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Prediction of Anti-SARS CoV-2 Activity from Green Tea Catechin (*Camellia sinensis* L. Kuntze) Compound Against To Receptors Non-structural Protein 3 (6W6Y) And Non-structural Protein 5 (6M2N)

Roihatul Mutiah[1], Chamlah Ayatillah[2*], Yen Yen Ari Indrawijaya[1], Arief Suryadinata[1]

[1] Department of Pharmacy, Faculty of Medical And Health Science, State of Islamic University Maulana Malik Ibrahim Malang, East Java, Indonesia

[2] Undergraduate Program of Pharmacy, Faculty of Medical And Health Science, State of Islamic University Maulana Malik Ibrahim Malang, East Java, Indonesia

ABSTRACT

Green tea catechin compounds (*Camellia sinensis* L. Kuntze) have an antiviral activity such as influenza, hepatitis B, hepatitis C, herpes simplex virus, HIV, and proven in vitro antiviral influenza against NSP5 in SARS CoV. These considerations are used in this study using Non-structural Protein (NSP), namely NSP3 and NSP5 in SARS CoV-2, which have a role in viral replication and transcription. This study aims to predict the physicochemical properties according to the five rules of Lipinski's using swissADME. Prediction of toxicity with LD50 classification using the Protox II online tool. Catechin compound activity based on ligand interaction with NSP3 (PDB ID: 6W6Y) and NSP5 (PDB ID: 6M2N) receptors using Molegro Virtual Docker (MVD) 6.0. The results showed the predictions of physicochemical properties of the *(-)-epigallocatechin* (EGC), *(-)-epicatechin-3-gallate* (ECG), and *(-)-epicatechin* (EC) compounds fulfilled the five rules of Lipinski's. Catechin compounds have toxicity at levels 4 and 6. The activity of catechin compounds on NSP3 (PDB ID: 6W6Y) and NSP5 (PDB ID: 6M2N) receptors indicated that all catechin compounds had inhibitory activity. The best potential activity compound is *(-)-epigallocatechin-3-gallate* (EGCG) with a rerank score of -102.8200 and -134.1800 Kcal/mol so EGCG can be recommended as a candidate for the SARS CoV-2 antiviral compound.

Keywords: *Camellia sinensis* L. Kuntze; NSP3; NSP5; Toxicity; Anti-SARS CoV-2

INTRODUCTION

The disease caused by SARS CoV-2 is in the β-CoV group with the viral form enveloping unsegmented positive-chain RNAs, including the subgenus sarbecovirus and subfamily Ortocoronavirinae. The correlation between SARS CoV-2 has similar symptoms to CoV, namely SARS-CoV (2002-2003) and MERS-CoV (2012) with the phylogenetic SARS CoV by 80% and MERS-CoV by 50% against SARS CoV-2 (Unhale *et al*., 2020; Guo *et al*., 2020). SARS CoV-2 first appeared in the city of Wuhan in China's Hubei province on December 8, 2019, with a rapid spread worldwide. The World Health Organization (WHO) has declared Coronavirus Disease 2019 (COVID-19) a worldwide public health emergency and announced a pandemic on March 11, 2020 (Muralidar *et al*., 2020; WHO, 2020).

The pathogenicity of SARS CoV-2 to humans is a significant source of aggressive transmission both symptomat ically and asymptomatically (Han and Yang, 2020). In addition, rapid and high viral infection rates are a global problem, and the use of antiviral drugs for their effectiveness and vaccines is still in clinical trials (Salman *et al*., 2020). The strategy is being carried out in developing new antiviral therapies by utilizing herbal plants as an effective and safe alternative to curative and preventive treatment in the spread of COVID-19 (Jahan *et al*., 2020).

Green tea (*Camellia sinensis* L. Kuntze) with abundant polyphenol content is one of the flavonoid groups with the flavonol subgroup or flavan-3-ol (Meltzer *et al*., 2009; Pedro *et al*., 2020). The classification of flavan-3-ol units is included in the condensed tannin group, namely, the main catechins which include *(-)-epicatechin* (EC), *(-)-epigallocatechin* (EGC), *(-)-epicatechin-3-gallate* (ECG), *(-)-epigallocatechin-3-gallate* (EGCG) (Soares *et al.,* 2020; Reygaert, 2018). Several studies have reported these compounds to have antiviral activity, including influenza virus, hepatitis B, hepatitis C, herpes simplex virus, and HIV (Xu *et al.,* 2017; Ghost *et al.,* 2020). In addition, several catechin compounds such as EGCG, EGC, and ECG have been shown to have influenza antiviral activity and inhibit Chymotrypsin-Like

***Corresponding author : Chamlah Ayatillah**
Email: chamlahayatillah13@gmail.com

protease (3CLPro) from SARS-CoV in vitro (Song *et al.,* 2005; Nguyen *et al.,* 2012).

NSP or non-structural protein is a protein used as a target in the inhibition of the SARS CoV-2 virus because of its role in genomic transcription and viral replication (Astuti and Ysrafil, 2020). The NSP3 or Papain-Like protease (PLPro) receptor plays an active role in viral replication. It is responsible for the N-terminal cleavage of polyprotein duplication because it is the largest protein constituent in the SARS CoV-2 genome (Chen *et al.,* 2015). The NSP5 receptor or Chymotrypsin-Like protease (3CLPro) plays a vital role in the hydrolysis of polyprotein replication (Kumar *et al.,* 2020). Importance of these proteins plays a role in proteases in producing functional nonstructural proteins from protein processing (Alanagreh *et al.,* 2020; Wu *et al.,* 2020). This study aims to predict the catechin class compounds in green tea (*Camellia sinensis* L. Kuntze), which can interact with the NSP3 receptors (PDB ID: 6W6Y) and NSP5 (PDB ID: 6M2N) in the potential inhibition of the SARS CoV-2 virus.

METHODOLOGY

Materials

Software

The software used is ChemDraw Professional 16.0, ChemDraw 3D version 16.0, SwissADME, pKCSM online tool, Protox II online tool, and Molegro virtual Docker 6.0.

Target and Template Selection

The target used is the Nsp3 receptor with the PDB ID code 6W6Y and Nsp5 GDP ID code 6M2N downloaded from the Protein Data Bank (www.rcsb.org). The test compounds are EGCG, EGC, ECG, EC, Ribavirin, and Lopinavir in 3D from ChemDraw 3D 16.0 and SMILES code from ChemDraw Professional Version 16.0.

Methods

Preparation Compound

Catechin compounds EGCG, EGC, ECG, EC, Ribavirin, and Lopinavir, are prepared by entering 2D molecular structures through the ChemDraw Professional version 16.0 program by clicking the Structure button and Convert Name to Structure then to bring up the 3D structure, click the Launch button so that it appears on the Chem Bio 3D 16.0. Furthermore, energy minimization is carried out by the stages of Calculation → *MMFF94* → Perform → *MMFF94* → Minimization. The result of the preparation compound is stored in the form of mol2 (SYBYL2.*Mol2) and is followed by a docking process to the receptor.

Prediction of Physicochemical Properties and Toxicity

The SMILES code for each compound obtained from the ChemDraw Professional version 16.0 program was inputted into the SwissADME online application (physicochemical), the pkCSM online tool application, and Protox II Online Tools (toxicity). As a result of physicochemical properties, the values of molecular weight, HBA, HBD, and Log P. As a result of the toxicity, Ames toxicity, skin sensitization, hepatotoxicity, and LD50 were obtained. The level of toxicity refers to the Globally Harmonized System (GHS).

Molecular Docking

The proteins Nsp3 (PDB ID: 6W6Y) and Nsp5 (PDB ID: 6M2N) are downloaded via (www.rcsb.org). Molecular Docking was performed using Molegro Virtual Docker 6.0 to determine the interaction between the test compound and the receptor. Molecular docking validation using parameter RMSD value less than 2Å. The molecular docking results are based on the rerank score replicated three times and the interaction of amino acid residues from hydrogen bonds.

RESULT AND DISCUSSION

Prediction of Physicochemical Properties and Toxicity

The physicochemical parameters of catechin compounds were determined by applying the five rules of Lipinski's, including molecular weight, Hydrogen Bond Donors (HBD), Hydrogen Bond Acceptors (HBA), and Log P (Lipinski *et al.,* 2001). The results showed that all the catechins complied with the five rules of Lipinski's except EGCG compounds. The results of the predictions of physicochemical properties can be seen in Table I.

As a result of toxicity, prediction includes parameters Ames Toxicity, Skin Sensitization, Hepatotoxicity, and LD50. The results are shown in Ames Toxicity all catechin compounds experienced toxicity to bacteria except for EC compounds and comparative drugs (lopinavir and ribavirin). Skin Sensitization parameters showed that all catechin compounds and comparison drugs (lopinavir and ribavirin) had no skin sensitivity. The results of the hepatoxicity parameters of catechin compounds are not toxic to the liver except for comparison drugs (lopinavir). The results of LD50 values classified according to the Globally Harmonized System (GHS) indicate EGCG and ECG compounds are in class 4, namely 1,000 mg/kg, and EGC and EC compounds are in class 6, that is, 10,000 mg/kg. The comparison drugs (ribavirin and lopinavir) are

Table I. Prediction of Physicochemical properties catechin compound in *Camellia sinensis* L.Kuntze

Compound	Parameter of Physicochemical Properties				Lipinski Rules of Five
	BM (g/mol)	Log P	HBD	HBA	
(EGCG) (-)-epigallocatechin-3-gallate	458.37	2.2332	8	11	No
(EGC) (-)-epigallocatechin	306.27	1.2517	6	7	Yes
(ECG) (-)-epicatechin-3-gallate	442.37	2.5276	7	10	Yes
(EC) (-)-epicatechin	290.27	1.5461	1	5	Yes
Ribavirin	244.20	-3.0115	4	7	Yes
Lopinavir	628.80	4.53	4	5	Yes

Table II. Prediction Of Toxicity Catechin Compound in *Camellia sinensis* L.Kuntze

Compound	Toxicity				
	Ames Toxicity[a]	Skin Sensitization[a]	Hepatoxicity[a]	LD_{50} (mg/kg)[b]	Class[b]
(EGCG) (-)-epigallocatechin-3-gallate	Yes	No	No	1.000	4
(EGC) (-)-epigallocatechin	Yes	No	No	10.000	6
(ECG) (-)-epicatechin-3-gallate	Yes	No	No	1.000	4
(EC) (-)-epicatechin	No	No	No	10.000	6
Ribavirin	No	No	No	2.700	5
Lopinavir	No	No	Yes	5.000	5

[a] *pkCSM online tool;* [b] *Protox II online tool*

in class 5, 2,700 – 5,000 mg/kg. The results can be seen in Table II.

Protein preparation And Validation

Protein preparation was carried out automatically in the Molegro Virtual Docker 6.0 program by adding H atoms and correcting several residual amino acids with valence and charge errors for repairs. Protein validation includes determining the cavity due to the detection of the ligand and receptor interaction sites referring to the RMSD value. RMSD as the validity or success of a method is priced below 2 Å (Das *et al.,* 2020). The results of protein preparation and validation are presented in Figures 1 and 2.

The result of protein validation on Nsp3 (PDB ID: 6W6Y) the selected cavity was cavity 2 with native ligand AMP (Adenosine Monophosphate) having an RMSD value of 0.7245 Å. On Nsp5 (PDB ID: 6M2N), the selected cavity was cavity 4 with native ligand 3WL_401 (B) (5,6,7-trihydroxy-2-phenyl-4H-chromene-4-one) has an RMSD value of 1.1561 Å.

Docking Molecular

As a result of molecular docking, the parameters involved include the docking simulation process using several parameters, including the MolDock Score, Rerank Score, and H bonding. The rerank score indicates a critical parameter for determining the bond energy between the ligand and the receptor and determining the interaction. The results are presented in Table 3.

Interaction of Amino Acid

The characteristic of receptors is that they have amino acid residues, which play a critical role in determining the interactions between ligand binding with the receptors (Ekins *et al.,* 2007). The interactions involved, namely hydrogen bonds and steric bonds, are presented in Figures 3 and 4.

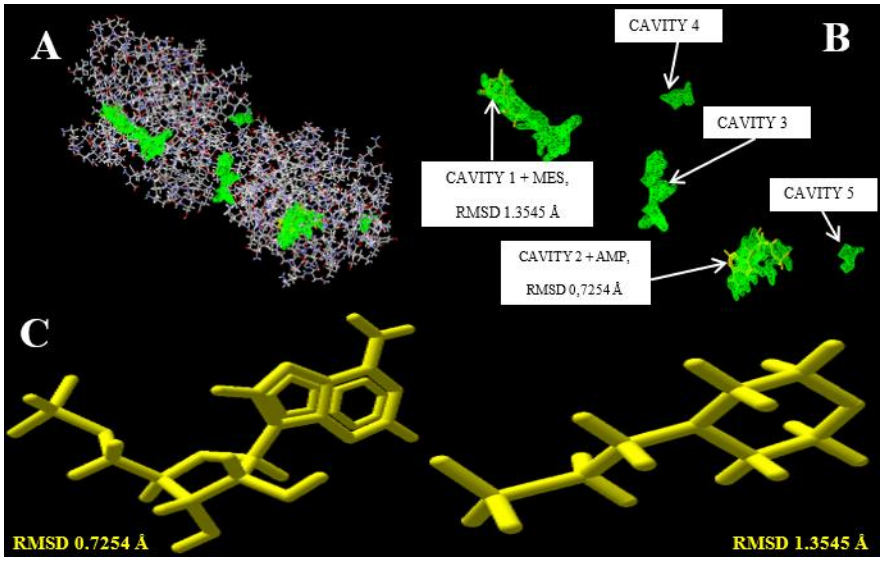

Figure 1. (A) Protein preparation with cavities; (B) RMSD value of each cavity with native ligands at the NSP3 receptor (PDB ID: 6W6Y); (C) The smaller RMSD <2Å (PDB ID: 6W6Y)

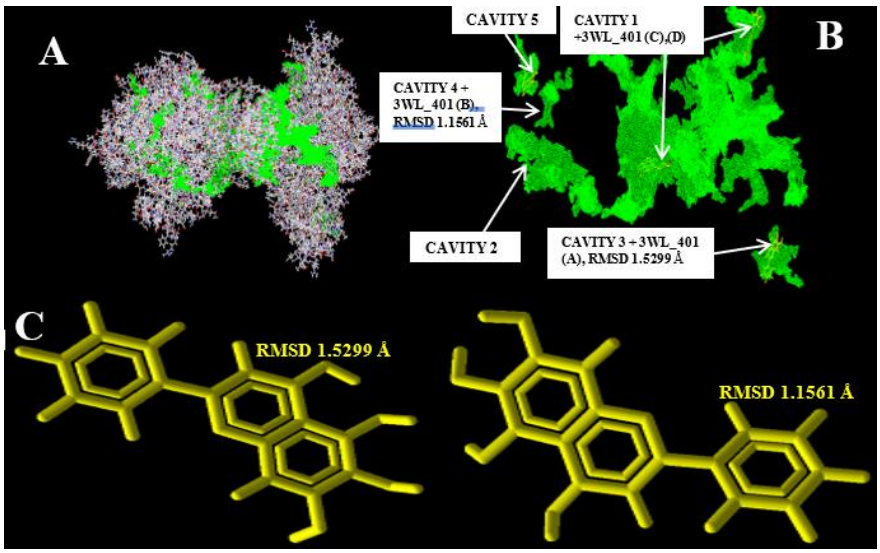

Figure 2. (A) Protein preparation with cavities; (B) RMSD value of each cavity with native ligands at the NSP5 receptor (PDB ID: 6M2N); (C) The smaller RMSD <2Å (PDB ID: 6M2N)

The results of the amino acid residues on the hydrogen bond indicated that all catechin compounds had some similarities to the native ligand and the ribavirin comparators. EGCG has a Hydrogen bonds Phe 156, Ile 23. EGC has a Hydrogen bonds Ile 23. ECG has a Hydrogen bonds Phe 156. EC has a Hydrogen bonds Phe 156. Ribavirin has a hydrogen bonds Phe 156, Ile 23. The result of the similarity of most hydrogen and steric bonds is the EGCG compound so that it has better activity with a lower rerank score.

The amino acid residues on the hydrogen bonds shown in the figure show that all catechin compounds have some similarities to the native ligand and the lopinavir comparators. EGCG has Hydrogen bonds Glu 166, Cys 44, Gly 143. EGC has a Hydrogen bonds Glu 166. ECG has a Hydrogen bonds Gly 143. EC has Hydrogen bonds Gly 143, His. Lopinavir has a Hydrogen bonds Glu 166. The similarity between the most hydrogen and steric bonds was the EGCG compound so that it had a better activity with a low rerank score.

The purpose of this study was to determine the potential antiviral activity of green tea catechin compounds (*Camellia sinensis* L. Kuntze), namely EGCG, EGC, ECG, and EC, along with the prediction

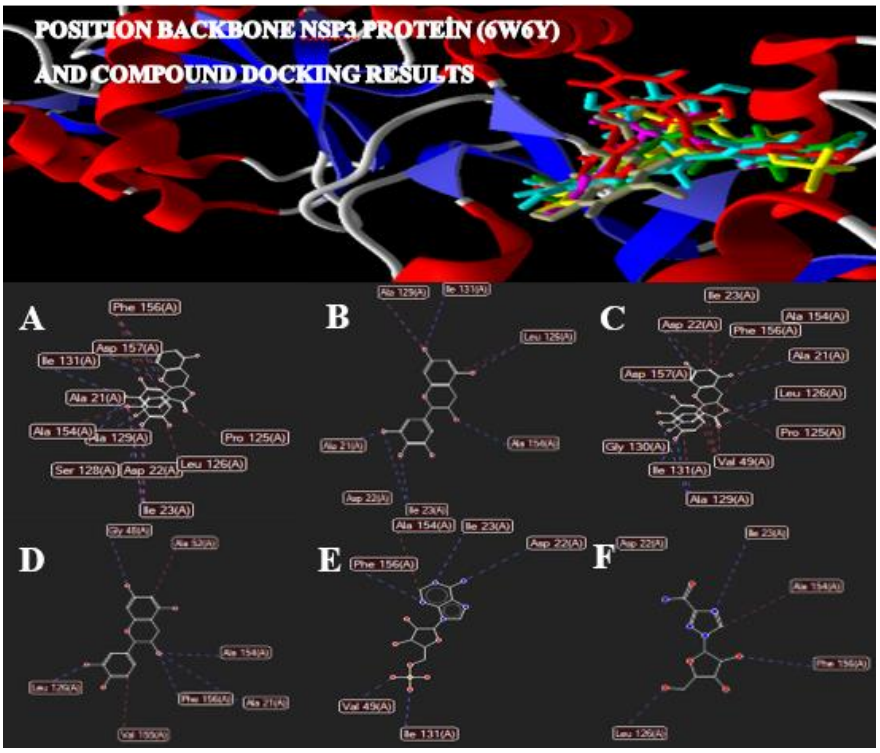

Figure 3. The results of docking and amino acid interactions from hydrogen bonds (blue lines), steric bonds (red lines); (A) EGCG (red); (B) ECG (green); (C) ECG (light blue); (D) EC (gray); (E) Native ligand (yellow) and (F) Ribavirin (purple) for the Nsp3 receptor (PDB ID: 6W6Y).

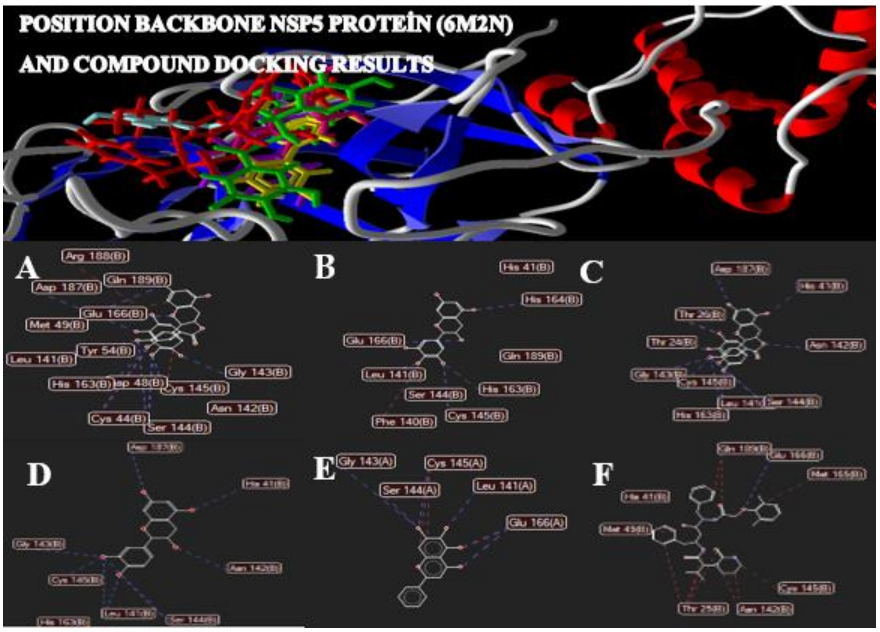

Figure 4. The results of docking and amino acid interactions from hydrogen bonds (blue line), steric bonds (red line); (A) EGCG (green); (B) ECG (pink); (C) ECG (light blue); (D) EC (purple); (E) Native ligand (yellow); and (F) lopinavir (red) for the Nsp5 receptor (GDP ID: 6M2N).

of physicochemical properties and toxicity in silico. The prediction results of the physicochemical properties of catechin compounds (EGC, ECG, and EC) have met the five rules of Lipinski's with a minimum of 1 error, namely the molecular weight value less than 500 g/mol, the log P value less

than 5, the Hydrogen Bond Donors (HBD) value not more 5, and the value of Hydrogen Bond Acceptors (HBA) is not more than 10. Fulfillment of the five rules of Lipinski's shows the compound has good absorption and permeability (Lipinski *et al.,* 1997). EGCG compounds do not comply with the five rules of Lipinski's with parameters of HBD and HBA values showing low permeability, oral bioavailability, and absorption of these compounds. Due to 2, the number of gallate structures and the number of phenolic hydroxy groups can reduce the permeability and absorption properties. Some literature shows that structural modification is performed to improve the oral bioavailability of EGCG compounds (Dai *et al.,* 2020).

The prediction of the toxicity of catechin compounds indicates that the LD50 value falls into class 4 (EGCG and ECG) and class 6 (EGC and EC). In comparison, drugs (ribavirin and lopinavir) are in class 5—the greater the LD50 value, the lower the toxicity (Priyanto, 2009). Ribavirin and lopinavir's drugs can still be used because they consider the benefits that outweigh the toxicity. In the Ames Toxicity parameter results, all catechin compounds have toxicity to bacteria except for EC compounds because they do not have gallate, carboxylate, and phenol groups. The gallate group in the structure of catechin acts as an antibacterial agent (Cushnie and Andrew, 2005). Skin Sensitization parameters, all catechin compounds, ribavirin, and lopinavir are not toxic to the body's skin membranes. Hepatoxicity parameters, all catechin compounds are not harmful to the liver to be safe when used orally. However, the comparator drug lopinavir showed toxicity to the liver because, in clinical trials, the treatment of HIV and hepatitis caused three times to increase in the average values of ALT and AST so that it was detected as toxic in the liver (Nunez, 2006; Canta *el at*., 2005).

The result of the Nsp3 (6W6Y) receptor has two active sites that bind to different ligands, namely MES (2- (N-Morpholino)-EthanesulfonicAcid) and AMP (Adenosine Monophosphate). The choice of native AMP ligand was because the RMSD value was smaller than MES, namely 0.7245 Å. At the Nsp5 (6M2N) receptor, four active sites bind to the native ligands 3WL_401 (A), (B), (C), (D). The 3WL_401 (B) ligand has a smaller RMSD value than the other ligands, namely 1.1561 Å. A method is valid or successful if the RMSD value is below 2 (Das *et al.,* 2020). The smaller the RMSD value, the more accurate it is so that the value of the deviation of a bond with the receptor is getting smaller (Puspaningtyas, 2013).

Prediction of the docking results of catechin compounds with the lowest rerank score against the comparator (Ribavirin = -87.2391 Kcal/mol and Lopinavir =-108.6800 Kcal/mol) at the Nsp3 receptor (PDB: 6W6Y), namely EGCG, EGC, ECG, and EC and the Nsp5 receptor (PDB: 6M2N) namely EGCG and ECG with a better rerank score than the native ligand and comparators. The interpretation of the rerank score shows that the lower (more negative), the greater the bond energy produced, and the more stable the ligand bond to the receptor, the greater the activity (Thomsen *et al.,* 2006). The activity of a compound does not only refer to the rerank score, but it is necessary to have the same amino acid interaction as the hydrogen bond and the steric bond of the comparator.

The determination of amino acid interactions from the molecular docking of catechin compounds has the same hydrogen bonding as the comparator drug. Hydrogen bonding affects the activity of protein-ligand complexes (Itoh *et al.,* 2019). The literature states that amino acids from the hydrogen bonding of the Nsp3 receptor (PDB ID: 6W6Y) with native AMP ligands including Ile 23, Val 49, Pro 125, Val 155, and Phe 156 can determine the interaction of ligands to protease receptors (Littler *et al.,* 2020). EGCG, EGC, ECG, EC have some similarities to amino acids, namely Ile 23 and Phe 156, to have the same activity against the comparators. However, the EGCG compound is the best because it has these two amino acids and a low rerank score. The role of the amino acid phenylalanine (Phe 156) residue as a modulated base arginine derivative has a significant effect on the protease inhibitory activity against viruses (Weigel *et al.,* 2015). The amino acid residue isoleucine (Ile 23) is a hydrophobic amino acid with a role in AVP (Antiviral Peptides). AVP is an antiviral peptide that can inhibit viral attachment, prevent viral fusion from hosting cells, interfere with virus signaling processes, or inhibit viral replication in host cells, involving DNA polymerase, reverse transcription, integration, and protease (Chang and Je, 2013).

As a result of the interaction with the Nsp5 receptor (PDB ID: 6M2N), it is known that all catechin compounds have some amino acid in common, namely Gly 143, Glu 166, His 41, and Cys 44 (Hartini *et al.,* 2020). EGCG, EGC, ECG, EC compounds have similarities to the comparator amino acids and the native ligands. However, the EGCG compound is the best because it has the most amino acid bonds, Glu 166, His 41, and Cys 44, and has a low rerank score. The role of glycine Gly 143 amino acid residues is a non-essential amino acid that can increase the potential for strengthening the body's connective tissue and inhibit the progress of invasive viral or bacterial agents so that the immune system increases (Hevia *et al.,*

2021; Abdulfatai *et al.,* 2020). The amino acid glutamic acid Glu (166) is a key to retain and form stable complexes of compounds in forming hydrogen bonds and interacting with the active sites of the main protease, especially in the replication and expression of the SARS CoV-2 virus (Lokhande *et al.,* 2020). The cysteine amino acid Cys 44 is part of the protease monomer by triggering the opening of a partial helix which can interfere with the protease function (Garza-Lopez *et al.,* 2020). The amino acid His 41 residue plays a vital role in stabilizing the leading protease active site inhibiting transcription or replication blocking activity (Srivastava *et al.,* 2020).

CONCLUSION

The conclusion of this study shows that all the catechin compounds of green tea (*Camellia sinensis* L. Kuntze) are predicted to have the potential for inhibitory activity against the receptors NSP3 (PDB ID: 6W6Y) and NSP5 (PDB ID: 6M2N) with the compounds with the best inhibitory activity are compounds EGCG, EGC, ECG, and EC compounds showed good absorption and permeability. Catechin compounds have low toxicity in class 6 and class 4. And further research is suggested that further research and development of catechin compounds with a variety of receptors and in vitro and in vivo test studies determine the real potential as anti-SARS CoV-2.

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