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Original Article

Tea catechin as antiviral agent via apoptosis agonist and triple inhibitor mechanism against HIV-1 infection: A bioinformatics approach

[La catequina del té como agente antiviral a través de un agonista de la apoptosis y un mecanismo de triple inhibidor contra la infección por VIH-1: un enfoque bioinformático]

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Abstract

Context: Human immunodeficiency virus (HIV) antiretrovirals that target the binding of viral enzyme are chosen as the lead solution in the treatment of HIV-1 infection, such as non-catalytic site integrase inhibitor (NCINI), nevirapine, and darunavir. There are natural compounds from specific plants that can be effective in treating HIV-1 infection such as tea catechin. Tea catechin administration causes a decrease in viral load and inhibition of entry mechanisms and an increased effect of apoptosis in infected cells.

Aims: To identify the triple inhibitor mechanism in tea catechins against the three HIV-1 enzymes and apoptosis agonists through *in silico* approach as an innovation in handling HIV-1 infection.

Methods: The 3D structure of tea catechin compounds from the database was examined, and then all target compounds were analyzed for drug-likeness, molecular docking, pathway prediction, and molecular interactions to determine the potential of tea catechin compounds as antiviral HIV-1 *in silico*.

Results: Tea catechin compounds have the potential to serve as antiviral against HIV-1 through apoptosis agonist and triple inhibitor mechanisms. Apoptosis occurs due to the interaction of tea catechins with pro-apoptotic proteins in cells, and the epigallocatechin gallate (EGCG) compound is a class of tea catechins with the same binding position as control.

Conclusions: The binding of the EGCG molecule complex results in low binding energy. Therefore, it allows EGCG acts as a triple inhibitor in HIV-1 infection.

Keywords: antiretrovirals; apoptosis; catechin; herbal medicine; human immunodeficiency virus.

Resumen

Contexto: Los antirretrovirales del virus de la inmunodeficiencia humana (VIH) que se dirigen a la unión de la enzima viral se eligen como la solución principal en el tratamiento de la infección por VIH-1, como el inhibidor de la integrasa del sitio no catalítico (NCINI), la nevirapina y el darunavir. Existen compuestos naturales de plantas específicas que pueden ser eficaces en el tratamiento de la infección por VIH-1, como la catequina del té. La administración de catequinas del té provoca una disminución de la carga viral e inhibición de los mecanismos de entrada y un aumento del efecto de la apoptosis en las células infectadas.

Objetivos: Identificar el mecanismo triple inhibidor en las catequinas del té contra las tres enzimas del VIH-1 y los agonistas de la apoptosis a través de un enfoque *in silico* como una innovación en el manejo de la infección por VIH-1.

Métodos: Se examinó *in silico* la estructura 3D de los compuestos de catequina del té de la base de datos y luego se analizaron todos los compuestos objetivo para determinar su similitud con el fármaco, acoplamiento molecular, predicción de vías e interacciones moleculares para determinar el potencial de los compuestos de catequina del té como antivírico VIH-1.

Resultados: Los compuestos de catequina del té tienen el potencial de actuar como antivirales contra el VIH-1 mediante mecanismos agonistas de apoptosis y triple inhibidor. La apoptosis ocurre debido a la interacción de las catequinas del té con proteínas proapoptóticas en las células y el compuesto de galato de epigalocatequina (EGCG) es una clase de catequinas del té con la misma posición de unión que el control.

Conclusiones: La unión del complejo de moléculas EGCG da como resultado una baja energía de unión. Por tanto, permite que el EGCG actúe como un triple inhibidor en la infección por VIH-1.

Palabras Clave: antirretrovirales; apoptosis; catequina; medicina herbaria; virus de inmunodeficiencia humana.

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INTRODUCTION

Human immunodeficiency virus type 1 is included in the retrovirus family that has an envelope consisting of spike glycoprotein gp120 and gp41 structures (Checkley et al., 2011; Kharisma et al., 2018). Viruses use receptors and co-receptors of the cluster of differentiation 4+ (CD4+), C-C chemokine receptor type 5 (CCR5), and C-X-C receptor 4 (CXCR4) types to enter through virion fusion into host cells (Wilen et al., 2012). The genetic material that makes up this virus consists of single-stranded ribonucleic acid (RNA). HIV-1 enzymes such as reverse transcriptase (RT), integrase (INT), and protease (PR) have an essential role in the replication process. RT functions to produce complementary DNA (cDNA) from ssRNA, INT delivers the viral genome into the nucleus, and PR cuts polypeptides for the viral assembly process (Yang et al., 2012). This viral infection triggers opportunistic conditions due to decreased T-cell $CD4^+$ populations in the body (Patrikar et al., 2014). There are some opportunistic infections or pathognomonic oral lesions that may found during the HIV infection in juvenile or adult patients, such as oral candidiasis, oral hairy leukoplakia, linear gingival erythema, necrotizing ulcerative gingivitis, and necrotizing ulcerative periodontitis (Parmadiati et al., 2017; Nugraha et al., 2017; Mensana et al., 2018; 2019; Nugraha et al., 2019a). The suppression immunity or immunodeficiency condition in HIV/AIDS also makes the patients susceptible to dental caries and periodontal diseases (Nugraha et al., 2019b). The prolonged duration of antifungal administration to treat candidiasis in people living with HIV/AIDS (PLWHA) may lead to adverse drug effects or antifungal drug resistance (Nugraha et al., 2018a; Wicaksono et al., 2020). The oral manifestation that occurred due to opportunistic infection during HIV/AIDS infection may increase the morbidity that decreases PLWHA quality of life (Nugraha et al., 2018b). HIV-1 infection of host cells also causes apoptosis inhibition (Cummins and Badly, 2013). Generally, this apoptosis is needed by the body to select cells infected by viruses (Kvansakul, 2017).

The management of HIV-1 infection is currently through antiretrovirals targeting HIV-1 protease, integrase, and reverse transcriptase (Rhee et al., 2016). Drug compounds that bind to inactivate the target enzyme in viruses are called inhibitors (Zimmermann et al., 2009). HIV-1 inhibitors consisting of non-catalytic site integrase inhibitor (NCINI) is an example of HIV-1 integrase inhibitors that have entered clinical trials (Fader et al., 2014). Darunavir has bound to the amino acid residues that make up the protease's active site through hydrogen and hydrophobic bonds (Wang et al., 2011). Nevirapine binds reverse transcriptase via hydrophobic domain and causes an inhibitory effect (Ren et al., 2006). Long-term use of combinatory antiretroviral also does not positively impact the patient's body (Mutwa et al., 2014). Therefore, we need a chemical compound that can inhibit the activities of the three enzymes.

Antiretroviral therapy also involves a high cost. Therefore, this attracts alternative solutions such as the use of natural compounds from specific plants that can be effective in treating HIV-1 infection. *Camellia sinensis* contains various catechins such as catechin, catechin gallate, gallocatechin, gallocatechin gallate, (-)-epicatechin, (-)-epicatechin gallate, (-)-epigallocatechin, and (-)-epigallocatechin gallate (Wein et al., 2016; Susanto et al., 2018; Kharisma et al., 2020a; Narmada et al., 2020). Catechin compounds in green tea were reported to have antiviral activity against HIV-1 when used in specific doses (Xu et al., 2017). Catechin administration causes a decrease in viral load and inhibition of the entry mechanism against host cells *in vitro* (Yamaguchi et al., 2002). The administration of tea catechins also triggers the infected cells to enter apoptotic mechanisms (Ranjith-Kumar et al., 2010). However, previous studies have not explained in detail the molecular mechanisms related to the antiviral activity of tea catechins and apoptotic agonists. Thus, this study was conducted to identify the triple inhibitor mechanism in tea catechins against the three HIV-1 enzymes and apoptosis agonists through *in silico* approach as an innovation in handling HIV-1 infection.

MATERIAL AND METHODS

Sample preparation

The target compounds used in this study were catechin, catechin gallate, gallocatechin, gallocatechin gallate, (-)-epicatechin, (-)-epicatechin gallate, (-)-epigallocatechin, and (-)-epigallocatechin gallate (Wein et al., 2016; Susanto et al. 2018; Kharisma et al., 2020b). The HIV-1 antiretroviral drugs used in the study consisted of BI compound or NCINI, darunavir or protease inhibitors, and nevirapine or reverse transcriptase inhibitors (Fader et al., 2014; Bardsley-Elliot and Perry, 2000; Deek, 2014). All ligand sample preparations were retrieved on the PubChem database (pubchem.ncbi.nlm.nih.gov). Pubchem is a specific database that stores information on organic and synthetic compounds or other chemical substances (Kim et al., 2016). This information consists of a CID, 2D/3D structure, physicochemical properties, smile canonical, references, toxicity, and others (Kim, 2016). The purpose of sample preparation in PubChem in this study is to obtain samples of the target compound's 3D structure and canonical smile. Then, the ligand minimization process was carried out with OpenBabel through the PyRx software so that the ligands can be flexible and change the file structure data format (sdf) into protein databank format (pdb) (Adi et al., 2016). The target proteins in this study consisted of reverse transcriptase (2RF2), integrase (4NYF), and HIV-1 protease (3SO9), obtained from the RCSB PDB database (rcsb.org).

Drug-likeness and biological activity prediction

All samples of catechin compounds were analyzed for probability as drug candidates through the SWISS ADME server (swissadme.ch). This analysis aims to calculate and predict several good drug candidates' parameters and pharmacokinetics (Wang and Xie, 2019). This study identified the physicochemical properties and drug-likeness of catechin compounds on the SWISS ADME server. Then, catechin compounds were predicted to have their biological activity on the PASSOnline server (http://www.pharmaexpert.ru/passonline) (Kharisma et al., 2018). This server can predict about 4000 types of biological activity consisting of pharmacological effects, interactions, expressions, enzymes, and others (Parasuraman, 2011). PASSOnline in this study was used to predict the activity of catechin compounds as antiviral and apoptosis with a Pa score >0.3 or medium probability (Rahmaningsih and Pujiastutik, 2019).

Molecular docking and visualization

The ability to generate protein activity of the drug and control was identified through molecular docking simulations. Molecular docking is used to determine the binding energy value formed when the ligands interact with the receptor (de Ruyck et al., 2016). Specific docking in the study refers to the binding energy comparison of query and control compounds with the same binding site (Dallakyan and Olson, 2015). This study uses VinaWizard in PyRx software to perform molecular docking simulations (Zidan et al., 2019; Luqman et al., 2020). 3D molecular visualization of docking results is displayed in the PyMol software (Kharisma and Ansori, 2020).

Pathway prediction

The canonical smile of the target compound was used to predicts the biological pathway that triggers an antiviral response through the apoptotic mechanism. The analysis was carried out on the Search Tool for Interactions of Chemicals (STITCH) (http://stitch.embl.de/) with a high probability of confidence (0.700) (Szklarczyk et al., 2016).

Molecular interaction

The interaction of protein-ligand complexes from molecular docking simulation results identified the types of chemical bonds that comprise them through the Discovery Studio 2.0 software (Liu et al., 2017). The analysis aims to determine the similarity of query and control ligand binding at the binding site of the target protein. The types of molecular interactions identified are weak bonds consisting of hydrogen, hydrophobic, and π bonds (Jamal et al., 2012). A molecular complex is stable if it has low unfavorable interactions (Freire, 2008).

RESULTS

The biological activity prediction of tea catechin

Tea catechin compound consisting of catechin (C) CID 9064, catechin gallate (CG) CID 6419835, gallocatechin (GC) CID 65084, gallocatechin gallate (GCG) CID 5276890, (-)-epicatechin (EC) CID 72276, (-)-epicatechin gallate (ECG) CID 107905, (-)-epigallocatechin (EGC) CID 72277, and (-)-epigallocatechin gallate (EGCG) CID 65064, a control compound consisted of BI Compound, darunavir, and nevirapine. All samples were displayed as 3D sticks structure with coloring based on constituent atoms through PyMol software (Fig. 1). Target proteins consisting of reverse transcriptase (2RF2), integrase (4NYF), and HIV-1 protease (PII3), were obtained from the RCSB PDB database (https://www.rcsb.org/). The drug-likeness prediction results show that all tea catechin compounds are predicted as potential candidates for drug molecules because they qualify based on the drug-likeness parameters (Table 1). All tea catechin compounds allow for further analysis to determine their general potential as apoptosis agonists and antiviral agents. The result of biological activity prediction shows that tea catechin compounds have activity as antiviral agents and apoptotic agonists based on predictions of Pa> 0.3 or medium probability (Table 2).

Molecular mechanism of tea catechin as apoptosis agonist

Compounds (-)-epigallocatechin gallate and catechin were identified to trigger apoptotic activity in cells with a high probability of confidence (0.700) (Fig. 2). The line thickness found from the STITCH analysis results shows the level of interaction strength that is formed between the shells. The green line shows the interaction of the chemical compound with the target protein, the interaction between the proteins on the dark blue line, and the red, the interaction between chemical compounds and the color of each shell acts as a differentiator from one another. Interaction (-)-epigallocatechin gallate with the activation mode was identified on the target consisting of CASP3, TP53, and NOS3, while catechin allows only interacting with NOS3. We chose these three targets for STITCH because they are classified as pro-apoptotic. This allows HIV-1 infected cells to lysis due to apoptosis and can reduce viral load.

The potency of tea catechin as an antiviral agent via HIV-1 triple inhibitor

The prediction of the ability of tea catechin compounds is also carried out through the molecular docking method. The docking grid is used to adjust the ligand-binding position to the target domain. The following is the grid position used in this study center, x: 11.56 y: -20.01 z: 0.29 and dimension x: 25.00 y: 25.00 z: 25.00 for integrase and protease, while for reverse transcriptase center, x: 5.52 y: 32.07 z: 28.18 and dimension x: 25.00 y: 25.00 z: 25.00. Tea catechin compounds have the potential to exhibit biological activity as antiviral agents through a triple inhibitor mechanism because EGCG has a lower binding affinity than controls when interacting with the three target proteins of HIV-1 (Table 3).

Molecular interaction between tea catechin and target domain

Based on the results of the molecular docking simulation results, EGCG compounds have lower binding energies than other compounds, it is possible that the binding of EGCG to the domains of the three target proteins can affect the activity of biological responses. The biological response referred to is based on the objectives of this study as a triple inhibitor of the HIV-1 protein. Molecular docking complex simulation results were analyzed in Discovery Studio 2.0, the interaction type of conventional hydrogen bonds with green lines, orange alkyls, purple Van der Waals, and red for unfavorable. We compared the position of the interaction between the query compound and the control to identify the ability of the inhibitor to the three HIV-1 viral protein activities. The results showed that there was a similarity in the position of the amino acid interaction between EGCG tea catechin and control on integrase 2 (Pro90), protease 2(Val82), 2(Asp25), Ile50, and Pro81, and His96 and Glu378 reverse transcriptases (Fig. 3).

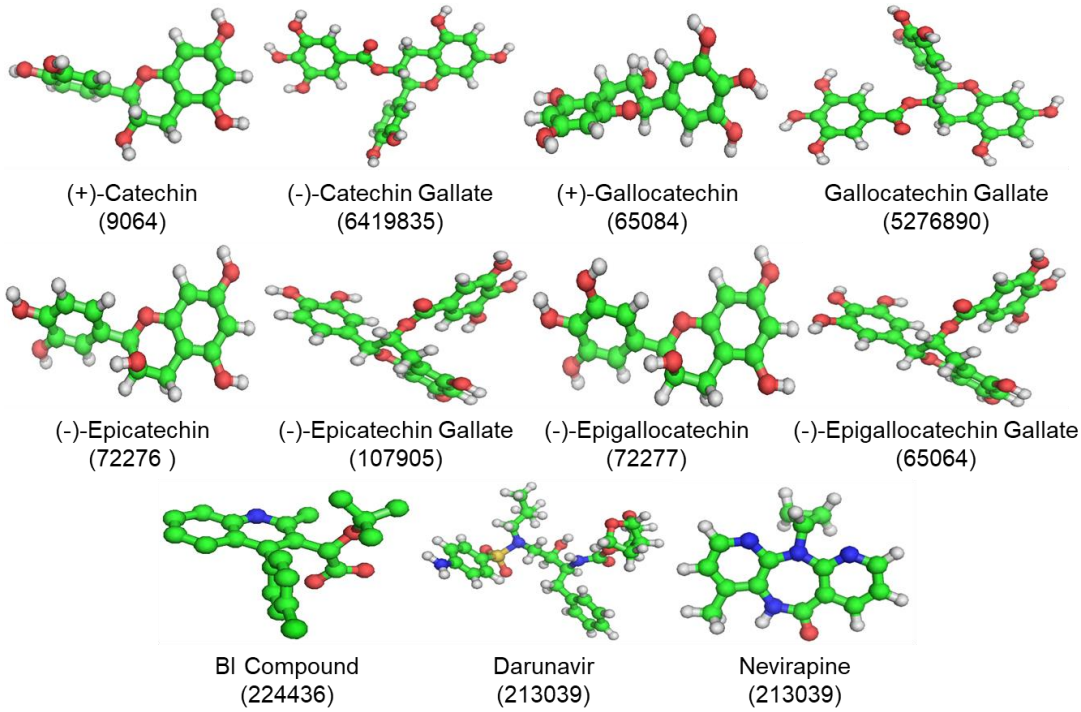

Figure 1. Molecular visualization of the structure of tea catechin and controls.

Table 1. Tea catechin drug-likeness.

Compound	Drug-likeness parameters				
	Lipinski	**Ghose**	**Veber**	**Egan**	**Muege**
Catechin	Yes	Yes	Yes	Yes	Yes
Catechin gallate	Yes	Yes	No	No	No
Gallocatechin	Yes	Yes	Yes	Yes	No
Gallocatechin gallate	No	Yes	No	No	No
(-)-Epicatechin	Yes	Yes	Yes	Yes	Yes
(-)-Epicatechin gallate	Yes	Yes	No	No	No
(-)-Epigallocatechin	Yes	Yes	Yes	Yes	No
(-)-Epigallocatechin gallate	No	Yes	No	No	No

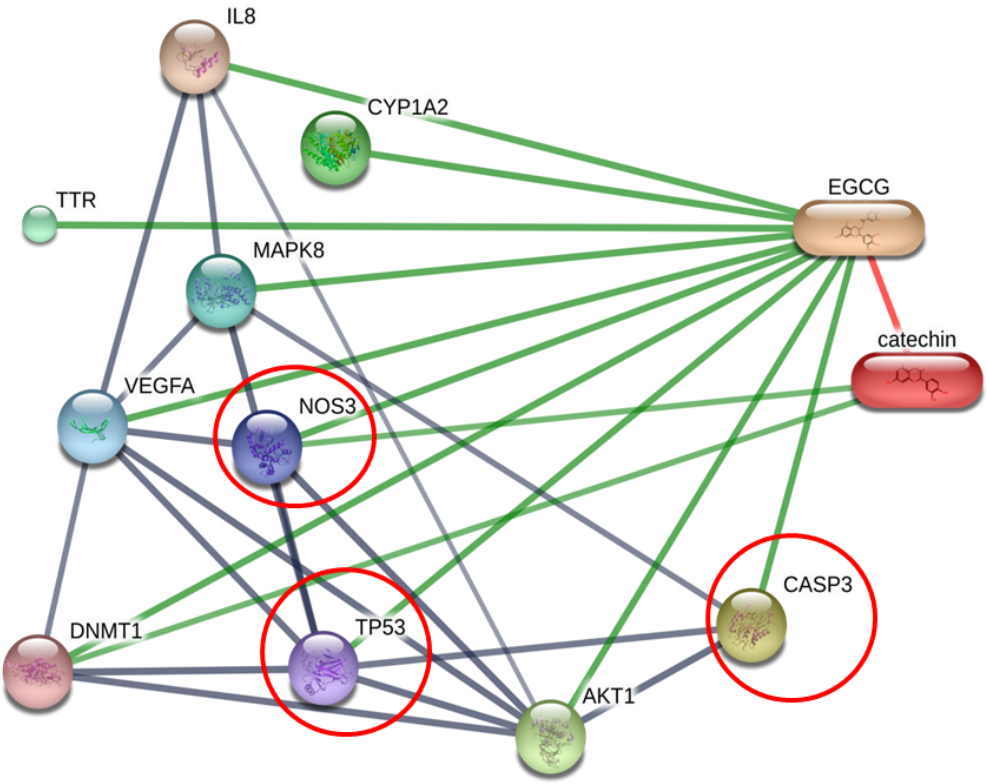

Figure 2. Ligand-protein interaction pathway from tea catechin in *Homo sapiens* bodies.
The shell with a red circle is a pro-apoptotic protein.

Table 2. Biological activity prediction of tea catechin on PASSOnline.

Compound	Pa	Pi	Biological activity
Catechin	0.400	0.014	Antiviral
	0.741	0.012	Apoptosis agonist
Catechin gallate	0.378	0.017	Antiviral
	0.698	0.015	Apoptosis agonist
Gallocatechin	0.376	0.018	Antiviral
	0.724	0.013	Apoptosis agonist
Gallocatechin gallate	0.400	0.014	Antiviral
	0.741	0.012	Apoptosis agonist
(-)-Epicatechin	0.378	0.017	Antiviral
	0.698	0.015	Apoptosis agonist
(-)-Epicatechin gallate	0.376	0.018	Antiviral
	0.724	0.013	Apoptosis agonist
(-)-Epigallocatechin	0.459	0.009	Antiviral
	0.759	0.010	Apoptosis agonist
(-)-Epigallocatechin gallate	0.400	0.014	Antiviral
	0.741	0.012	Apoptosis agonist

Table 3. The docking results of tea catechins with the HIV-1 enzyme.

Ligand	Binding affinity (kcal/mol)		
	Integrase	Protease	Reverse transcriptase
Catechin	-6.2	-7.6	-6.3
Catechin gallate	-6.1	-9.8	-7.7
Gallocatechin	-6.4	-8.1	-6.9
Gallocatechin gallate	-6.9	-9.2	-8.6
(-)-Epicatechin	-6.2	-7.9	-6.7
(-)-Epicatechin gallate	-5.7	-9.0	-8.5
(-)-Epigallocatechin	-6.4	-7.9	-6.9
(-)-Epigallocatechin gallate	-6.6	-9.3	-8.6
BI compound	-6.3	-	-
Darunavir	-	-9.3	-
Nevirapine	-	-	-6.7

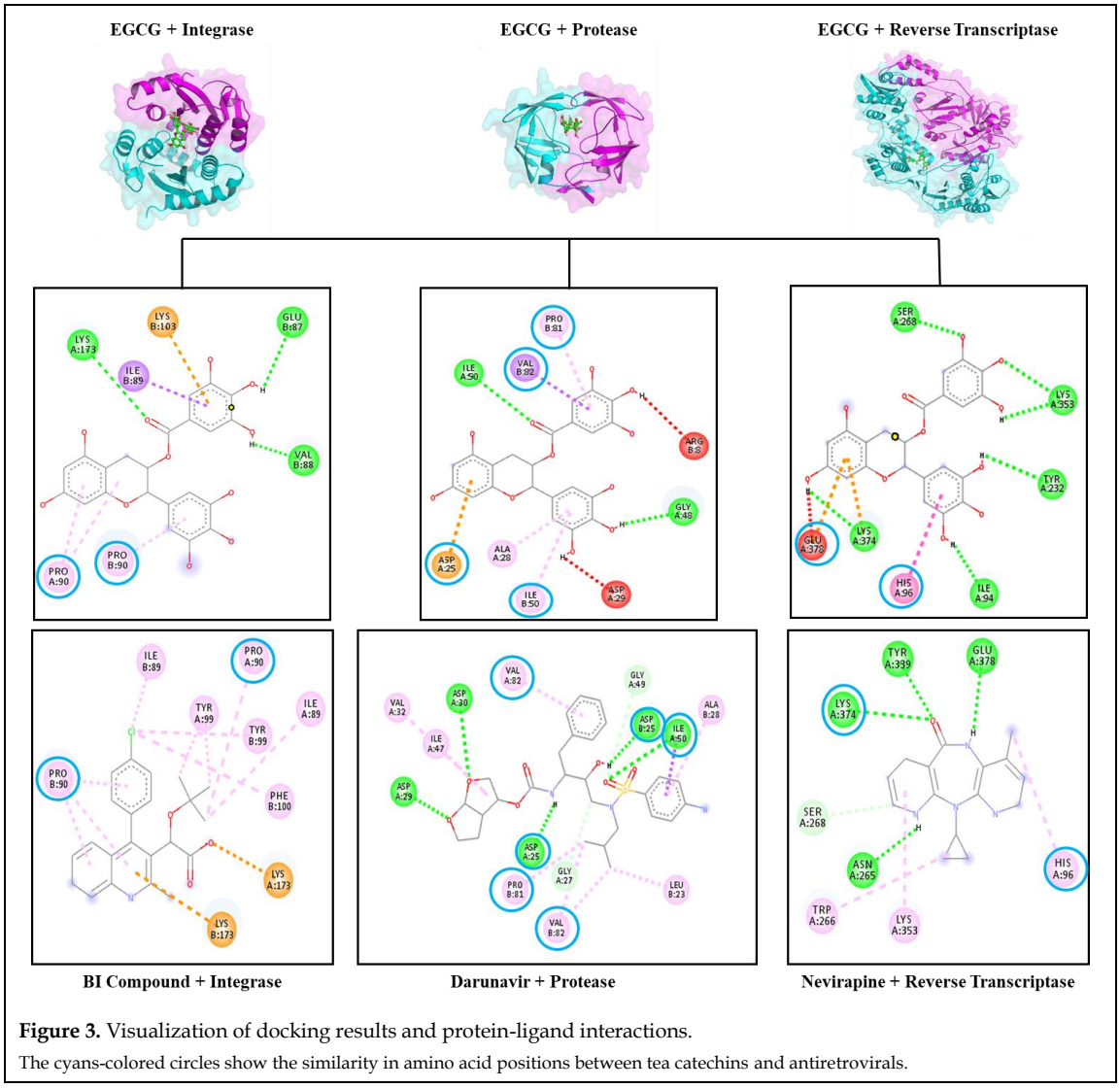

Figure 3. Visualization of docking results and protein-ligand interactions.
The cyans-colored circles show the similarity in amino acid positions between tea catechins and antiretrovirals.

DISCUSSION

The drug-likeness analysis is carried out in order to determine the ability of a molecule to enter the body to become a potent drug candidate (Wang and Xie, 2019). Tea catechin compounds must qualify based on the rules to be categorized as good drug candidates and pass through the cell membrane layer because the target protein is located in the intracellular region. The parameters for determining drug candidates in this study were Lipinski, Ghose, Veber, Egan, and Muege on the SWISS ADME server (http://www.swissadme.ch/). In general, the rule of the five parameters consists of molecular mass ≤500 Dalton, ≤5 hydrogen bond donor, ≤10 hydrogen bond acceptors, molar refractivity between 40-130, and ≤5 lipophilicity (Daina et al., 2017). Each parameter's rules describe the solubility of a molecule in water or fat, potentially as a target agent to trigger specific biological activity, lipophilicity efficiency, and molecular weight (Wang and Xie, 2019).

The general potency determination of a chemical compound in this study was carried out on the PASSOnline server (http://www.pharmaexpert.ru/passonline/). This server can predict biological activity consisting of pharmacological effects, interactions, toxicity on 4000 compounds through probability activation (Pa) and inhibition (Pi) scores (Parasuraman, 2011). Pa shows the probability score for the potential query compound appearing and inhibition shown in the Pi score (Susanto et al., 2018; Rahmaningsih and Pujiastutik, 2019). However, the analysis results must be tested again to determine the mechanism of tea catechin compounds in performing these biological activities, and further tests must be carried out to determine the mechanism of tea catechin compounds that can act as apoptosis agonists and antiviral agents.

The biological pathway prediction serves to study the mechanism of action of a chemical compound that interacts with target proteins in the body and produces specific biological functions (Szklarczyk et al., 2016). This study used the STITCH database (stitch.embl.de) to determine the interaction of tea catechin compounds on target proteins associated with agonist apoptotic activity. The prediction results on STITCH indicate the existence of an interaction between tea catechin compounds and target proteins in the body of *Homo sapiens*. This is indicated by the presence of a pro-apoptosis interactor protein consisting of p53, CASP3, and NOS3 as interaction targets (Tyas et al., 2000; de la Monte et al., 2003; Aubrey et al., 2018). Furthermore, the tea catechin mechanism for inhibiting HIV-1 infection is possible through interaction with target proteins that have an essential role in triggering apoptosis.

This study used a molecular docking method to identify the binding activity of tea catechin compounds to the three HIV-1 enzymes through a large binding affinity (Dallakyan and Olson, 2015). Binding affinity is negative energy formed when an interaction occurs between molecules and allows it to form stable complexes (Kharisma et al., 2018). Triple inhibitor refers to the presence of a ligand capable of producing the most negative binding of the three enzymes compared to the control compound. In this study, the control compounds were BI compound as an integrase inhibitor, darunavir for protease, and nevirapine for reverse transcriptase. Interestingly, the binding affinity of EGCG has the same value as the control of darunavir and allows the two compounds to trigger the same activity against the HIV-1 enzyme. Further tests confirmed the comparison of the positions and types of chemical bond interactions formed between tea catechins and control compounds.

The docking result molecule complex then analyzed the position and type of chemical bond interactions formed in the Discovery Studio 2.0 software. Molecular complexes are formed due to the presence of non-covalent bonds such as conventional hydrogen bonds, π, alkyl, Van der Waals, and hydrophobic (Jamal et al., 2012). These bonds contribute to producing specific biological activity on target proteins, and the ligand-binding domain of the query ligand in this study refers to control compounds (Kharisma et al., 2018). Tea

catechin is predicted to act as a triple inhibitor of the HIV-1 enzyme because it has the same binding position as the drugs that have been found. Similarities in the interaction positions between tea catechins and controls have been identified. This allows the molecular complex to be stable (Susanto et al., 2018; Kharisma and Ansori, 2020).

CONCLUSIONS

Tea catechin compounds have the potential to serve as antiviral HIV-1 through apoptosis agonist and triple inhibitor mechanisms. Apoptosis occurs due to the interaction of tea catechins with pro-apoptotic proteins in cells, and the EGCG compound is a class of tea catechins with the same binding position in the target protein domain as the three control compounds. The binding of the EGCG molecule complex results in low binding energy. Therefore, it allows EGCG to act as a triple inhibitor in HIV-1 infection.

CONFLICT OF INTEREST

The authors declare no conflicts of interests.

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AUTHOR CONTRIBUTION:

Contribution	Kharisma VD	Widyananda MH	Ansori ANM	Nege AS	Naw SW	Nugraha AP
Concepts or ideas	x	x	x			x
Design	x	x	x			x
Definition of intellectual content	x	x				
Literature search	x	x				
Experimental studies	x	x	x	x	x	x
Data acquisition	x	x	x			x
Data analysis	x	x	x			x
Statistical analysis	x	x	x			x
Manuscript preparation	x	x	x	x	x	x
Manuscript editing	x	x	x	x	x	x
Manuscript review	x	x	x	x	x	x

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