Jurnal Kedokteran Hewan
P-ISSN : 1978-225X; E-ISSN : 2502-5600
September 2020, 14(3):59-65
DOI: https://doi.org/10.21157/j.ked.hewan.v14i3.16652

POTENTIAL ANTIVIRAL OF CATECHINS AND THEIR DERIVATIVES TO INHIBIT SARS-COV-2 RECEPTORS OF M^{pro} PROTEIN AND SPIKE GLYCOPROTEIN IN COVID-19 THROUGH THE IN SILICO APPROACH

Frengki[1]*, Deddi P. Putra[2], Fatma Sri Wahyuni[2], Daan Khambri[3], Henni Vanda[1], and Vivi Sofia[4]
[1]Faculty of Veterinary Medicine, Universitas Syiah Kuala, Banda Aceh, Indonesia
[2]Faculty of Pharmacy, Andalas University, Padang, West Sumatra, Indonesia
[3]Faculty of Medicine, Andalas University, Padang, West Sumatra, Indonesia
[4]Faculty of Pharmacy, Ahmad Dahlan University, Yogyakarta, Indonesia
*Corresponding author: frengki_fkh@unsyiah.ac.id

ABSTRACT

Catechin and their derivatives have been studied to have antiviral potential against COVID-19 through in silico method "pharmacokinetics screening and molecular docking". Pharmacokinetics and toxicity profiles were obtained through the ADMETSAR server and SwissADME server. Then proceed with the prediction of affinity through the method molecular docking using the software application MOE 2007.09. The test material is in the form of a 3D catechin structure and its derivatives as well as several control ligands downloaded via Pubmed. While template the Receptor M^{pro} protein and the Spike glycoprotein are downloaded from pdb.org (PDB ID: 6LU7 and 6LXT). The pharmacokinetic profile of catechins is relatively better than all control ligands with the lowest toxicity. Molecular docking results also show that catechins and their derivatives have a stronger affinity than control ligands. This research proves that catechin has antiviral potential through inhibition of M^{pro} protein and Spike glycoprotein COVID-19 virus.

Key words: catechin, COVID-19, in silico, stereoisomer

ABSTRAK

Penelitian ini bertujuan mengetahui potensi katekin dan turunannya sebagai antiviral COVID-19 secara in silico melalui metode skrining farmakokinetik dan docking molekuler. Profil farmakokinetika dan toksistas diperoleh melalui server ADMETSAR dan server SwissADME. Kemudian dilanjutkan dengan prediksi afinitas melalui metode docking moleculer menggunakan aplikasi software MOE 2007.09. Bahan uji berupa struktur 3D katekin dan turunannya serta beberapa ligan kontrol yang diunduh melalui Pubmed, sedangkan template reseptor M^{pro} protein dan spike glikoprotein diunduh dari pdb.org (PDB ID*: 6LU7 dan 6LXT). Profil farmakokinetika katekin relatif lebih baik dibandingkan semua ligan kontrol dengan toksisitas terendah. Hasil docking molekuler juga menunjukkan katekin dan turunannya memiliki afinitas lebih kuat dibanding ligan kontrol. Penelitian ini membuktikan katekin memiliki potensi sebagai antiviral melalui inhibisi M^{pro} protein dan Spike glikoprotein virus COVID-19.*

Kata kunci: katekin, COVID-19, in silico, stereoisomer

INTRODUCTION

The presence of the new SARS-CoV2 coronavirus (COVID-19) in the Hubei-China province had become a global pandemic in early 2020 that almost paralyzed the whole world. The latest WHO release until on May 3, 2020 shows the confirmed number of COVID-19 in the world has reached 3,349,786 infections with 238,638 deaths. In Indonesia, the sufferers confirmed 10,843 infections with 831 deaths (WHO, 2020).

There is no effective therapy to overcome this viral infection, but various efforts continue. The use of antimalarial and antiviral compounds is one of the recommended uses. Use of chloroquine and remdesivir *in vitro* has been reported by Wang *et al.* (2020) and use of hydroxychloroquine *in vitro* has been reported by Liu *et al.* (2020) also ritonavir, ramdesivir, and favipiravir (De Clercq, 2019; Jin *et al.*, 2019; Habibzadeh and Stoneman, 2020). However, the use of those compounds as antiviral COVID-19 in humans is still controversial both in terms of their effectiveness and side effects.

This condition challenges researchers around the world to find more potential antiviral drug on COVID-19 with minimal side effects. Digital screening of tens to thousands of compounds from the PubChem database was carried out by several researchers. The digital screening was carried out after several targets of COVID-19 protein were identified and the most commonly reported were M^{pro} protein and Spike glycoprotein COVID-19. M^{pro} protein is a main protease COVID-19 which has been successfully crystallized by Jin *et al.* (2020) and available in the protein database server www.pdb.org (PDB ID. 6LU7). The glycoprotein spike (PDB ID. 6LXT) was also successfully identified as Shang *et al.* (2020). The glycoprotein spike is shaped like nails that stick to the surface of the virus. The glycoprotein spike is believed to be a bridge of virus transmission into human cells (Xu *et al.*, 2020) through strong binding affinity with ACE2, as a simulation model of biochemical interaction and crystal structure analysis reported by Li *et al.* (2005). The glycoprotein spike has a high resemblance to the previous coronavirus, SARS-CoV. Among the potential compounds reported based on digital screening are hesperidin, kaempferol, naringenin, quersetin, catechins, and curcumin (Adem *et al.*, 2020; Chen and Du, 2020; Khaerunnisa *et al.*, 2020; Trina *et al.*, 2020; Utomo *et al.*, 2020).

Catechins and their derivatives are reported to be active as anti-oxidants, antihypertensives, anti-

inflammatory, antithrombogenic, and reduce fat content (Babu and Liu, 2008; Auclair *et al.,* 2008). As an anticancer catechins and their derivatives have also been widely reported, even has reached the stage of clinical trials such as lung cancer (Wang *et al.,* 2012), gastric cancer (Ju *et al.,* 2005), skin cancer (Afaq *et al.,* 2003), and liver cancer (Jia *et al.,* 2002). Potential antiviral in catechins contained in green tea plant extracts have also been reported by Xu *et al.* (2017). The green tea catechin has broad antiviral activity including hepatitis B virus (HBV), hepatitis C virus (HCV), Epstein-Barr virus (EBV), human immunodeficiency virus (HIV), dengue viruses, chikungunya virus (CHIKV) and Zika virus (ZIKV). It is hoped that catechins and their derivatives also have the potential to be antiviral on COVID-19.

Although there are several reports that mention catechins to have antiviral potential on COVID-19, but the explanation is still limited to the results of digital screening as previous reports. The fact shows that catechin is a chiral compound with more than one spatial structure namely (-) - catechin [2R, 3S], (+) - catechin [2S, 3R], (-) - epicatechin [2R, 3R] and (+) - epicatechin [2S, 3S] (Cui *et al.,* 2015). This was not explained in the report. Therefore, in addition to digital screening of suitable compounds as COVID-19 antiviral candidates, the authors will also analyze the effect of stereoisomer differences on affinity and the ligand-receptor interaction model formed using the molecular docking method. The docking results will be supplemented with pharmacokinetic and toxicity profile data aimed at predicting the eligibility of candidates for the antiviral drug COVID-19 which is expected to work effectively and to consume safely.

MATERIALS AND METHODS

The ligand compounds used are (-) - catechin, (+) - catechin, (-) - epicatechin, (+) - epicatechin, (-) - catechin gallate, (+) - catechin gallate, catechin 3 '-O-gallate, catechin 5-O-gallate, catechin 7-O-gallate, catechin 3'-glucoside, catechin 5-glucoside, hesperidin, chloroquine, hydroxychloroquine, redesivir, ritonavir, favipiravir obtained from the Pubchem database. Whereas the template for the COVID-19 M^{pro} protein and spike glycoprotein were downloaded from www.pdb.org (PDB ID: 6LU7 and 6LXT).

Pharmacokinetic Prediction Test Ligands

Pharmacokinetic profiles of all ligands use the ADME-Toxicity method and the parameters of drug likeness (Lipinski's rules of five) through ADMETSAR server (http://lmmd.ecust.edu.cn:8000/predict/) and Swiss ADME server (http://www.swissadme.ch/index.php).

Affinity Prediction

A total of 11 download test ligands obtained from the Pubmed database and the receptors obtained from the protein database are prepared and optimized for their 3-dimensional structure by adding hydrogen, eliminating water molecules, adding partial charges, minimizing energy and site binding is selected. Then docking is run using default MOE system at the binding site. Complex receptor-ligand is stored in the format of pdb, while the value of docking stored in format of mdb. The docking then visualized in the 3D structure via LigPlot using application software of MOE. While chiral ligands (catechin, epicatechin and catechin gallate) are designed in 2D and 3D structures through the help of ChemOffice software. Furthermore, it is prepared and optimized using MOE software as 11 ligands above.

RESULTS AND DISCUSSION

Prediction of Ligand Pharmacokinetic Profiles

Each drug compound has physicochemical characteristics that affect its pharmacokinetic profile. The process of adsorption of compounds is influenced by several factors, such as lipophilicity, hydrogen bonds, molecular size, and pKa charge (Lawson *et al.,* 2013). Log P and Topological Polar Surface Area (TPSA) are parameters used to assess the adsorption power of a compound. Catechin, epicatechin, chloroquine, hydroxychloroquine, and favipiravir have log P <5 and TPSA <140 Å, so they have good adsorption ability. However, the absorption of catechins is thought to be lower than that of chloroquine, hydroxychloroquine, and favipiravir because catechins are Pgp protein substrates. Pgp protein in membrane protein acts as drugs efflux that functions to re-emerge compounds that enter the cell to the outside of cells so that the intracellular concentration of these compounds is low. Pgp is widely reported in the digestive system, especially in the intestine (Siddik, 2013). Catechin derivatives and other test compounds have a TPSA <140 Å, so that the value of human intestinal absorption is low. Nevertheless the predicted pharmacokinetic results of catechins and epicatechins still show high adsorption power.

Catechins, epicatechin, and favipiravir do not interact with the cytochrome P450 enzymes (CYP2C9, CYP2D6 and CYP3A4), as well as catechin derivatives. Conversely chloroquine and hydroxychloroquine undergo metabolism by acting as a substrate or inhibitor of these metabolic enzymes. The metabolites produced are predicted to be pharmacologically inactive or even produce undesirable toxic effects. This estimation is proven by the higher chloroquine toxicity value, as well as hydroxychloroquine and favipiravir. In contrast, catechins, epicatechins. and their derivatives showed lower levels of toxicity.

Data prediction of pharmacokinetic profiles and toxicity of all active compounds will be validated by Lipinski's Rules of Five. This is done to ensure the feasibility of potential compounds as candidates for drugs in humans. Characteristics of a good pharmacokinetic profile with low toxicity and compliance with Lipinski's rules of five, shows that catechin and epicatechin are very potential to be used as an alternative to antiviral COVID-19. Complete data on the predicted results of pharmacokinetic profiles and toxicity are shown in Table 1.

Table 1. Results of prediction of pharmacokinetic parameters and *druglieness* (Lipinski's rules of five) ligands test

Compounds	Adsorption and biovability					Metabolism						Toxicity		Lipinskis' Rules of five
	Bbb	Hib	Pgp_S	Log P	Tpsa (°A)	Cyp2c9_sub	Cyp2d6_sub	Cyp3a4_sub	Cyp2c9_Inh	Cyp2d6_Inh	Cyp3a4_Inh	Carc	Aot	
(-)-Catechin	-	High	S	1.47	110.38	NS	NS	NS	NI	NI	NI	NC	IV	+
(+)-Catechin	-	High	S	1.47	110.38	NS	NS	NS	NI	NI	NI	NC	IV	+
(-)-Epicatechin	-	High	S	1.47	110.38	NS	NS	NS	NI	NI	NI	NC	IV	+
(+)-Epicatechin	-	High	S	1.47	110.38	NS	NS	NS	NI	NI	NI	NC	IV	+
(-)-Catechin gallate	-	Low	NS	1.31	177.14	NS	NS	NS	NI	NI	NI	NC	IV	+
(+)-Catechin gallate	-	Low	NS	1.31	177.14	NS	NS	NS	NI	NI	NI	NC	IV	+
Catechin 3'-O-gallate	-	Low	NS	1.52	177.14	NS	NS	NS	NI	NI	NI	NC	IV	+
Catechin 5-O-gallate	-	Low	NS	1.55	177.14	NS	NS	NS	NI	NI	NI	NC	III	+
Catechin 7-O-gallate	-	Low	NS	1.67	177.14	NS	NS	NS	NI	NI	NI	NC	III	+
Catechin 3'-glucoside	-	Low	NS	0.53	189.53	NS	NS	NS	NI	NI	NI	NC	III	+
Catechin 5-glucoside	-	Low	NS	0.95	189.53	NS	NS	NS	NI	NI	NI	NC	III	+
Control														
Hesperidin	-	Low		2.60	234.29	NS	NS	S	NI	NI	NI	NC	III	+
Chloroquine	+	High	NS	3.95	28.16	NS	S	S	NI	I	I	NC	II	+
Hydrochloroquine	+	High	NS	3.58	48.39	NS	NS	NS	NI	I	NI	NC	III	+
Remdesivir	-	Low	S	3.24	213.36	NS	NS	S	NI	NI	I	NC	III	+
Ritonavir	-	Low	S	4.42	202.26	NS	S	S	NI	NI	I	NC	III	+
Favipiravir	+	High	NS	0.39	88.84	NS	NS	NS	NI	NI	NI	NC	III	+

Bbb= Blood brain barrier, Hib= Human Intestinal absorption, S/NS= Substrate/non substrate, C/NC= Carcinogen/non carcinogen, I/NI= Inhibitor/non inhibitor, Aot= Acut oral toxicity

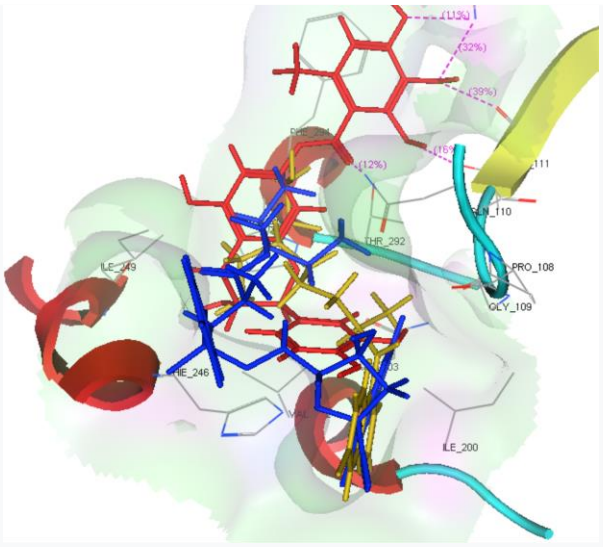

Figure 1a. Interaction model of catechin 7-O-gallate (red), hydrocloroquine (yellow), and remdesivir (blue) to the main protease receptor Mpro COVID-19 (Pdb id. 6lu7)

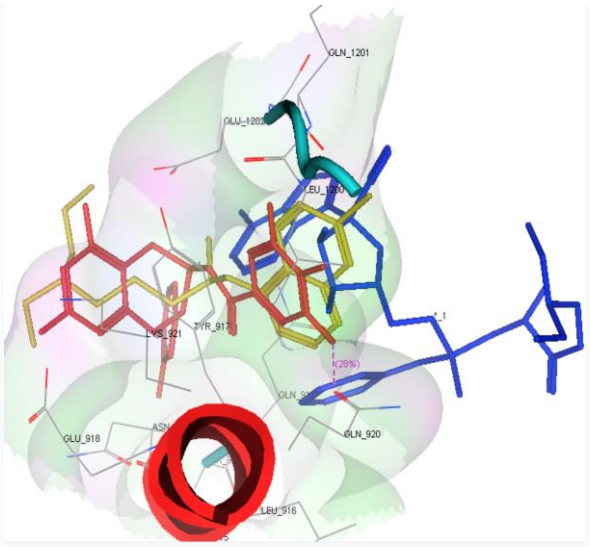

Figure 1b. Interaction model of catechin 5-O-gallate (red), hydrocloroquine (yellow), and remdesivir (blue) against COVID-19 glycoprotein spikes receptor (Pdb id. 6lxt)

Docking

The docking results show that all test and control ligands were able to interact to form complexes with receptors (M^{pro} protein and spike glycoprotein) COVID-19 virus. Interaction models of ligand-receptor are shown in Figure 1a and Figure 1b. All of them showed a tendency to release energy when forming complexes with the two receptors, but the strength of the affinity was different. The more negative the docking score obtained indicates its affinity with the receptor the stronger (Frengki *et al.*, 2019).

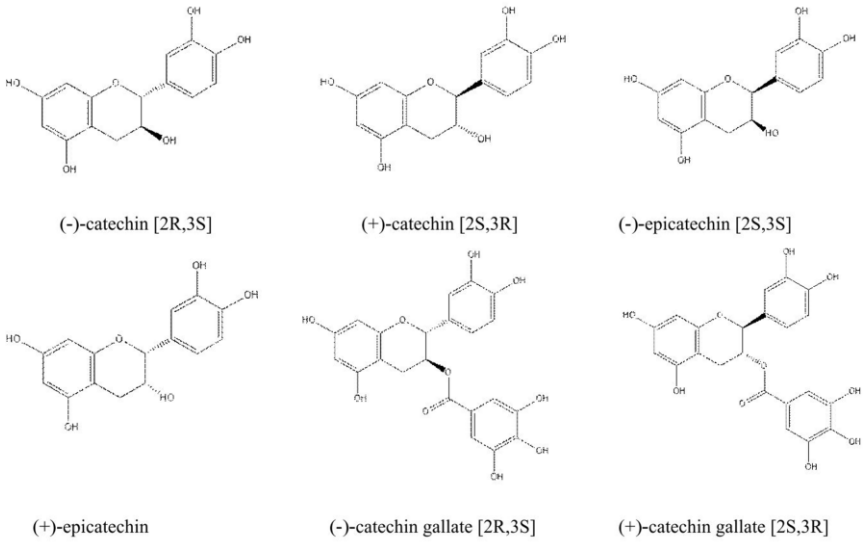

Figure 2. Stereoisomers of (+/-) – catechin, -epicatechin, and -catechin gallate [2R, 3S]

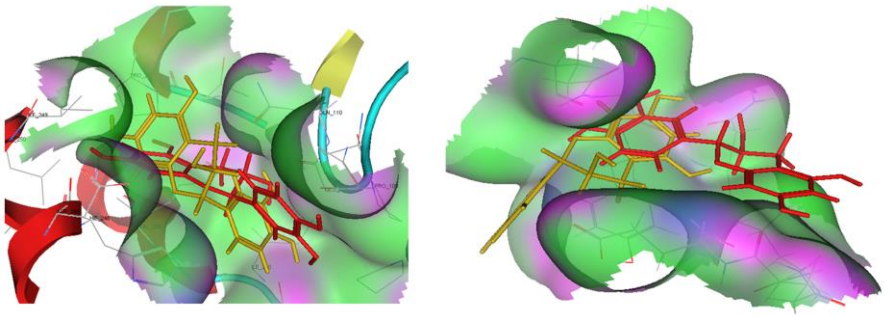

Figure 3a. 3D ligand conformation (-) - catechin [2R, 3S] (yellow) and (+) - catechin [2S, 3R] (red) when forming complexes with 6LU7 and 6LXT receptors

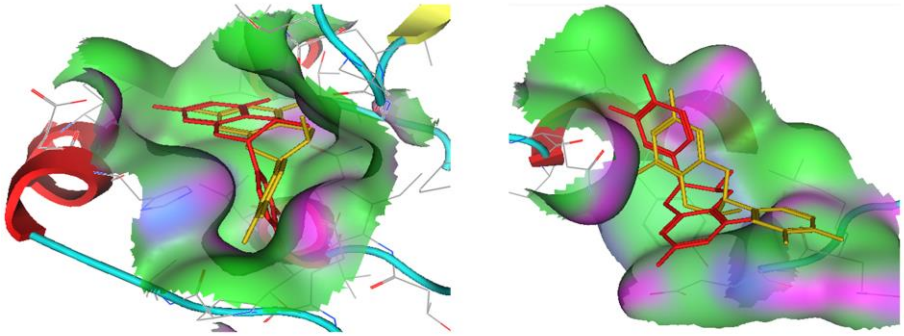

Figure 3b. 3D ligand conformation (-) - epicatechin [2S, 3S] (yellow) and (+) - epicatechin [2R, 3R] (red) when forming complexes with 6LU7 and 6LXT receptors

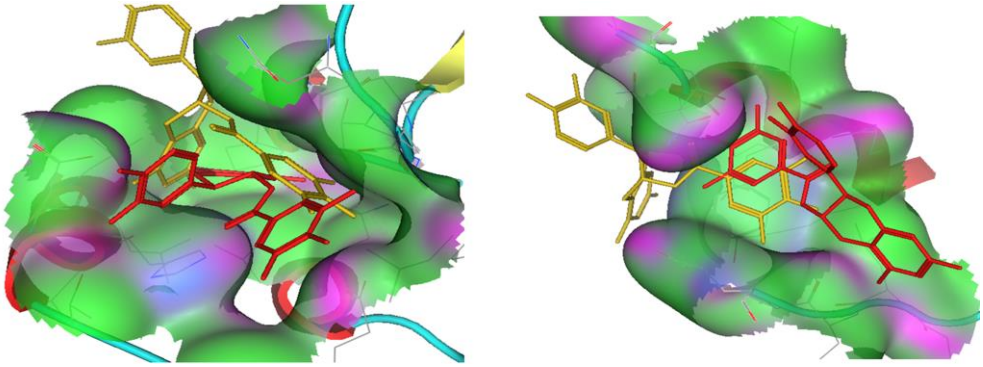

Figure 3c. 3D ligand conformation (-) - catechin gallate [2R, 3S] (yellow) and (+) - catechin gallate [2S, 3R] (red) when forming complexes with 6LU7 and 6LXT receptors

Table 2. Free energy, number, and distance of hydrogen bonding from docking ligand with M^{pro} protein and spike glycoprotein

Compounds	Receptor main protease (Pdb ID. 6LU7)			Receptor spike glycoprotein (Pdb ID. 6LXT)		
	ΔG kcal/mol	H-bond with residue	H-bond distance (Å)	ΔG kcal/mol	H-bond with residue	H-bond distance (Å)
(-)-Catechin	-14.1370	Pro 108	2.83	-11,32223	Asp 367	3.07
		Asp 245	3.50		Gln 442	2.32
		His 246	2.54			
(+)-Catechin	-13.5387	Pro 108	3.15	-10.4993	Gln 442	2.32
		Glu 240	2.08			
		Gln 110	2.90			
(-)-Epicatechin	-13.6338	Pro 108	1.88	-11.5055	Lys 441	2.97
		Gln 110	3.40		Thr 445	2.86
		Thr 201	2.52		Ser 409	3.18
		Val 202	2.00		Lys 441	2.76
					Thr 445	2.86
					Gln 522	3.33
(+)-Epicatechin	-12.2790	Pro 108	1.20	-10.3292	Glu 375	2.59
		Asn 203	2.81			
		Pro 241	1.84			
(-)-Catechin gallate	-12.9942	Gln 110	3.00	-12.4199	Asp 367	2.32
		Asn 203	2.25		Thr 519	2.61
		His 246	2.22		Thr 519	2.61
(+)-Catechin gallate	-13.7186	Glu 240	3.57	-13.0183	Glu 375	3.00
		Asp 245	2.81		Thr 449	1.89
					Thr 449	1.89
Catechin 3'-O-gallate	-14.4852	Gln 110	2.89	-11.8377	His 345	1.75
		Thr 201	2.66		Tyr 515	3.31
					His 345	1.75
Catechin 5-O-gallate	-14.6331	Pro 108	3.61	-11.3650	Thr 276	3.13
		Pro 108	3.46		Thr 276	2.98
		Asp 245	3.52		Thr 445	2.12
		His 246	2.83		Thr 276	3.13
		Gln 110	2.87		Thr 275	2.98
					Thr 445	2.12
Catechin 7-O-gallate	-15.0299	Thr 111	2.97	-11.9637	Thr 276	2.97
		Thr 111	1.79		Thr 276	1.76
		Gln 110	1.09		Asp 367	3.03
		Thr 111	2.97		Glu 406	2.08
		Asn 151	2.83		Thr 445	2.19
		Asn 151	2.56		Hid 505	2.77
					Thr 276	2.97
					Thr 276	1.76
					Thr 445	2.19
					Hid 505	2.77
Catechin 3'-glucoside	-12.3104	Gln 110	3.07	-10.5722	Glu 406	3.12
		Phe 294	3.10		Glu 406	3.14
					Gln 442	1.97
					Arg 518	2.26
					Arg 518	2.59
					Arg 518	2.93
Catechin 5-glucoside	-11.9737	Pro 108	2.23	-10.8447	Asp 367	2.72
		Asn 203	2.49		Glu 402	2.52
		Pro 241	3.88		Glu 402	2.19
		His 246	2.76		Glu 406	2.16
					Lys 441	2.41
					Arg 518	2.77
Control						
Hesperidin	-11.5881	Pro 108	2.83	-11.2115	Gln 1201	2.48
		Asp 245	3.50		Gln 913	3.17
		His 246	2.54		Gln 913	3.01
					Gln 913	2.23
Chloroquine	-9.8398	Thr 243	2.84	-9.0316	No H-bond	-
Hydrochloroquine	-11.3684	Glu 240	1.48	-9.5593	Gln 913	2.26
		Val 202	2.69			
Remdesivir	-10.1329	Asp 245	1.69	-9.5209	No H-bond	-
		Thr 243	2.38			
		His 246	1.98			
Ritonavir	-9.6618	No H-bond	-	-9.3655	Glu 1202	2.04
					Gln 913	1.61
Favipiravir	-8.7215	Pro 108	1.54	-8.3935	Gln 920	1.91
		Gln 110	1.83		Gln 1201	1.48

Catechins and some of their derivatives showed a stronger affinity for M^{pro} protein and glycoprotein spikes than hesperidin, chloroquine, hydroxyl-chloroquine and some antivirals such as remdesivir, ritonavir, and favipiravir. This showed that catechins and their derivatives form a more stable ligand-receptor complex so that the potential for antiviral activity is thought to be stronger. Molecular docking results are shown in Table 2.

Differences in stereoisomers of catechin, epicatechin, and catechin gallate (Figure 2) also cause differences in the strength of affinity for the two receptors above. The strength of successive affinities in the M"main protease"^{pro} protein receptor is catechin 7-O-gallate > catechin 5-O-gallate > catechin 3'-O-gallate > (-)-catechin > (+)- catechin gallate > (-)-epicatechin> (+)-catechin > (-)-catechin gallate > catechin 3'-glucoside > (+)-epicatechin > catechin 5-glucoside > hesperidin > hydrocloroquine > remdesivir > chloroquine > ritonavir > favipiravir. Meanwhile, glycoprotein spike is (+)-catechin gallate > (-)-catechin gallate > catechin 7-O-gallate > catechin 3'-O-gallate > (-)-epicatechin > catechin 5-O-gallate > (+)-epicatechin > (-)-catechin > hesperidin > catechin 5-glucoside > catechin 3'-glucoside > (+)-catechin > hydroxychloroquine > remdesivir > ritonavir > favipiravir.

Khairunnisa *et al.* (2020) reported that catechins and some potential flavonoid derivatives have been developed as antiviral COVID-19, which supported the result of the present research, although there are differences in the selection of binding site. Khairunnisa *et al.* (2020) traced binding site based on the native ligand of M^{pro} protein, while this study preferred binding site to search for system default MOE software. In addition, this study also optimized catechins based on differences in spatial structure into 4 different stereoisomers [(-)- catechin, (+)- catechin), (-)- epicatechin and (+) - epicatechin], as well as gallate catechins to 2 stereoisomer [(-)- catechin gallate and (+)- catechin gallate)]. The results of the analysis based on this stereoisomer reference are believed to be more valid.

The stereoisomer [2R, 3S] conformation of catechin gives a distinct affinity stronger than the conformation of [2S, 3R] with an affinity of -14.1370 kcal/mol and -13.5387 kcal/mol respectively for M^{pro} protein. Similar results occur in interactions between catechin and glycoprotein spike receptors. The affinity of catechin with [2R, 3S] conformation also shows the release of energy of -11,322 kcal/mol compared to catechins with [2S, 3R] conformation which shows the release of energy of -10.4993 kcal/mol.

Conformation of [2S, 3S] on epicatechin also gives a stronger affinity than conformation of [2R, 3R] with an affinity of -13.6338 kcal/mol and -12.2790 kcal/mol respectively for M^{pro} proteinSimilar results also occur in interactions between catechins and glycoprotein spike receptors. The affinity of epicatechin with conformation [2S, 3S] also shows the release of energy of -11.5055 kcal/mol compared to epicatechin with [2R, 3R] conformation which shows the release of energy of -10.32292 kcal/mol. The hydroxyl (OH) group in the 3S position has a very important role in increasing the affinity of catechins and epicatechins in the two receptors above.

On the other hand, the addition of a galloyl group in the 3S position shows a lower affinity compared to the 3R position galloyl group. This is observed in conformation (-)- catechin gallate [2R, 3S] which gives an affinity value of -12.9942 kcal/mol weaker than conformation (+)- catechin gallate [2S, 3R] which gives an affinity value of -13.7186 kcal/mole. This was observed in M^{pro} protein. Likewise in the glycoprotein spike the addition of galloyl groups at position 3S shows a weaker affinity compared to position 3R. This is observed in conformation (-)- catechin gallate [2R, 3S] giving an affinity value of -12.4199 kcal/mol slightly weaker than conformation (+) - catechin gallate [2S, 3R] which gives an affinity value of -13.0183 kcal/mole. In Figure 3c, a catechin gallate B ring shift is observed away from the site binding Mpro protein or spike glycoprotein, thus the B ring shift also determines the change in affinity besides the presence of hydroxyl (OH) groups in the 3S position. While catechins and epicatechin still in Figures 3a and 3b still show the appropriate position at the binding site of the two receptors.

CONCLUSION

Catechins and their derivates show a better pharmacokinetic profile with lower toxicity and also show a docking score stronger compared to chloroquine and other antiviral control. Research In silico is able to explain the potential of catechins as an alternative antiviral COVID-19.

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