoms that form amino acid residues in an active protein. The molecular stability of the results of this study refers to the ligand's activity on the target as a good inhibitor [48–50]. However, this computational prediction requires further analysis through *in vivo* and *in vitro* approaches.

4. Conclusion

In summary, garciniaxanthon B, garcinone b, and beta-mangostin from *Garcinia mangostana* L. have potential as antiretroviral agents for the treatment of HIV-1 infection. The three compounds are predicted to inhibit the protease activity in HIV-1 with a more negative binding affinity score, form ligand-protein molecular complexes with van der Waals, hydrogen, pi/alkyl/anion/sigma bonds, form stable bonds and drug-like molecules.

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Authors equally relevant to the writing of the manuscript, and equally responsible for plagiarism.	Авторы в равных долях имеют отношение к написанию рукописи и одинаково несут ответственность за плагиат.
Conflict of interest	**Конфликт интересов**
The authors declare no conflict of interest.	Авторы заявляют об отсутствии конфликта интересов.